THE RELATIONSHIP OF MUSICAL ABILITIES WITH COGNITION AND NEURODEGENERATIVE PATHOLOGY IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

Darina V. Petrovsky

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Supervisor of Dissertation:

____

Pamela Z. Cacchione, PhD, CRNP, BC, FAAN
Associate Professor of Geropsychiatric Nursing

Graduate Group Chairperson:

____

Salimah Meghani, PhD, MBE, RN, FAAN
Associate Professor of Nursing

Dissertation Committee:
Roy Hamilton, MD, MS
Assistant Professor of Neurology

Nancy Tkacs, PhD, RN
Associate Professor of Nursing Emerita

Julene Johnson, PhD
Professor
University of California San Francisco School of Nursing

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DEDICATION

To my parents, for giving me the guidance and freedom to explore my strengths. For providing me and my brother so many opportunities to grow and explore when you made the ultimate sacrifice by leaving your home behind and moving across the world to give us a better chance for life.

To my husband John, the love of my life, for always encouraging me to pursue my dreams, taking care of our family and always being there when I needed you.

To my son Philip, who makes me smile and see the world as a big playground. I cannot wait to see you grow up and follow your dreams. May you remain steadfast in your faith, compassion and kindness towards others.

And to my late grandmother Galina, for instilling in me the love and appreciation for music that still drives all that I do today.

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ABSTRACT

THE RELATIONSHIP OF MUSICAL ABILITIES WITH COGNITION AND NEURODEGENERATIVE PATHOLOGY IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

Darina V. Petrovsky

Pamela Z. Cacchione

Older adults with mild cognitive impairment (MCI) are at increased risk for dementia. Despite the presence of cognitive deficits in persons with MCI and dementia, older adults with dementia preserve their ability to engage in music throughout their disease. However, musical abilities have not previously been explored in individuals with MCI. The purpose of this dissertation was twofold: 1) to better understand the relationship between musical and cognitive abilities in persons with MCI (Chapter II) and how preserved musical abilities may contribute to enhanced cognitive abilities despite the underlying atrophy in the brain (Chapter III); and 2) to develop and submit a post-doctoral application to investigate the feasibility and acceptability of an individualized music intervention to reduce sleep disturbances in older adults with dementia (Chapter IV).

We conducted a cross-sectional study at the University of Pennsylvania Alzheimer's Disease Core Center (ADCC). We combined existing data from the ADCC and asked 60 older adults with MCI to complete two questionnaires, one screening for depression and the other gauging their musical abilities. We broadly operationalized musical abilities as musical skills, expertise, achievements and related behaviors and used hippocampal volume as a biomarker for the underlying atrophy in the brain. The

participants, on average, scored lower on the index of musical abilities compared to published norms. Using Pearson's correlations and linear regression analyses, we found that participants who scored lower on the index of musical abilities had lower scores on the measure of verbal naming. Additionally, musical abilities moderated the relationship between hippocampal volume and one of the cognitive abilities – executive function in 38 older adults for whom magnetic resonance imaging was available.

Enhanced musical abilities emerged as a possible compensatory mechanism for persons with MCI who are struggling with cognitive deficits. Given the relationship between musical and cognitive abilities, music may be an effective intervention to maintain cognition and improve the well-being of older adults with cognitive impairment. This body of work, my passion for music, and a desire to garner skills in intervention research served as a platform for writing and submitting a post-doctoral application exploring how a music intervention may help alleviate one of the most distressing behavioral symptoms of dementia – sleep disturbances.

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CHAPTER 1: INTRODUCTION

Introduction to the Problem

Dementia is a growing global epidemic. In the United States alone more than 5 million Americans are suffering from dementia (Alzheimer's Association, 2017). Dementia negatively impacts the quality of life and the emotional well-being of older adults living with dementia as well as their caregivers (Schulz & Martire, 2004). In recent years, a strong emphasis has been placed on the early clinical diagnosis of dementia in order to examine the natural trajectory of cognitive decline and to identify factors associated with the disease progression (Petersen et al., 2014). As such, Petersen et al. (1997) first introduced mild cognitive impairment (MCI) as the stage between normal cognition and dementia. Individuals with MCI are at increased risk for dementia. Not all individuals, however, convert to dementia (Petersen, 2004; Petersen et al., 2014). Clinical characteristics of MCI include subjective cognitive complaints later confirmed with objective neuropsychological testing. Persons with MCI may have deficits in memory, executive function, attention, language and/or visuoconstructive abilities (Petersen, 2004). The deficits, however, do not extend to functional abilities (Petersen, 2004).

Even though individuals with MCI and dementia experience cognitive deficits, anecdotal (Cuddy & Duffin, 2005) and recent scientific evidence (Jacobsen et al., 2015) suggests that older adults with dementia remain responsive to music as their disease progresses. The preserved ability to engage in music is attributed to areas of the brain associated with music perception are some of the last ones to deteriorate (Jacobsen et al., 2015). While preserved musical abilities have been described in persons with dementia, this body of work is the first to describe musical abilities and their association with cognition among older adults with MCI. This dissertation is a first step in a research trajectory focused on the use of music interventions to improve the health and well-being in older adults with MCI and dementia. This study contributes to the knowledge of association of musical and cognitive abilities in persons with MCI and serves as a motivation for developing music interventions to address behavioral and psychological symptoms in persons with dementia.

Background and Significance

Dementia is characterized by widespread deficits in cognition, memory, and everyday function (Alzheimer's Association, 2017). According to global estimates, approximately 35.6 million people lived with dementia in 2010. Due to the ageing population these numbers are projected to rise, reaching 115.4 million in 2050 (Prince et al., 2013). Older adults with mild cognitive impairment (MCI) are at increased risk for dementia (Petersen, 2004; Stephan et al., 2012). The global prevalence rates for older adults over the age of 60 with MCI vary between 6 and 12 percent (Sachdev et al., 2015). The US-based prevalence rates for MCI range from 18.8 to 28.3 percent (Ward, Arrighi, Michels, & Cedarbaum, 2012).

Current clinical guidelines distinguish MCI from other cognitive deficits using three main criteria (Albert et al., 2011; Petersen, 2004). First, persons with MCI (or reports from their caregivers) present with subjective cognitive complaints. Next, the presence and the extent of subjective cognitive complaints is confirmed with objective neuropsychological test data (Petersen, 2004; Petersen et al., 2014). The last criteria specifies that unlike dementia, older adults with MCI maintain their independence in everyday function (Petersen, 2004; Petersen et al., 2014). Research and clinical observations identified four subtypes of MCI: amnestic single domain, amnestic multiple domain, non-amnestic single domain, and non-amnestic multiple domain (Petersen et al., 2014). The subtypes are helpful in characterizing the nature of deficits in persons with MCI as well as predicting the future progression to dementia (Petersen, 2004).

The hallmark features of MCI include deficits in memory, executive function, attention, language, and visuoconstructive abilities. Several neuropsychological tests examine cognitive deficits in persons with MCI. Tests of episodic verbal memory (defined as an ability to remember and retain new information) often include immediate and delayed recalls (Albert et al., 2011). Executive function is defined as a complex set of behaviors responsible for an independent response to novel situations (Lezak, 2004) which may include reasoning, goal-setting and problem solving (Albert et al., 2011). Attention refers to the ability of a person to process outside stimuli (Lezak, 2004). Language skills tested in older adults with MCI include naming, letter fluency and comprehension (Albert et al., 2011). Finally, assessment of visuoconstructive abilities consists of asking adults to copy figures and redraw shapes. The individual test scores as well as the composite cognitive scores indicate the severity of cognitive deficits and contribute to the diagnosis of MCI.

The underlying neurodegenerative pathology of Alzheimer's disease (AD) includes accumulations of abnormal extracellular β-amyloid (Aβ) fibrils in the brain (Skovronsky, Lee, & Trojanowski, 2006). Neuropsychological assessment in addition to in-vivo Alzheimer's disease (AD) biomarkers provide a complete profile of cognitive deficits aiding in the diagnosis and a more accurate prediction of disease progression (Beckett et al., 2010). These biomarkers include cerebrospinal fluid and regional brain atrophy derived from magnetic resonance imaging (MRI) (Caroli et al., 2015). One of the regions of interest includes the hippocampus. Located medially to the temporal lobe, the hippocampus plays a major role in memory formation and retrieval (Golomb et al., 1994). Memory impairment is a hallmark symptom of AD (McKhann et al., 2011). It is, therefore, not surprising that changes in hippocampal volume (HV) correlate with MCI to AD conversion rates (Clerx et al., 2013; Fleisher et al., 2008; Jack et al., 1999; Risacher et al., 2009) and faster cognitive decline (Beckett et al., 2010; Yavuz et al., 2007).

Despite the presence of cognitive deficits in persons with MCI and AD, research findings support that older adults with AD preserve their ability to interact and engage in music throughout their disease (Cuddy & Duffin, 2005; Cuddy et al., 2012; Jacobsen et al., 2015). Individuals with AD were found to be able to play a musical instrument (Beatty, Brumback, & Vonsattel, 1997), learn a new song (Cowles et al., 2003), detect wrong notes in a familiar melody (Cuddy & Duffin, 2005) and recognize emotions expressed in music (Drapeau, Gosselin, Gagnon, Peretz, & Lorrain, 2009; Gagnon, Peretz, & Fulop, 2009). Taken together, prior research suggests that various musical abilities remain intact during the course of AD.

Only a handful of studies have examined musical abilities in MCI. In one study persons with MCI retained their ability to assign emotional expressions (happy, sad, or unsure) to musical excerpts between older adults with MCI, early AD, and normal cognition (Kerer et al., 2014). In the same study, compared to healthy controls, participants with MCI and early AD showed significantly lower performances on the tests of verbal music memory (Kerer et al., 2013). A closer examination of musical abilities in older adults living with MCI is essential so future music interventions can then be developed to address cognitive deficits in this high-risk population. Musical abilities in persons with MCI may not be uniformly impacted. For example, while the connection between emotions and music remains intact, verbal music memory may be affected by the underlying brain pathology (Kerer et al., 2014). Furthermore, investigating the relationship between musical and cognitive abilities in MCI will add to our knowledge of how musical abilities shape non-musical cognitive abilities. This dissertation is an important addition to the body of knowledge addressing musical and cognitive abilities in MCI. In addition, this dissertation will contribute to our understanding of how musical abilities may moderate the relationship between the underlying disease pathology (AD biomarkers) and cognitive abilities. The findings of this dissertation will generate new hypotheses and provide a platform for future investigations in the area of music and cognitive impairment.

Musical Abilities

Given that one of the most fundamental and universal human abilities is to engage in music (Merriam, 1964) scientists have long explored ways for persons to engage in music. Western societies, in particular, have defined a musician in terms of years of formal music education (Müllensiefen, Gingras, Musil, & Stewart, 2014). However, recently ethnomusicologists have expanded this hierarchical notion of musical abilities to include musical understanding, appreciation, evaluation, and having a sense of pitch and rhythm (Hallam & Prince, 2003). In this dissertation we operationalized musical abilities using a musical sophistication construct, defined as “musical skills, expertise, achievements and related behaviors” (Müllensiefen et al., 2014, p. 2). Previous measures relied heavily on the years of formal musical education as a proxy measure for musical abilities. By expanding this definition, this body of work will capture music engagement outside of formal training for persons with MCI.

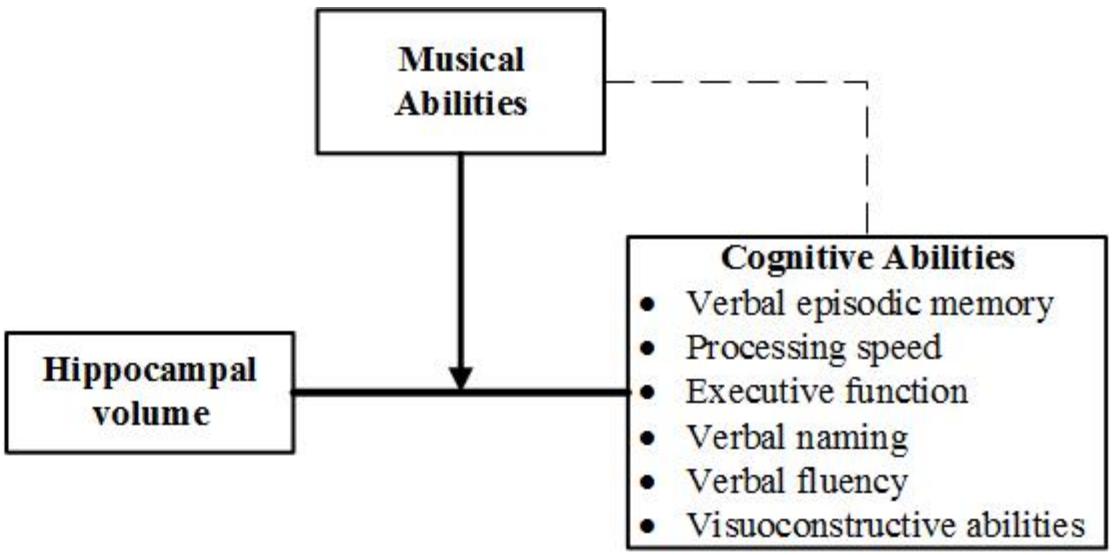
Conceptual Model

The conceptual model underpinning this study is presented in Figure 1.1. One of the premises of this model is that older adults who face memory deficits may rely on alternate cognitive abilities to compensate for their memory deficits, such as reasoning and attentional speed (Willis, Tennstedt, Marsiske, & et al., 2006). Thus, the benefits of participating in music may extend to non-music cognitive abilities. For example, studies in young musicians have demonstrated enhancement of verbal memory abilities, auditory learning and language functions (Hanna-Pladdy & MacKay, 2011). In our study, we are examining the following cognitive abilities: verbal episodic memory, processing speed, executive function, verbal fluency, verbal naming and visuoconstructive abilities (Figure 1.1). Learning a musical instrument later in life has shown additional benefits as well. Following four months of piano lessons and daily training healthy older adults demonstrated benefits in executive function processing speed when compared with age-matched control group (Seinfeld, Figueroa, Ortiz-Gil, & Sanchez-Vives, 2013). Taken together, increased musical abilities, whether they result from a lifetime of playing a musical instrument or short-term training, may be related to cognitive abilities and play a role in protecting the brain against the underlying pathology.

Converging evidence from epidemiological studies suggests that mentally stimulating activities in late life have a protective effect against symptomatic AD (Verghese et al., 2006; Verghese et al., 2003). For instance, participation in leisure activities slows down hippocampal atrophy in cognitively intact individuals (Valenzuela

& Sachdev, 2006). In particular, in large observational studies older adults who played a musical instrument (Eriksson Sörman, Sundström, Rönnlund, Adolfsson, & Nilsson, 2014; Hughes, Chang, Vander Bilt, & Ganguli, 2010; Karp et al., 2006; Verghese et al., 2003) or listened to music (Akbaraly et al., 2009; Scarmeas, Levy, Tang, Manly, & Stern, 2001) were less likely to progress to dementia later in life. Participating in everyday music activities in addition to learning how to play a musical instrument may offer lifetime health benefits and protection against dementia in older adults (Figure 1.1).

Figure 1.1 Proposed Relationships between Cognitive Abilities and Hippocampal Volume Moderated by Musical Abilities



Notes: Solid arrow represents a moderating effect of musical abilities. Dotted line denotes possible associations between musical and cognitive abilities.

Gaps in the Literature

Despite the body of evidence demonstrating the preserved ability of persons with dementia to engage in music even in the later stages of the disease, little is known about the nature of musical abilities in persons with MCI. Furthermore, there is little research on how musical abilities relate to non-music cognitive abilities in this population. Previous research focused on cognitive benefits associated with years of playing a musical instrument. Although musical training is directly related to musical abilities, there are other ways to enhance one's musical abilities in everyday life. Currently there is little research on how musical abilities are related to cognition in older adults. We found only one study focusing on the effects of early- to mid-life musical training on cognition in older adults. However in this study the research team did not include older adults with MCI, only investigated a limited number of cognitive abilities (verbal naming and episodic memory), and explored only the effects of musical training (Gooding, Abner, Jicha, Kryscio, & Schmitt, 2014). To our knowledge, this dissertation was the first to examine musical abilities from a broader perspective in persons with MCI and to elucidate how preserved musical abilities may contribute to enhanced cognitive abilities in this high-risk population.

Purpose and Specific Aims

The purpose of this dissertation was twofold: 1) to better understand the relationship between musical and cognitive abilities in persons with MCI (Aim 1) and how preserved musical abilities may contribute to enhanced cognitive abilities despite the underlying atrophy in the brain (Aim 2); and 2) to develop and submit a post-doctoral application to investigate the feasibility and acceptability of a personalized music intervention to reduce sleep disturbances in older adults with dementia. To achieve the first purpose we conducted a cross-sectional study at the University of Pennsylvania Alzheimer's Disease Core Center (ADCC). To reduce the burden of research participation we combined existing data from the ADCC database and asked participants to complete two questionnaires, one screening for depression and the other gauging their musical abilities.

The first aim was to determine the association between musical and cognitive abilities in older adults with MCI. Using the database we examined how well participants scored on the tests of verbal episodic memory, processing speed, executive function, language verbal fluency, verbal naming and visuoconstructive abilities. Next, we combined the prospective data collection with the data extracted from the database. Using Pearson's correlations and simple linear regressions we investigated the associations between musical and cognitive abilities and how well musical abilities predicted each cognitive ability separately. We hypothesized that musical abilities would correlate more strongly with tests of verbal episodic memory, processing speed, executive function, verbal naming and visuoconstructive abilities compared to language verbal fluency.

The second aim was to determine whether musical abilities moderate the relationship between hippocampal volume and cognitive abilities in persons with MCI. We hypothesized that the relationship between hippocampal volume in persons with MCI and cognitive abilities would be weaker in persons with greater musical abilities than in persons with lesser musical abilities. For this aim, we used regression analyses and explored the interaction between musical abilities and hippocampal volume for each cognitive ability. The findings from this aim contributed to our understanding of the benefit enhanced musical abilities play in maintaining cognition.

To address the second purpose of this dissertation we developed and submitted a post-doctoral application to examine the feasibility of a tailored music intervention to reduce sleep disturbances in older adults with dementia. Sleep disturbances are pervasive across all three stages of dementia – mild, moderate, and severe (Rose et al., 2011). Given older adults across all stages of dementia are able to respond to music, (Gerdner, 1996, Rev. 2013) soothing music may also decrease sleep disturbances later in the disease progression when cognitive approaches might not be as effective. The results of this post-doctoral application will address sleep disturbances using individualized music interventions and provide additional post-doctoral training related to clinical trial methodology.

Table 1.1 Specific Aims with Corresponding Chapters

Purpose 1	**Chapter**
Aim 1: Determine the association between musical and cognitive abilities in older adults with MCI	II
Aim 2: Determine whether musical abilities moderate the relationship between hippocampal volume and cognitive abilities in persons with MCI	III
Purpose 2	
Develop and submit a post-doctoral application, the purpose of which is to examine the feasibility and acceptability of an individualized music intervention to improve sleep disturbances in older adults with dementia. **Aim 1**: Examine the feasibility of processes that are key to the success of the subsequent study including rates of: adherence to the protocol, completion of the study measures, recruitment, attrition and refusal. **Aim 2**: Examine the acceptability of the intervention using survey and qualitative data. **Aim 3**: Provide preliminary efficacy of the intervention on four sleep quality outcomes: 1) wake time after sleep onset, 2) sleep-latency onset, 3) total sleep duration, and 4) perceived sleep quality.	IV

Summary

The purposes of this dissertation were to explore the relationship of musical and cognitive abilities including hippocampal volume in persons with MCI and to prepare and submit a post-doctoral application. First, we determined the association between music and cognitive abilities in persons with MCI. Next, we investigated whether musical abilities moderate the relationship between hippocampal volume and cognition. Lastly, based on my passion for music, persons with dementia, and a desire for training in intervention research, we submitted a post-doctoral F32 application to the National Institutes of Health. The purpose of this application was to examine the feasibility and acceptability of an individualized music intervention to improve sleep disturbances in persons with dementia. Having a greater understanding of musical abilities in persons with MCI supported the development of the post-doctoral application. More importantly, the results of this body of work will inform health care practices for persons at risk for dementia, the prevalence of which will continue to rise.

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CHAPTER 2: THE RELATIONSHIP BETWEEN MUSICAL AND COGNITIVE ABILITIES IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

Darina V. Petrovsky,[1] MN, RN; Julene K. Johnson,[2] PhD, Nancy Tkacs, PhD,[4] Dawn Mechanic-Hamilton,[3,4] PhD, Roy H. Hamilton,[4] MD, MS, Pamela Z. Cacchione,[1] PhD, CRNP, BC, FAAN

[1] University of Pennsylvania, School of Nursing, Philadelphia, PA

[2] University of California at San Francisco, Institute for Health & Aging, School of Nursing, San Francisco, CA

[3] Penn Memory Center, University of Pennsylvania, Philadelphia, PA

[4] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

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Abstract

Background: Persons with mild cognitive impairment (MCI) are three to eight times more likely to convert to Alzheimer's disease (AD) compared to persons without cognitive impairment. Even though persons with MCI and AD experience deficits in cognition, anecdotal and emerging neuroscientific evidence suggests the sparing of musical abilities in AD. Only a handful of studies examined musical abilities in MCI. Little is known about the relationship between musical and the cognitive abilities that are often impacted in older adults with MCI.

Objective: To determine the relationship between musical and cognitive abilities in older adults with MCI.

Methods: We enrolled 60 participants from the University of Pennsylvania Alzheimer's Disease Core Center (ADCC) and administered the Goldsmiths General Musical Sophistication Subscale (GMSS) to gauge their musical abilities. We examined correlations between the GMSS and neuropsychological measures of verbal learning and memory, processing speed, executive function, verbal fluency, verbal naming and visuoconstructive abilities as well as estimated baseline intelligence. Using linear regression, we examined how well GMSS predicts performance on each of the neuropsychological tests.

Results: We found participants' GMSS scores to be lower when compared to the published norms for the GMSS. There was a modest negative correlation between general musical sophistication and the verbal naming test. The Boston Naming Test (BNT) was the only neuropsychological test associated with the GMSS ($r = -0.31$, 95% CI: -0.53 - 0.07; $p<0.05$; Table 3). GMSS did not correlate with age, intelligence, years of education, depressive symptoms or cognitive function. Results of the linear regression analyses indicated that GMSS explained 18% of the variance in verbal episodic memory recognition scores (adjusted $R^2=0.18$, $F(7,44)$, $p=0.03$) scores. GMSS did not predict performance on any of the remaining neuropsychological tests.

Conclusion: While our study findings provide further support for the relationship between musical and cognitive abilities in older adults with MCI, the nature of this relationship warrants further research. Future studies should include larger and more diverse samples followed longitudinally to better establish the link between musical and cognitive abilities.

Introduction

Alzheimer's disease and related disorders (ADRD) are a growing global concern with 115.4 million older adults projected to be living with dementia by 2050 (Prince, Guerchet, & Prina, 2013). The worldwide cost of dementia is expected to exceed $1 trillion by 2018 (Wimo et al., 2017). Persons with mild cognitive impairment (MCI) are three to eight times more likely to convert to Alzheimer's disease (AD) compared to persons without cognitive impairment (Bennett et al., 2002; Boyle, Wilson, Aggarwal, Tang, & Bennett, 2006; Fisk, Merry, & Rockwood, 2003; Larrieu et al., 2002). One widely used definition of MCI includes patients who present with subjective and objective deficits in memory, executive function, attention, language, and/or visuospatial skills and retain functional independence in daily activities (Petersen, 2004; Petersen et al., 2014). Despite the fact that persons with MCI and AD experience deficits in cognition, anecdotal (Cuddy & Duffin, 2005; Cuddy et al., 2012) and emerging neuroscientific evidence (Jacobsen et al., 2015) suggests the sparing of musical abilities in AD.

In a series of small exploratory studies, individuals with AD, demonstrated preserved musical memory (Cuddy & Duffin, 2005; Fornazzari et al., 2006; Johnson et al., 2011), ability to play a musical instrument (Beatty, Brumback, & Vonsattel, 1997), learn new songs (Cowles et al., 2003), and recognize emotions derived from music (Drapeau, Gosselin, Gagnon, Peretz, & Lorrain, 2009; Gagnon, Peretz, & Fulop, 2009). In addition, previous studies demonstrated that persons with AD retain the ability to discriminate between melodies (Hsieh, Hornberger, Piguet, & Hodges, 2011) and pitches

(Johnson et al., 2011). Similarly, select spared musical abilities also exist in other types of dementia, such as Frontotemporal dementia (Cho et al., 2015; Johnson et al., 2011).

Only a handful of studies have examined musical abilities in MCI. Kerer et al. (2014) found no differences in assigning emotional expressions (happy, sad, or unsure) to musical excerpts between older adults with MCI, early AD, and normal cognition. In the same study, compared to healthy controls, participants with MCI and early AD showed significantly lower performances on the tests of verbal music memory (Kerer et al., 2013a). In contrast, compared to healthy controls, participants with MCI and early AD did better on the tests of musical discrimination (Kerer et al., 2013b).

There is growing evidence that music training is associated with non-music cognitive domains in older adults. In a large cross-sectional study, playing a musical instrument or singing in older adults was associated with improved attention, episodic memory and executive function (Mansens, Deeg, & Comijs, 2017). When Seinfeld, Figueroa, Ortiz-Gil, and Sanchez-Vives (2013) explored the effects of a 4-month piano training regimen on older adults, they found that older adults who received piano lessons had higher scores on the measures of executive function, inhibitory control and divided attention compared to a control group. Consequently, the relationship between musical and cognitive abilities is a growing area of interest. The diverse findings in this area indicate the need to further investigate musical abilities in persons with MCI and how these abilities are related to cognition.

Almost all of the questionnaires related to musical abilities in the Western world quantify the degree of musical abilities based on the years of formal music training (Levitin, 2012). Individuals without formal music training, however, may become musically sophisticated later in life by engaging in music-related behaviors and activities (Hallam, 2010). These activities may include attending concerts and informal music gatherings, singing, and appraising different genres of music. An alternative way to gauge musical engagement in non-musicians is to categorize leisure activities under cognitive, physical or social domains (Blasko et al., 2014). The issue with this approach is that music may fall under one or all three categories, making it difficult to reach conclusions about the degree of musical abilities and skills. Taken together, neither of these approaches may be appropriate to assess musical abilities in non-musicians. To address this gap Müllensiefen, Gingras, Musil, and Stewart (2014) introduced the concept of musical sophistication defined as skills and achievements on a range of largely independent dimensions such as musical perception and music-making, amount of practice, emotional and functional usage of music, and creativity.

The degree of self-identified musical abilities and skills may be associated with cognitive abilities impacted in older adults with MCI. The purpose of this study was to examine the association between musical abilities and verbal episodic memory, processing speed, executive function, verbal fluency, verbal naming, and visuoconstructive abilities in persons with MCI. We hypothesized that musical abilities would correlate with tests of verbal episodic memory, processing speed, executive function, verbal naming and visuoconstructive abilities in older adults with MCI.

Methods

Sample

For this cross-sectional study our team recruited sixty participants with a recent diagnosis of MCI (< 12 months) and those participants who remained with a diagnosis of

MCI in a recent (< 12 months) follow-up appointment. Participants were included if they spoke and understood English. We excluded participants from our study if they were younger than 55 years old, had a primary psychiatric disorder, a systemic illness that could interfere with cognitive functioning, history of stroke and/or hydrocephalus, or were unable to provide informed consent.

Setting

We enrolled study participants from the University of Pennsylvania Alzheimer's Disease Core Center (ADCC) research and clinical cohort [P30-AG010124; PI: Trojanowski, MD, PhD]. As part of the ongoing clinical assessment, these patients completed yearly battery of cognitive measures and physical assessments (Beekly et al., 2007; Morris et al., 2006; Xie et al., 2011). The ADCC clinical team assigned an MCI diagnosis through consensus using previously published guidelines and a standardized clinical protocol (Petersen, 2004). All participants completed a neuropsychological battery aimed to assess many of the cognitive abilities most impacted by MCI. Our study received Institutional Review Board approval from the University of Pennsylvania. All participants provided written informed consent approved by the University of Pennsylvania Institutional Review Board. In the informed consent document we requested the permission to extract participants' data from the ADCC records (see Measurements section). We met with the study participants at the ADCC or a location of mutual convenience.

Measurements

To reduce respondent burden, multiple measures were extracted from the ADCC database on our study participants at the time of enrollment in our study. The patients at the ADCC had neuropsychological data stored in the Integrative Neurodegenerative Database (Beekly et al., 2007; Morris et al., 2006; Xie et al., 2011). For all participants we extracted their demographic and neuropsychological test data collected closest to their date of enrollment in our study. For our prospective study, we asked the participants to complete two questionnaires: one gauging their musical abilities and one used to screen for depression.

Neuropsychological Tests. We extracted scores for the following neuropsychological tests: verbal episodic memory, processing speed, executive function, verbal fluency, verbal naming and visuoconstructive abilities. The verbal episodic memory test was a 10-item Word List that included immediate recall (total of 3 learning trials), delayed recall and recognition testing (Morris et al., 1989). Higher scores corresponded to better performance. We used the results from the Trail Making Tests A and B (TMT A and B) (Reitan & Wolfson, 1993) to gauge processing speed and executive function, respectively. In both executive function measures, higher scores indicated poorer performance. The verbal fluency measure was a semantic fluency task (total number of animals produced in 60 seconds) (Morris et al., 1989). Greater number of animals named indicated better performance. We examined scores for verbal naming using the 30-item Boston Naming Test (BNT) (Goodglass & Kaplan, 1983; Kaplan, 2001), in which higher scores corresponded to better verbal naming ability. Lastly, we used the results from the Clock Drawing Test (CDT) (Shulman, Pushkar Gold, Cohen, & Zucchero, 1993) to measure visuoconstructive abilities. Higher numbers indicated poorer performance.

Demographic characteristics. We collected the following demographic information about the study participants from the ADCC database: age, gender, Mini-Mental State

Examination (MMSE) scores, years of education, and a number of chronic illnesses. To further characterize the sample, we extracted the following information from the database: marital status, race, ethnicity, living status and caregiving relationship. In addition, we used the Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001) as an estimate of educational attainment and premorbid intelligence. Each patient completed the WTAR at his/her initial ADCC visit.

Musical Abilities. The General Musical Sophistication Subscale (GMSS) was derived from the Goldsmiths Musical Sophistication Index (Gold-MSI). The Gold-MSI is a self-report questionnaire that measures musical abilities in a comprehensive way in the general (i.e. non-professional musician) population (Müllensiefen, Gingras, Musil, et al., 2014). The Gold-MSI is sensitive to differences among "non-musicians" in five distinct categories: (1) active musical engagement (e.g. how much personal (time) and financial resources spent on music), (2) self-reported perceptual abilities (e.g. accuracy of musical listening skills), (3) musical training (e.g. amount of formal musical training received), (4) self-reported singing abilities (e.g. accuracy of one's own singing), and (5) sophisticated emotional engagement with music (e.g. ability to talk about emotions that music expresses) (Müllensiefen, Gingras, Musil, et al., 2014).

All Gold-MSI items, except for one open-ended question, are scored on the same 7-point Likert scale and receive equal weights for scoring, which is known to make the scale more robust. In the open-ended question, we asked the participants to name any musical instruments (including voice) that they currently played. The Gold-MSI self-report questionnaire items demonstrate excellent convergent (Werner, Swope, & Heide, 2006) and discriminant validity with various musical aptitude scales (Müllensiefen, Avron, & Skiada, 2014; Müllensiefen, Gingras, Musil, et al., 2014). Imbedded within the Gold-MSI is General Musical Sophistication Subscale (GMSS), which includes 18 items with excellent internal consistency (Cronbach's alpha, 0.926). For our analysis we used the GMSS since these items load highest on the general factor of what it means to be musical and have roughly the same weights (Müllensiefen, Gingras, Musil, et al., 2014). Higher scores on the GMSS correspond to higher self-reported musical abilities.

Depression. The Geriatric Depression Scale (GDS-15) is a brief measure of depressive symptoms in older adults found to be an effective screening tool for depression in older adults (Burke, Roccaforte, & Wengel, 1991; Yesavage et al., 1982). The GDS-15 includes 15-forced answer, yes or no questions. A score of ≥ 5 is considered a positive screen for the presence of depressive symptoms. Depression can influence cognitive functioning and mimic some of the presentation of MCI. Therefore, it was essential to control for depression in the analysis. Depression may also decrease engagement in all types of activities, including music-related ones. In previous studies, depression was included as a covariate in the analysis of leisure activity in cognitively intact and impaired older adults (Hughes, Chang, Vander Bilt, & Ganguli, 2010; Sörman, Sundström, Rönnlund, Adolfsson, & Nilsson, 2014).

Analysis

To conservatively estimate the power required to detect a moderate Pearson correlation of 0.35 between GMSS and cognitive abilities measures at the 0.05 significance level (power=0.80), we used a correlation observed in related literature between Gold-MSI and Wechsler Abbreviated Scale of Intelligence (WASI) (Müllensiefen, Avron, et al., 2014; Müllensiefen, Gingras, Musil, et al., 2014). A power analysis revealed that 60 participants are required to detect a relationship between musical and the cognitive abilities measures.

We described the demographics of the overall and continuous measures of neuropsychological testing and musical abilities using means and standard deviations. We calculated Pearson correlation coefficients between measures of verbal episodic memory (Word list learning, memory and recognition), processing speed (TMT A), executive function (TMT B), verbal naming (BNT), visuoconstructive abilities (CDT), and the measure of musical abilities (GMSS). To examine the relationship of the GMSS as a predictor and measures of cognitive abilities as the outcome, we completed linear regression analyses for each cognitive ability separately while adjusting for covariates (age, gender, years of education, number of chronic conditions, premorbid intelligence (WTAR), and depressive symptoms). The data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows (Copyright © 2002-2012 SAS Institute Inc. Cary, NC, USA).

Results

The sample consisted of 60 participants with a diagnosis of MCI. The demographic characteristics of the sample are summarized in Table 2.1. The mean age was 76.3 (standard deviation, SD=6.8). Sixty percent of the sample was male. The participants were highly educated (mean years 16.1), the majority were married (75%), predominantly White and non-Latino (82%), living with a spouse/partner (72%), and cared for by a spouse or a partner (74%). The mean MMSE score among the participants was 25.8 consistent with the Petersen criteria for MCI (Petersen, 2004). On average, participants had 2.9 (SD=2.1) chronic conditions. Fifty-two percent of the sample was diagnosed with amnestic multiple domain MCI (Table 2.2) consistent with previous prevalence based studies (Petersen et al., 2010; Ravaglia et al., 2008). The mean GMSS score was 62.8 (SD=18.2; Table 2.2).

Table 2.1 Demographics of the Sample

Characteristics	**Mean (SD), Range**
Age (year)	76.3 (6.8), 57-89
Education (year)	16.1 (3.0), 9-22
Number of chronic conditions	2.9 (2.06), 0-7
	N (%)
MCI subtypes	
Amnestic Plus Other	31 (52)
Amnestic Single Domain	16 (27)
Non-Amnestic Single Domain	8 (13)
Non-Amnestic Multiple Domains	5 (8)
Gender	
Male	36 (60)
Female	24 (40)
Marital Status	
Married	45 (75)
Divorced	7 (12)
Widowed	4 (7)
Never married	3 (5)
Other	1 (2)
Race/Ethnicity	
White/Non-Latino	49 (82)
Black/Non-Latino	6 (10)
Multi-racial/Non-Latino	2 (3)
Unknown/Unknown	1 (2)
Unknown/Non-Latino	1 (2)
Other/Unknown	1 (2)
Living Status	
Spouse/Partner	43 (72)
Independent/Alone	12 (20)
Unknown	3 (5)
Other	1 (2)
Other family	1 (2)
Caregiver Relationship	
Spouse/Partner	37 (74)
Unknown	10 (17)
Child	8 (16)

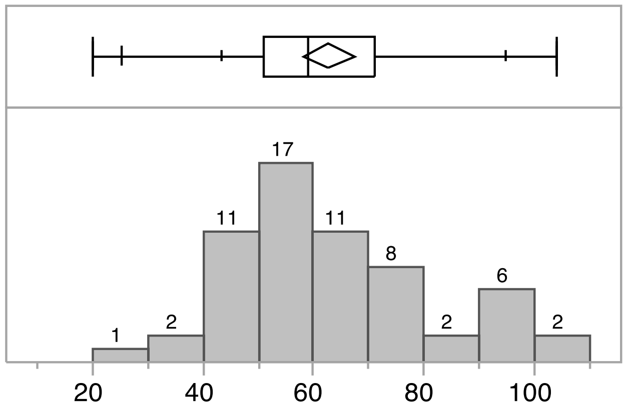
Sibling	3 (6)
Friend/Neighbor	1 (2)
Other	1 (2)

Table 2.2 Neuropsychological, Depression, and General Musical Sophistication Subscale Test Results (N=60)

Name, range	**Mean (SD), Range**
Mini Mental State Examination	25.8 (3.1), 0-30
Animal list generation,	14.0 (5.1), 0-77
Trail making A	43.1 (19.0), 0-150
Trail making B	122.1 (73.2), 0-300
Word list memory	15.4 (4.0), 0-30
Word list recall	4.3 (2.2), 0-10
Word list recognition	18.0 (3.2), 0-20
Clock drawing test	2.4 (1.8), 0-15
Boston naming total	24.1 (5.3), 0-30
Wechsler test of adult reading	39.4 (9.6), 0-50
Geriatric Depression Scale	2.3 (2.1), 0-15
General Musical Sophistication Subscale	62.8 (18.2), 18-126

Figure 2.1 demonstrates the GMSS' distribution and score count. The participants scored in the nineteenth percentile on the GMSS compared to the non-age based published norms (Müllensiefen, Gingras, Stewart, & Musil, 2014). As shown, the scores for the GMSS are normally distributed clustered around the mean with a possible bimodal distribution at the upper percentiles. The frequency of responses for each statement on the Gold-MSI is presented in Appendix A. The majority of participants reported spending a lot of their free time doing music related activities, but stated that they did not engage in regular, daily practice of a musical instrument. Sixty-three percent of the sample did not play a musical instrument (Appendix A). The GMSS Cronbach's alpha in our study was 0.934.

Figure 2.1 Distribution of Scores on the General Musical Sophistication Subscale: Response Frequency and Quantiles.



There was a weak negative correlation between GMSS and the verbal naming test (BNT). The BNT was the only neuropsychological test associated with GMSS (r= -0.31, 95% CI: -0.53 -0.07; p<0.05; Table 2.3). Higher performance on the GMSS was associated with worse performance on the BNT. The GMSS did not correlate with age, WTAR, years of education, depressive symptoms or MMSE (not shown).

Table 2.3 Pearson Correlation Coefficients between General Musical Sophistication Subscale and Neuropsychological tests

Measure	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. GMSS	1.00								
2. Animals list generation	0.25	1.00							
3. Trail making test A	-0.06	**-0.39****	1.00						
4. Trail making test B	-0.21	**-0.48****	**0.36****	1.00					
5. Word list memory	0.25	**0.38****	-0.15	-0.21	1.00				
6. Word list recall	0.19	0.21	-0.25	-0.10	**0.55****	1.00			
7. Word list recognition	-0.01	**0.29***	-0.01	-0.25	**0.50****	**0.44****	1.00		
8. Clock drawing test	-0.20	-0.19	**0.27***	**0.39****	-0.14	-0.01	0.04	1.00	
9. Boston naming test	**-0.31***	**-0.28***	0.08	-0.03	-0.05	-0.22	- 0.01	0.11	1.00

Notes: GMSS: General Musical Sophistication Subscale; * p≤0.05; ** p≤0.01

Results of the multivariate regression analyses for each neuropsychological test indicated that GMSS explained 18% of the variance in Word List Memory Recognition scores (adjusted R^2=0.18, F (7,44), p=0.03) scores. GMSS did not predict performance on any of the remaining neuropsychological tests (p=n.s.; Table 2.4), including the BNT.

Table 2.4 General Musical Sophistication Subscale as a Predictor for Cognitive Abilities

Neuropsychological test	**Adjusted R^2**	**F value**	**P value**
1. Animal list generation	0.08	1.63	0.15
2. Trail making test A	0.08	1.63	0.15
3. Trail making test B	0.09	1.63	0.16
4. Word list memory	0.11	1.87	0.10
5. Word list recall	0.05	1.37	0.24
6. Word list recognition	0.18	2.55	**0.03**
7. Clock drawing test	0.06	1.44	0.22
8. Boston naming test	0.10	1.84	0.10

Notes: All models adjusted for age, sex, education, comorbidities, depressive symptoms and premorbid intelligence.

Discussion

To our knowledge, this was the first study to assess the relationship of musical and cognitive abilities in older adults with MCI. In summary, in this prospective, cross-sectional study we examined musical abilities assessed by the general musical sophistication subscale (GMSS) in older adults with MCI. We found a negative association between self-reported musical abilities and verbal naming in a sample of older adults with MCI. Older adults with higher musical abilities had lower scores on the measure of verbal naming. The participants, on average, scored lower on the general musical sophistication subscale compared to the published norms (Müllensiefen, Gingras, Stewart, et al., 2014). When we examined how well musical abilities predicted individual cognitive abilities, we found that musical abilities predicted verbal memory recognition performance taking into account age, years of education, premorbid intelligence, comorbidities, gender, and depressive symptoms. The results suggest that there is a relationship between musical and cognitive abilities, specifically verbal naming and verbal memory recognition (word list recognition), in a sample of older adults with MCI.

Given the breadth of musical abilities we hypothesized that musical abilities would be associated with several cognitive abilities in older adults with MCI, such as verbal episodic memory, processing speed, executive function, verbal naming, and visuoconstructive abilities. Interestingly, we found a single negative weak correlation between musical abilities and verbal naming, partially supporting our initial hypothesis. Initially, we predicted a positive correlation between musical abilities and verbal naming. Although we did not find a significant association between musical abilities and verbal memory recognition, we found musical abilities explained 18% of variance in the verbal episodic memory recognition scores. Regression analyses did not support the correlation found between musical abilities and verbal naming initially found looking at Pearson's correlations. These disparate findings may stem from the complexity of the relationship between musical abilities, verbal naming and covariates controlled for in the regression analyses. Additionally, individuals with MCI have difficulty recalling recent events possibly influencing their ability to accurately respond to items of musical abilities. Additionally, the index of musical abilities (GMSS) we selected for this study covered a broader spectrum of subjective musical abilities beyond objective measures of musical training which may have contributed to our inconsistent findings.

Previous research has suggested that musical training is associated with improved verbal memory in adults (Chan, Ho, & Cheung, 1998) and older adults (Gooding, Abner, Jicha, Kryscio, & Schmitt, 2014). Verbal naming (i.e. ability to recall the name of objects in our environment) is one of the most fundamental language abilities in humans (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). Older adults with MCI who exhibit deficits in verbal naming may compensate for their deficits by engaging in activities that are less reliant on language and memory, such as singing, playing an instrument, and attending live music events. These individuals may find enjoyment by engaging in activities that are less reliant on semantic memory. Our findings are contrary to the study in which Hanna-Pladdy and Gajewski (2012) compared healthy older adults with less than ten years of music training to older adults with greater than ten years of musical training controlling for levels of general lifestyle activities. The researchers found that older adults with more than ten years of musical training scored higher on the test of verbal naming compared to older adults with less than ten years of musical training (Hanna-Pladdy & Gajewski, 2012). These disparate findings may be explained by only slightly more than a third of our participants reported playing a musical instrument, but they denied having formal musical training.

Activities associated with musical abilities tend to peak at a young age (Müllensiefen, Gingras, Musil, et al., 2014). Based on findings from the Müllensiefen, Gingras, Musil, et al. (2014) study we expected older adults with MCI to score lower on the GMSS compared to published norms. For instance, compared to younger adults, healthy older adults scored lower on the subscale of general musical sophistication, except for those older adults whose occupation required continuous involvement with music (Müllensiefen, Gingras, Musil, et al., 2014). These findings partially explain that in our study, on average, older adults with MCI scored in the nineteenth percentile for the GMSS (Müllensiefen, Gingras, Stewart, et al., 2014). Alternatively, older adults with

MCI may choose not to partake in music-based activities due to their cognitive deficits. Previous research has demonstrated that participation in leisure activities declines with age (Agahi, Ahacic, & Parker, 2006). Furthermore, in a US nationally representative survey of older adults, individuals who screened positive for MCI had 8% less social engagement in the community compared to cognitively normal individuals (Kotwal, Kim, Waite, & Dale, 2016). Individuals with MCI may withdraw from social activities due to feeling anxious about their performance, both in the areas of language and memory. Taken together, the decline in musical abilities in healthy adults, along with the decline in persons with MCI participating in musical activities due to their perceived deficits may help explain our finding of lessened musical abilities in older adults with MCI.

One of the central questions then becomes – how do persons with MCI acquire musical skills? Nearly 40% of our sample reported playing a musical instrument at some point in their lives. Several definitions exist for musical abilities, including music aptitude, musicality, music skills, and musical talents among others. From a biological standpoint musicality can be defined as “a natural, spontaneously developing set of traits based on and constrained by our cognitive and biological system” (Honing, ten Cate, Peretz, & Trehub, 2015, p. 2), Whereas music is a social and cultural construct rooted in musicality (Honing et al., 2015). Individuals who are predisposed to musical abilities from birth might gravitate towards music throughout their lives. In our sample, persons with MCI seemed to acquire their musical abilities through indirect contact with music via listening, judging, singing, and attending music events. The findings of this study contribute to our understanding of how persons with MCI may engage in music outside of formal training. Whether older adults with MCI may benefit from music even with little prior exposure to music remains to be determined.

There are limitations to our study. First, cross-sectional data do not support a causal relationship between musical and cognitive abilities making it impossible to conclude that greater musical abilities result in worse performance on the verbal naming domain. Second, we did not ask participants in this study about their involvement in other leisure activities. Participation in leisure activities may be a confounding factor that may influence participation in music related activities. For instance, individuals with MCI may isolate themselves from social activities, including music. Alternatively, in doing so persons with MCI may engage with music at home. To our knowledge this study was the first one to use the GMSS in older adults with MCI. The index of musical abilities (GMSS) might not have been reliable in persons with MCI. Several statements in the GMSS rely on participants' memory. Older adults with MCI may have had intact sense of their musical abilities at an earlier time in their lives, but possibly, due to their memory deficits, lacked the insight into their present musical abilities. In addition, a combination of positive and double negative questions on the GMSS may have been difficult for persons with MCI and may have contributed to inaccurate responses. Lastly, the sample was not a random sample from a community population and consisted mainly of White, well-educated older adults participating in a longitudinal study.

Future studies need to consider larger, more diverse samples, followed longitudinally to better establish the validity and generalizability of these findings. Adding an objective measure of musical ability can provide a more accurate representation of musical abilities in older adults with MCI, as participants may have overestimated or underestimated their musical abilities. Additionally, obtaining a collateral source report (from someone who knows the individual well) may provide a more complete understanding of the nature of musical abilities in persons with MCI. Future studies should also control for the level of leisure activity participation and use an established index of comorbid illnesses. Finally, given the interest of protective and compensatory strategies that delay the MCI-AD conversion, future investigations should compare conversion rates in older adults with high vs low degree of musical abilities.

Conclusions

In this cross-sectional study, we examined the associations between musical abilities, measured by the general musical sophistication subscale, and cognitive abilities in a sample of sixty older adults with MCI. Resulting in unexpected finding, higher musical abilities were associated with lower verbal naming scores and musical abilities predicted performance on the verbal episodic memory recognition task. Our study findings provided further support of the relationship between musical and cognitive abilities in older adults with MCI. The findings, however, were not consistent and not necessarily in the expected direction. The index of musical abilities relies heavily on self-assessment of current musical abilities, which may be hindered by memory deficits in persons with MCI. Larger longitudinal studies with more diverse samples including subjective, objective and collateral source measures, are needed to better establish the link between musical and cognitive abilities.

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CHAPTER 3: THE ROLE OF MUSICAL ABILITIES IN MODERATING THE RELATIONSHIP BETWEEN HIPPOCAMPAL VOLUME AND COGNITIVE ABILITIES IN OLDER ADULTS WITH MILD COGNTIIVE IMPAIRMENT

Darina V. Petrovsky,[1] MN, RN; Julene K. Johnson,[2] PhD, Nancy Tkacs, PhD,[4] Dawn Mechanic-Hamilton,[3,4] PhD, Roy H. Hamilton,[4] MD, MS, Pamela Z. Cacchione,[1] PhD, CRNP, BC, FAAN

[1] University of Pennsylvania, School of Nursing, Philadelphia, PA

[2] University of California at San Francisco, Institute for Health & Aging, School of Nursing, San Francisco, CA

[3] Penn Memory Center, University of Pennsylvania, Philadelphia, PA

[4] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

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Abstract

Background and objectives: Playing a musical instrument may have protective properties against neurodegenerative changes in persons with mild cognitive impairment (MCI). Yet, enhanced musical abilities from informal musical training have not been studied to determine if they protect against cognitive deficits. The purpose of this study was to examine whether musical abilities moderated the relationship between the underlying brain pathology and cognitive abilities in persons with MCI.

Research Design and Methods: In this cross-sectional study, 38 persons with MCI who participated in a larger study, (N=60) from the Alzheimer's Disease Core Center exploring the association between cognitive and musical abilities, were included in this analysis if they had an MRI. The degree of the underlying brain pathology was quantified from the MRIs using a neuroanatomical biomarker associated with AD pathology – total hippocampal volume (HV). Cognitive abilities from the ADCC database of interest included: verbal episodic memory, processing speed, executive function, verbal fluency, verbal naming and visuoconstructive abilities. Additional prospective data collection included a general musical sophistication subscale (GMSS) gauging their musical abilities and the Geriatric Depression Scale (GDS-15). We used Pearson's correlations and multivariable linear regression to examine the relation of HV with musical and cognitive abilities controlling for select sociodemographic characteristics, intelligence and depression.

Results: We found a negative correlation between GMSS and executive function (Trail Making Test B, TMT B; r= -0.41; 95% CI -0.66, -0.09; p=0.02). Higher musical abilities scores correlated with faster performance on the TMT B. We also found a statistically significant interaction between HV and executive function (parameter estimate -0.00008, SE: 0.00003, p=0.036, R^2=0.328).

Discussions and Implications: Musical ability appears to moderate the relationship between HV and executive function in older adults with MCI. These data provide preliminary evidence for a possible compensatory effect of musical abilities against AD pathology driven changes in executive function of older adults with MCI.

Translational significance: The results suggest that enhanced musical abilities may be protective against cognitive deficits in older adults with MCI.

Keywords: *musical sophistication, musical training, musical behaviors, music, neuropsychological data, executive function*

Background and Objectives

On January 4, 2011, President Obama signed into law a National Alzheimer's Project Act to address the many challenges faced by older adults with Alzheimer's disease (AD) and their families (Civic Impulse, 2014). This public health initiative came as a response to a worldwide epidemic of AD and the devastating health consequences affecting approximately 5.5 million Americans (Alzheimer's Association, 2017). The global number of people with AD and related dementias is projected to double every 20 years reaching 115.4 million by 2050 (Prince et al., 2013). Mild Cognitive Impairment (MCI) is an intermediate state between normal cognition and Alzheimer's disease and related dementias (Albert et al., 2011; Petersen, 2004). Older adults with MCI are at a higher risk of progressing to AD (5-10% per year) compared to the general population (1-2% per year) (Petersen, 2011). Individuals with MCI may revert back to normal cognition, advance to dementia or remain stable. Several factors have been identified as protective against progression to AD in persons diagnosed with MCI. These include educational attainment (Scarmeas, Albert, Manly, & Stern, 2006), leisure activities (Crowe, Andel, Pedersen, Johansson, & Gatz, 2003; Scarmeas, Levy, Tang, Manly, & Stern, 2001) and cognitively stimulating activities (Fratiglioni, Paillard-Borg, & Winblad, 2004; Wilson et al., 2002).

Playing a musical instrument may also have protective properties against dementia (Verghese et al., 2003) and MCI (Verghese et al., 2006) due to evidence that music may engage several cognitive abilities including: executive function, working memory, attention, and judgment (Paraskevopoulos & Herholz, 2013; Wan & Schlaug, 2010). The evidence also suggests that playing an instrument is associated with a later onset of cognitive decline in cognitively normal older adults (Verghese et al., 2003). Additionally, formal music training is related to improved verbal naming in healthy older adults when comparing older musicians with more than ten years of musical training to older non-musicians with less than ten years of musical training (Hanna-Pladdy & Gajewski, 2012). Given these findings, playing a musical instrument may be beneficial in maintaining cognition in persons with MCI. Enhanced musical abilities as a result of music engagement outside of formal musical training on the other hand have not been studied to determine if they contribute to improved cognition in older adults diagnosed with MCI who might not have access to formal musical training.

There are many definitions of musical abilities. In our study we operationalized the definition of musical abilities broadly as music related behaviors and skills (Müllensiefen, Gingras, Musil, & Stewart, 2014). Different musical behaviors and the degree of sophistication in these behaviors vary widely in the population. Musical behaviors include but are not limited to listening to music, attending live music events, singing, and playing a musical instrument (Müllensiefen et al., 2014). With the multi-faceted nature of music processing and production in the brain (Koelsch, 2011; Zatorre, Chen, & Penhune, 2007), individuals with MCI who are highly engaged in everyday music behaviors may benefit from music and exhibit improved cognitive performance. In addition, engagement in stimulating activities, such as music, may increase the cognitive reserve of these individuals (Stern, 2002) protecting them against the neuropathological changes in the brain and conversion to dementia of the Alzheimer's type. It is unlikely that musical abilities directly alter the accumulation of the underlying brain pathology in AD. An alternative hypothesis is that musical abilities may attenuate the relationship between the underlying neuropathological changes in the brain and cognitive abilities. Therefore, the relationship between the underlying pathology and cognitive abilities may be weaker in persons with greater musical abilities compared to individuals with lesser musical abilities.

Biomarkers are often used to aid in the diagnosis and prognosis of adults with MCI (Beckett et al., 2010). Commonly used biomarkers include cerebrospinal fluid volume and indicators of brain atrophy identified on magnetic resonance imaging (MRI) (Caroli et al., 2015). Abnormal atrophy in the hippocampus, located in the medial temporal lobe, predicts future MCI to AD conversion (Clerx et al., 2013; Fleisher et al., 2008; Jack et al., 1999; Risacher et al., 2009). In addition, hippocampal atrophy is associated with faster cognitive decline (Beckett et al., 2010; Yavuz et al., 2007) and differentiating between normal cognition, MCI and AD (Colliot et al., 2008; de Leon et al., 2006; Liu et al., 2011; Pennanen et al., 2004; Schroder & Pantel, 2016). Furthermore, hippocampal volume (HV) is associated with cognitive function (measured by the Mini Mental State Examination, MMSE) (Morra et al., 2009; Peng et al., 2015) and severity of cognitive impairment in adults with MCI (Peng et al., 2015).

Little is known about the direct influence of enhanced musical abilities on the relationship between the neuropathological changes in the brain and cognition. In this study, we sought to examine whether musical abilities moderate the relationship between HV and cognitive abilities in older adults with MCI. We tested the a priori hypothesis that musical abilities weakened the relationship between HV and cognitive abilities in older adults with MCI.

Research Design and Methods

In this cross-sectional study, we collected both secondary and prospective data from persons with MCI from the Alzheimer's Disease Core Center (ADCC) on the east coast of the United States. The ADCC is one of 29 national Alzheimer's Disease Centers in the U.S. funded by the National Institute on Aging with the goal to create a network of experts, researchers and educators passionate about improving the lives of those with AD. As part of the ongoing study [P30-AG010124; PI: Trojanowski, MD, PhD], center clinicians evaluate participants with a set of cognitive measures, imaging, physical and neurologic examinations (Beekly et al., 2007; Morris et al., 2006) in order to arrive at a diagnosis. Each ADCC patient's diagnosis was reached via consensus using previously established diagnostic criteria (Petersen, 2004). To test the hypothesis whether musical abilities moderated the relationship between HV and cognitive abilities in older adults with MCI we combined prospective data with the neuropsychological and MRI data available from the ADCC cohort. This study received approval from the University of Pennsylvania Institutional Review Board.

Participants

This paper describes the results from a subsample of 38 individuals from a larger study (N=60) for whom MRI data were available. Participants were eligible for our study if they were diagnosed with MCI and had an MRI within a 12-month window prior to enrollment in our study or were reevaluated within the 12 months and confirmed to have a diagnosis of MCI. Patients were ineligible to participate in our study if they were younger than 55 years old, had a primary psychiatric disorder, a systemic illness that could interfere with cognitive functioning, history of stroke and/or hydrocephalus or were unable to complete informed consent.

Data collection

Written, informed consent was obtained from each participant prior to data collection. Demographic information on each participant (see Table 1) were extracted from the ADCC database along with detailed neuropsychiatric tests described below. To reduce subject burden, participants were only asked to complete two scales: a general musical sophistication subscale (GMSS) (Müllensiefen et al., 2014) and the Geriatric Depression Scale (short form, GDS-15) (Burke, Roccaforte, & Wengel, 1991; Yesavage et al., 1982) during an in-person meeting at the ADCC or a location of mutual convenience.

Measurements

Sociodemographic characteristics. Sociodemographic characteristics were extracted from the ADCC database for: age, gender, years of education, number of chronic conditions, race, ethnicity, marital, and living status (e.g., alone, with spouse, etc.). .). In addition, the Wechsler Test of Adult Reading (WTAR), completed on the participants' first visit to the ADCC, was used as an estimate of educational attainment and premorbid intelligence (Holdnack, 2001). To further describe the sample information regarding the subtypes of MCI, which included amnestic single domain, amnestic multiple domain, non-amnestic single domain, and non-amnestic multiple domain, was also extracted.

Musical Abilities. To assess musical abilities we used the Goldsmiths Musical Sophistication Index (Gold-MSI) (Müllensiefen et al., 2014). This self-report index contained 38 items and assessed a variety of music-related abilities, achievements and behaviors. Musical sophistication refers to "musical skills, expertise, achievements, and related behaviors across a range of facets" (Müllensiefen et al., 2014, p. 2). This index was designed to assess musical sophistication in non-professional musicians in five categories: active musical engagement, perceptual abilities, musical training, singing abilities, and emotional engagement with music (Müllensiefen et al., 2014). Eighteen out of the 38 items assess general music sophistication (General Musical Sophistication Subscale, GMSS), and has demonstrated high internal consistency reliability (Cronbach's alpha, 0.926) (Müllensiefen et al., 2014). Each item is scored on a 7-point Likert scale (Completely Disagree to Completely Agree).

Depression. We used the Geriatric Depression Scale (GDS-15) (Burke et al., 1991; Yesavage et al., 1982) to screen participants for depressive symptoms. Depression may mimic MCI symptoms and contribute to decreased participation in leisure activities, including music. Depression may also weaken the emotional response to music (Naranjo et al., 2011). The 15-item questionnaire consisted of forced Yes or No questions. A score greater than five indicates the presence of depressive symptoms requiring further evaluation. The GDS-15 has shown to be a reliable and valid tool to assess to screen for depression in persons with mild and moderate cognitive impairment (Lach, Chang, & Edwards, 2010).

MRI and Hippocampal volume. The ADCC collects the 3T MRI data during patients' yearly clinic visits on a Siemens Prisma machine with a 64 channel head-coil. We extracted hippocampal volumes (HV) from the MRI. The structural MRI sequences included a high resolution in-plane T2 scan (0.4x0.4x1.2 mm^3) perpendicular to the long axis of the hippocampus compatible with a fully automated segmentation protocol for measuring medial temporal lobe subregions (Yushkevich et al., 2006; Yushkevich et al., 2015). In our analyses we examined total hippocampal volume (calculated as a sum of both left and right halves). A research assistant from the ADCC who ran the segmentation protocol to determine the HV was blind to the purpose and the outcomes of this study.

Cognitive abilities. We used the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) to estimate the overall cognitive function. We extracted the scores for each cognitive ability from the ADCC database. Verbal episodic memory was assessed using a 10-item word list-learning task. The list was presented three times (in randomized order) to produce a verbal learning score. Delayed recall and recognition trials were also completed (Morris et al., 1989). Processing speed was assessed using Trail Making Test A, where patients were asked to connect numbers with a line in ascending order (Reitan & Wolfson, 1993). Trail Making Test B evaluated set-switching, one aspect of executive function. In TMT B, subjects drew a line to connect numbers and letters, alternating between sets in ascending order. The score for each part reflected the total time in seconds it took for participants to complete the task correctly. Higher score indicates poorer performance. Verbal fluency was evaluated with an animal fluency task in which subjects were asked to provide the names of as many animals as possible in one minute (Morris et al., 1989). The score indicated the number of animals provided during the one-minute trial (Morris et al., 1989). The Boston Naming Test assessed verbal naming (Goodglass & Kaplan, 1983; Kaplan, 2001). In this test, patients were asked to name 30 items. The maximum time allowed for each item is 20 seconds. The score corresponds to the number of items named correctly. To evaluate visuoconstructive abilities, the neuropsychological assessment included the Clock Drawing Test, in which patients were asked to draw a circle, fill in the circle with the numbers of a clock and draw the hands of the clock at “10 after 11” (Shulman, Pushkar Gold, Cohen, & Zucchero, 1993). Higher score corresponded to poorer performance. For all cognitive abilities we converted the raw scores of each neuropsychological test to a Z score using Weintraub et al. (2009) norms. Doing so allows for standardization of the sample scores against the published norms and aids in the interpretation of the results. These published norms included the Boston Naming Test, animal fluency test, Trail Making Tests A and B. The clock drawing, word list learning, recall and recognition norms were based on the ADCC computed normative data using the same methods published in the Weintraub et al. (2009) manuscript.

Analysis

We first calculated descriptive statistics for demographics, which included means and standard deviations for continuous measures. Using the data from the larger sample, we used Chi-square tests to see if participants with MRI results significantly differed from those who did not. We included frequencies for categorical variables and calculated Pearson correlation coefficients between GMSS, HV, cognitive status (MMSE) and raw scores from eight neuropsychological measures. As a measure of overall cognition, we did not include the MMSE in the regression analyses, only as a descriptor. We constructed multiple multivariable linear regression models that used each cognitive score z score as the dependent variable. We ran linear regression analyses for each cognitive variable as the dependent variable for GMSS and HV separately. We then repeated the analysis with the interaction term. The independent variables included HV, GMSS and their interaction. The interaction term directly tested the hypothesis of whether musical abilities moderated the effect of HV on the level of cognitive ability (Holmbeck, 1997). The final models were adjusted for the following covariates: age, gender, years of education, intelligence (WTAR), number of chronic illnesses, and number of depressive symptoms in the above analyses. All analyses were generated using SAS software, Version 9.4 of the SAS System for Windows (Copyright © 2002-2012 SAS Institute Inc. Cary, NC, USA).

Results

Thirty-eight participants for whom MRI data were available did not differ from those participants who did not have the MRI data in age, years of education, GMSS scores or cognitive function (MMSE). The average age of the 38 participants described in this paper was 75.1 (SD: 6.6), and the majority of participants were highly educated (mean years: 15.9), male, married, living with and cared for by a spouse or a partner, and were predominantly White, non-Latino. Table 3.1 provides a summary of the demographic data.

Table 3.1 Sociodemographic Characteristics (N=38)

Variables	**Mean (SD), Range**
Age	75.1 (6.6), 57-85
Years of education	15.9 (2.9), 9-20
Number of chronic illnesses	2.9 (2.1), 0-7
	N (%)
Gender	
Male	23 (61)
Female	15 (39)
Marital Status	
Married	32 (84)
Divorced	2 (5.3)
Never married	2 (5.3)
Other	1 (2.6)
Widowed	1 (2.6)

Variables	Mean (SD), Range
Living status Spouse/Partner Independent/Alone Unknown Other family	 30 (78.9) 4 (10.5) 3 (7.9) 1 (2.9)
Race/Ethnicity Non-Latino, White Non-Latino, Black Non-Latino, Multi-racial	 36 (94.7) 1 (2.6) 1 (2.6)

The mean MMSE score was 26.1 (SD: 2.9). The most common MCI subtype was amnestic multiple domain (47.4%). Cognitive scores ranged from half a standard deviation below the mean to nearly two and a half standard units below the mean (Table 3.2).

Table 3.2 MRI Biomarkers, Neuropsychological Tests and General Musical Sophistication Subscale Characteristics of the Sample (N=38)

Variables	Mean (SD), Range
Mini Mental State Examination	26.1 (2.9), 21-30
Geriatric Depression Scale – 15	2.4 (1.9), 0-7
MCI Diagnosis (Petersen criteria) Amnestic Plus Other Amnestic Single Domain Non-Amnestic Single Domain Non-Amnestic Multiple Domains	 18 (47.4) 9 (23.7) 7 (18.4) 4 (10.5)
Total HV, mm^3	3761.9 (663.9), 1833-5244
Wechsler's test of adult reading	112.1 (11.13), 78-123
General musical sophistication subscale	61.6 (17.3), 20-98
	Z score
Animal list generation	-1.23 (0.96)
Trail making test A	-0.41 (1.26)
Trail making test B	-0.87 (1.71)
Word list memory	-2.33 (1.29)
Word list recall	-2.39 (1.78)
Word list recognition	-0.91 (1.81)
Boston Naming Test	-1.24 (2.59)
Clock drawing test	-0.74 (1.53)

We found a negative correlation between GMSS and the TMT B (r= -0.41; 95% CI (-0.66, -0.09), p=0.02). Therefore, higher GMSS scores were correlated with better performance on the TMT B but not other neuropsychological scores. General musical sophistication did not correlate with HV (p=*n.s.*; Table 3.3). HV correlated with Word list memory (r=0.36; 95% CI (0.04, 0.61); p<0.05) and Word list recognition scores (r=0.50; 95% CI 0.22, 0.71; p<0.01; Table 3.3).

Table 3.3 Pearson Correlations Coefficients between Hippocampal Volume, General Musical Sophistication Subscale and Cognitive Abilities

	1	2	3	4	5	6	7	8	9	10	11	12
1. Mus. Sophistication												
2. Total HV	-0.12											
3. Animals	0.32	0.08										
4. TMT A	-0.19	0.1	**-0.46****									
5. TMT B	**-0.41***	0.23	**-0.45***	**0.44***								
6. WLMem	0.17	**0.36***	**0.42***	-0.17	-0.24							
7. WLRecall	0.07	0.33	0.25	-0.23	-0.12	**0.65****						
8. WLRecognition	0.05	**0.50****	0.31	-0.14	-0.03	**0.70****	**0.63****					
9. BNT	-0.2	-0.03	-0.25	0.1	0.05	-0.11	-0.19	-0.13				
10. CDT	-0.22	0.25	-0.24	**0.41***	**0.55****	-0.22	-0.19	0.05	0.15			
11. WTAR	0.26	0.08	0.17	0.04	-0.31	0.04	-0.27	-0.18	-0.24	-0.04		
12. MMSE	0.08	0.2	0.28	-0.3	**-0.50****	**0.43***	**0.39***	0.32	-0.16	-0.29	0.13	

Notes: Mus. sophistication – General musical sophistication Subscale, HV – hippocampal volume, Animals – Animal list generation, TMT – trail making test, WLMem – word list memory, WLRecall – word list recall, WLRecognition – word list recognition, BNT – Boston naming test, CDT – clock drawing test, WTAR – Weschler's test of adult reading, MMSE – Mini Mental State examination; * p<0.05; ** p<0.01

When we analyzed individual cognitive abilities as a function of HV in simple linear regression models, none of the analyses were significant. We then repeated the analyses with the interaction term between GMSS and HV. We found statistically significant interaction between total HV and executive function (TMT B) (Table 3.4, adj. R^2=0.328, parameter estimate 0.00008, Standard Error, SE: 0.00003, p=0.036).

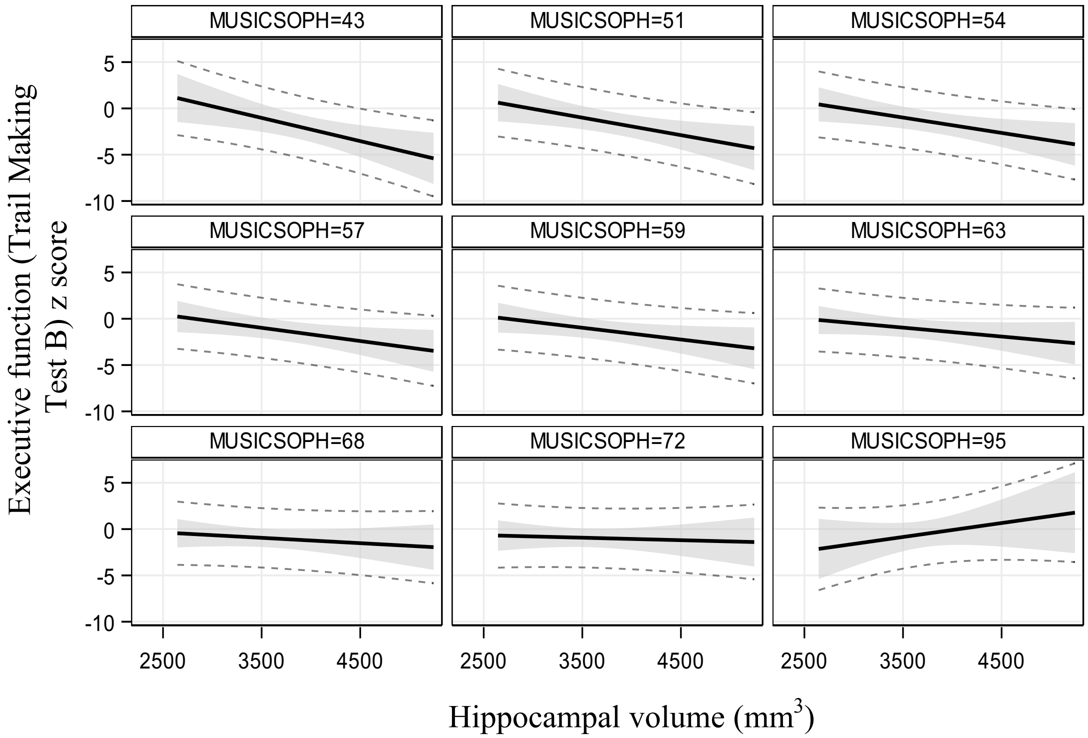
Table 3.4 Executive Abilities as a Function of General Musical Sophistication Subscale, Total Hippocampal Volume and Interaction between Total Hippocampal Volume and General Musical Sophistication Subscale

	Main effects		**With interaction term**	
	Estimate (SE)	**p**	**Estimate (SE)**	**p**
Model 1 (HV volume)				
Intercept	-0.636 (6.780)	0.926	-15.292 (9.463)	0.121
HV Total	-0.001(0.0006)	0.098	-0.006 (0.002)	**0.015**
GMSS	0.03368 (0.018)	0.075	-0.267 (0.135)	0.062
GMSS X HV			-0.00008 (0.00003)	**0.036**

Notes: GMSS – General Musical Sophistication Subscale, HV – hippocampal volume; SE – standard error. All models controlled for age, sex, education, premorbid intelligence, comorbidities and depressive symptoms.

To better illustrate the effect of GMSS, we constructed a series of plots with predictive association between HV and executive function (TMT B) for different percentiles of GMSS (Figure 3.1). In participants who scored low on the GMSS (those who scored in the bottom 50 percent), the relationship between hippocampal volume and TMT B z scores was negative. For these participants, greater hippocampal volume was related to worse performance on the TMT B. Alternatively, for participants who scored in the 90th percentile (corresponding to a GMSS score of 95) greater hippocampal volume was associated with better performance on the TMT B. From our findings, GMSS not only weakened the relationship between HV and executive function, but appeared to go in the opposite direction for participants who scored high on the GMSS.

Figure 3.1 Predicted Association between Total Hippocampal Volume and Executive Function



Notes: MUSICOPH – general musical sophistication subscale. Each box represents 10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, and 90th percentiles of general musical sophistication. Score of 43 corresponds to 10th percentile, score of 51 – 20th percentile and so on. Gray areas demonstrate 95% CIs, dotted lines - predicted limits. All models controlled for age, sex, education, premorbid intelligence, comorbidities, depressive symptoms.

Discussion and Implications

In our cross-sectional study, musical abilities modified the relationship between HV and executive function in older adults with MCI, taking into account age, gender, years of education, intelligence, number of chronic illnesses, and depressive symptoms. The findings partially supported our initial hypothesis. We originally predicted that musical abilities would weaken the relationship between HV and cognitive abilities. Instead, we found that musical abilities not only weakened the relationship between HV and executive function, but also eventually reversed this relationship for participants with greater musical abilities. In other words, for individuals scoring in the average or lower range of musical abilities, HV and executive function had a negative association, whereas for participants with greater musical abilities, HV reflected a positive association with executive function. One possible explanation for these findings is that persons with lower musical abilities may rely on executive function to moderate the relationship between HV and memory deficits. By contrast, persons with MCI with greater musical abilities who have a variety of cognitive tools at their disposal are theoretically less reliant on executive function to compensate for their memory deficits. These data provide preliminary evidence for the compensatory effect of musical abilities against AD pathology driven changes in executive function of older adults with MCI.

Similar to our findings, previous studies that examined the effects of education, social networks, perceptual speed and purpose in life. All found a moderating effect between the underlying AD pathology and cognitive function. For example, years of education modified the relationship between cognitive function and AD pathology when examining amyloid deposition neurotic and diffuse plaques in older adults with normal cognitive function, MCI and probable AD (Bennett, Schneider, Wilson, Bienias, & Arnold, 2005; Bennett et al., 2003). The size of social networks in 89 older adults without known dementia from the Rush Memory and Aging Project modified the relationship between neurofibrillary tangles, global disease pathology and cognitive function (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). In a different sample of 103 older adults from the Rush Memory and Aging Project (which included a mix of normal cognition, MCI, and probable AD) perceptual speed weakened the relationship of amyloid load with semantic memory, visuospatial abilities and episodic memory (Boyle, Wilson, Schneider, Bienias, & Bennett, 2008). Having purpose in life modified the relationship between AD pathology and cognitive function in 246 dementia-free participants from the Rush Memory and Aging Project (Boyle et al., 2012). Taken together, these findings suggest a protective moderating effect of education, social networks, perceptual speed and purpose in life on cognitive function in older adults with and without cognitive impairment. These data add to our understanding of protective and moderating factors on the relationship between a neuropathological disease marker and cognition.

Cognitive reserve hypothesis may explain the compensatory effect of musical abilities. Previous research demonstrated that the degree of brain pathology does not directly correlate with the degree of clinical symptoms in AD (Stern, 2002, 2012). Factors, such as educational attainment and leisure activities later in life may increase cognitive reserve and protect individuals against cognitive deficits (Stern, 2010, 2012). Converging evidence from epidemiological studies suggests that mentally stimulating activities in late life have a protective effect against symptomatic AD (Verghese et al., 2006; Verghese et al., 2003). In particular, in large observational studies older adults who played a musical instrument (Eriksson Sörman, Sundström, Rönnlund, Adolfsson, & Nilsson, 2014; Hughes, Chang, Vander Bilt, & Ganguli, 2010; Karp et al., 2006; Verghese et al., 2003) or listened to music (Akbaraly et al., 2009; Scarmeas et al., 2001) were less likely to progress to dementia later in life. Playing a musical instrument or consistent exposure to music over lifetime enhances one's musical abilities. Individuals with lower musical abilities may not have access to cognitive resources available for persons with higher musical abilities. As our findings suggest, individuals with lower musical abilities may rely on the executive function to compensate for their memory deficits. On the other end of the spectrum, participants who reported greater musical abilities may rely on musical abilities instead of executive function to compensate for their memory deficits. These findings need to be interpreted with caution in light of our analysis indicating that the slopes of the predicted association between HV and executive function in individuals who scored in the top 10% on the index of musical abilities cannot be definitively distinguished from zero (Figure 1). Taken together, musical abilities may increase cognitive reserve in persons with MCI, however, the exact contribution of enhanced musical abilities and their association with executive function needs to be further evaluated in future studies.

Executive function refers to a complex set of behaviors responsible for an independent response to novel situations (Lezak, 2004). Individuals with MCI with executive function deficits have difficulties with goal-directed behavior, inhibition, working memory and/or problem solving (Petersen, 2011). Deficits in executive function are often related to memory impairment in older adults with MCI, therefore we were not surprised for the relationship between executive function and hippocampal volume to emerge. A moderator variable modifies the strength of the relationship between two variables (Holmbeck, 1997). Our findings indicate that musical abilities moderated the relationship between hippocampal volume and executive function, one of the key cognitive abilities impaired in older adults with MCI. The moderating effect of musical abilities may be explained by research examining the relationship between musical abilities, cognition and executive function. Several studies demonstrated cognitive benefits in older adults who played a musical instrument or sang. For instance, in healthy older adults music training was associated with better performance on phonemic fluency, verbal working memory, verbal immediate recall, visuospatial judgment and motor dexterity domains (Hanna-Pladdy & Gajewski, 2012). Similarly, in a large cross-sectional study older adults who reported singing or playing a musical instrument scored better on the tests of attention, episodic memory and executive function (Mansens, Deeg, & Comijs, 2017). In a group of adults and children musical training was associated with enhanced executive function skills (Zuk, Benjamin, Kenyon, & Gaab, 2014). One explanation for these findings is that music training involves sustained attention and goal setting– all aspects of executive function.

This study has several limitations. Diminished self-awareness in older adults with cognitive impairment is known to affect the accuracy of self-report on questionnaires (Roberts, Clare, & Woods, 2009). In our study, we asked participants to assess their musical skills and the frequency of their musical behaviors. Participants may have under- or over-estimated their musical abilities and the frequency of participation in musical behaviors. Older adults with MCI may lack self-awareness when assessing their current musical abilities. They may report their musical abilities based on earlier childhood and adolescent musical training and overestimate their present abilities. In addition, several musical sophistication index questions relied on recall, short- and long-term memory often impaired in older adults with MCI. For example, participants were asked to reflect on times in their life when they sang or played music from memory, compared and discussed differences between two performances or versions of the same piece of music. One question in particular relied on participants' short-term memory asking older adults to recall the number of live music events as an audience member in the past twelve months. Several caregivers were present during the meeting with the participants, but were asked not provide clues for the participants in answering these questions, which might have affected the accuracy of their responses. We powered this exploratory study to examine the associations between musical and cognitive abilities, thus we did not power to examine the interaction effect of musical abilities on cognition. Our sample was small, homogenous, primarily White and highly educated. Keeping these limitations in mind, we carefully designed our study to address how musical abilities modified the relationship between underlying brain pathology and cognitive abilities.

This study also had strengths. First, we used a novel index of musical abilities aimed to assess musical behaviors and skills in non-musicians. This study adds to the knowledge of how musical skills beyond musical training may be beneficial for persons with MCI. Second, we combined musical abilities data with a well-described sample from the ADCC. The expert panel of clinicians at the memory clinic reached the diagnosis consensus following a systematic and standardized neuropsychological data collection. Third, the primary investigator (DVM) was not part of the previously collected data in the ADCC database and was not involved in the MRI data extraction.

Conclusions and Future Directions

Identifying cognitive factors amenable to change is an important and timely inquiry, given the public health crisis of AD and related dementias in a growing elderly population. Future studies should include larger, heterogeneous samples and follow older adults with MCI longitudinally to explore the trajectory of change in musical abilities and further investigate the relationship between musical abilities and executive function. To further examine musical abilities in MCI, future studies should use an objective measure of musical abilities and include an informant assessment of musical behaviors.

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CHAPTER 4: THE FEASIBILITY OF A MUSIC LISTENING INTERVENTION TO REDUCE SLEEP DISTURBANCES IN OLDER ADULTS WITH DEMENTIA: A PILOT RANDOMIZED CONTROLLED TRIAL

Abstract

Sleep disturbances in older adults living with Alzheimer's disease and related dementias (ADRD) are very debilitating and contribute to increased institutionalization, reduced cognitive function, and accelerated disease progression. Furthermore, sleep disturbances are linked to poor health outcomes in caregivers (CGs), such as poor quality of life and increased CG burden. Given the potential harmful side effects of pharmacologic treatment, non-pharmacologic approaches, such as music, may provide a safer alternative to reducing sleep disturbances in this vulnerable population. Listening to music has shown to decrease agitation, anxiety and depression in nursing home residents with ADRD. A growing body of literature suggests that individualized music may improve sleep quality in older adults with early memory loss, but its efficacy has not been demonstrated in older adults with ADRD in the community, where most older adults with ADRD live. If proven feasible and acceptable, tailored music interventions can then be tested for efficacy in reducing sleep disturbances. The purpose of this individual National Research Service Award (NRSA) application is to provide post-doctoral research training for a candidate to gain the knowledge and skills essential for an independent research career. In a cross-sectional dissertation study (funded by NIA F31AG055148) the applicant has previously examined cognitive abilities associated with engagement in music activities and music-related behaviors in older adults with mild cognitive impairment. The applicant's long-term career objective is to address sleep disturbances in

older adults with ADRD using non-pharmacologic approaches. The specific aims of this proposal are to examine the 1) feasibility; 2) acceptability; and 3) preliminary efficacy of a tailored music intervention in home-dwelling older adults with ADRD suffering from sleep disturbances. Sixty dyads (older adults with ADRD and their CGs) will be randomized to receive the tailored music intervention immediately or following a four week delay. Music selections will be individualized for each older adult with ADRD and account for known sleep-inducing properties. Feasibility of processes that are key to the success of the subsequent study will be examined. Preliminary efficacy of the intervention will be assessed using objective (actigraphy) and subjective (proxy report) sleep quality measures. In addition, qualitative data will be solicited from the dyads examining the acceptability and satisfaction with the intervention. Under the guidance of the mentoring team, the applicant has carefully selected research training activities to gain knowledge and expertise in five core areas: 1) clinical trial methodology; 2) sleep assessment measures in older adults; 3) advanced statistical methods pertaining to the analysis of clinical trials; 4) research ethics; and 5) grantsmanship. Results from the proposed research project will not only inform a future efficacy trial, but also provide an opportunity for the applicant to gain the necessary skills to launch her career as an independent investigator.

Specific Aims

More than 5 million older Americans currently suffer from Alzheimer's disease and related dementias (ADRD).[1] The worldwide costs of ADRD exceeded $818 billion in 2015, an increase of 35% since 2010.[2] The mean survival time from the time of onset for older adults with ADRD is approximately 10.5 years.[3] During this timeframe approximately 25-44% of older adults with ADRD suffer from sleep disturbances, including: nighttime sleep fragmentation, decreased sleep efficiency, and increased daytime napping.[4,5] Sleep disturbances are debilitating and contribute to increased institutionalization,[5-7] as well as poor quality of life for older adults with ADRD and their caregivers (CGs).[8] According to the Progressively Lowered Stress Threshold (PLST) theory older adults with ADRD experience a lowered stress threshold as the day progresses making them more susceptible to outside stressors and at risk for sleep disturbances and related behavioral symptoms.[9]

Given the potential harmful side effects of pharmacologic treatment, non-pharmacologic approaches are recommended for older adults with ADRD.[10] One promising approach is music. Listening to music has been shown to decrease agitation in nursing home residents with ADRD.[11] The potential therapeutic benefits have been attributed to music's capacity to evoke pleasant memories, reduce stress and modulate arousal levels[12] in older adults with ADRD with a reduced stress threshold.[9] However, such interventions have primarily focused on nursing home residents, included a mix of therapist and nurse-led interventions, and have not examined the impact of listening to music that precedes nighttime sleep.[13-15] Moreover, most older adults with ADRD live at home with CGs, thus do not have access to therapist-led music interventions traditionally employed in institutional care settings.[13] There are no evidence-based, low-cost, widely available interventions to improve sleep disturbances in older adults with ADRD. In my dissertation work, funded by an individual NRSA (F31AG055148), I examined cognitive measures associated with engagement in everyday music and music-related behaviors in older adults with mild cognitive impairment living at home. I became increasingly interested in how music can be used to improve sleep quality in community-dwelling older adults with ADRD.

The long-term goal of my research program is to address sleep disturbances in community-dwelling older adults with ADRD using tailored non-pharmacologic approaches. My central hypothesis, based on prior data and PLST theory, is that evidence based music intervention previously shown to be effective in decreasing agitation in nursing home residents with ADRD,[11] can reduce significant related behavioral symptoms - sleep disturbances, if shown to be feasible and acceptable in this population. To test this hypothesis I propose a feasibility randomized controlled trial of a 4-week tailored home music intervention in a sample of 60 dyads (older adults with ADRD and their CGs). This study will provide essential preliminary data to test the efficacy of the intervention to reduce sleep disturbances in a future RCT supported by a K99/R00 award. The postdoctoral award will enable me to complete this mentored research project, obtain training in clinical trials, advanced biostatistics, sleep methodology, research ethics, grantsmanship and move me closer to my ultimate goal of becoming an independent investigator.

Aim 1: Examine the feasibility of processes that are key to the success of the subsequent study including rates of: adherence to the protocol, completion of the study measures, recruitment, attrition and refusal.

H: I hypothesize that most participants with ADRD will complete the study measures and adhere to the protocol (primary outcome). I will also document reasons for excluding or declining, willingness to be randomized and assess the appropriateness of the eligibility criteria.

Aim 2: Examine the acceptability of the intervention using survey and qualitative data.

H: I hypothesize that most CGs will be highly satisfied with the music intervention. I will evaluate satisfaction using a validated satisfaction questionnaire and qualitative interview data.

Exploratory Aim 3: Provide preliminary efficacy of the intervention on four sleep quality outcomes: 1) wake time after sleep onset (WASO), 2) sleep-latency onset, 3) total sleep duration, and 4) perceived sleep quality.

H: Compared to the control group participants, older adults with ADRD in the intervention group will experience (H1) shorter WASO, (H2) shorter sleep-latency onset, (H3) longer sleep duration, and (H4) improved sleep quality using objective (actigraphy) and subjective (self-report) data.

This research project has important implications regardless of the study outcome yielding preliminary feasibility data needed to conduct a larger RCT powered to assess music's impact on sleep quality, CGs' long-term health outcomes and rates of institutionalization in older adults with ADRD. The aims of the project are achievable because it builds on known evidence based music interventions for older adults with ADRD.[11] The work is feasible because my sponsor and co-sponsor are committed to mentoring young investigators, have a proven record of success conducting non-pharmacologic intervention trials in older adults with ADRD, and because of my previous success as a trainee in recruiting cognitively impaired older adults.

Research Strategy

Significance

Overview of sleep disturbances and Alzheimer's disease and related dementias. Approximately 25-44% of older adults with ADRD suffer from nighttime sleep fragmentation, decreased sleep efficiency, and increased daytime napping .[4,5] The origin of sleep disturbances in ADRD stems from multiple factors, including degeneration of neural pathways responsible for sleep-wake function and presence of psychiatric co-morbidities.[16] Sleep disturbances are pervasive across all three stages of ADRD – mild, moderate, and severe.[17] The impact of sleep disturbances is devastating for both older adults with ADRD and their caregivers (CGs).[5-7] In older adults with ADRD untreated sleep disturbances are associated with poor quality of life,[8] reduced cognitive function,[18,19] and accelerated disease progression.[20] In CGs sleep disturbances are linked to poor quality of life,[8] nocturnal disruptions,[21] increased CG burden[22], and increased likelihood of institutionalization of the adult with ADRD.[23,24] Pharmacologic treatment remains the first-line treatment for sleep disturbances in ADRD, however its use is often limited due to potentially harmful side effects.[4,5,10,16] The absence of effective and safe pharmacologic treatment for sleep disturbances warrants closer investigation into alternative approaches.

Music interventions to reduce sleep disturbances. Music has shown promising results in improving sleep quality in adults with schizophrenia,[25] insomnia,[26] cancer,[27] pregnant women,[28] and ICU patients.[29,30] In healthy older adults, listening to individualized (defined as "music that has been integrated into the person's life and is based on personal preference"[11]) soothing music was associated with shorter wake time after sleep onset (WASO),[31] shorter sleep-latency onset,[32] better perceived sleep quality and longer sleep duration.[33] The potential therapeutic effects of listening to music have been attributed to its ability to reduce stress and initiate a brainstem response in turn modulating cardiovascular measures, such as heart rate, blood pressure, and body temperature.[12] A body of evidence suggests agitation-reducing benefits of listening to music in nursing home residents with ADRD,[11] but no empirically validated music protocol exists to address significant related behavioral symptoms - sleep disturbances in older adults with ADRD living at home. Such absence indicates a critical barrier to developing widely available non-pharmacologic interventions to improve sleep quality in older adults with ADRD. Music interventions have primarily focused on symptoms of agitation,[34] anxiety,[35] and depression[35] in nursing home residents, included a mix of therapist and nurse-led interventions, and did not consider how listening to music prior to bedtime promoted sleep in older adults with ADRD.[13-15] Most older adults with ADRD live at home with CGs, but lack access to therapist-led music interventions traditionally employed in institutional care settings.[13] Therefore, the overall goal of my project is to test the feasibility of a tailored home music intervention to reduce sleep disturbances in older adults with ADRD and to provide preliminary evidence of its efficacy for a future trial.

The long-term impact of this work. First, this research will advance our knowledge of music interventions beyond the nursing home population and into the community, where most older adults with ADRD live. Second, this research will examine the feasibility of an evidence based music intervention in a vulnerable population. Third, this research will inform our knowledge about the benefits of bedtime music listening in older adults with ADRD and the impact it has in improving sleep quality. Lastly, knowledge gained from this trial related to feasibility and acceptability will guide a larger

RCT where the bedtime music protocol is tested for efficacy and later for effectiveness (if shown efficacious). This will increase the options for non-pharmacologic approaches to reduce sleep disturbances in older adults with ADRD.

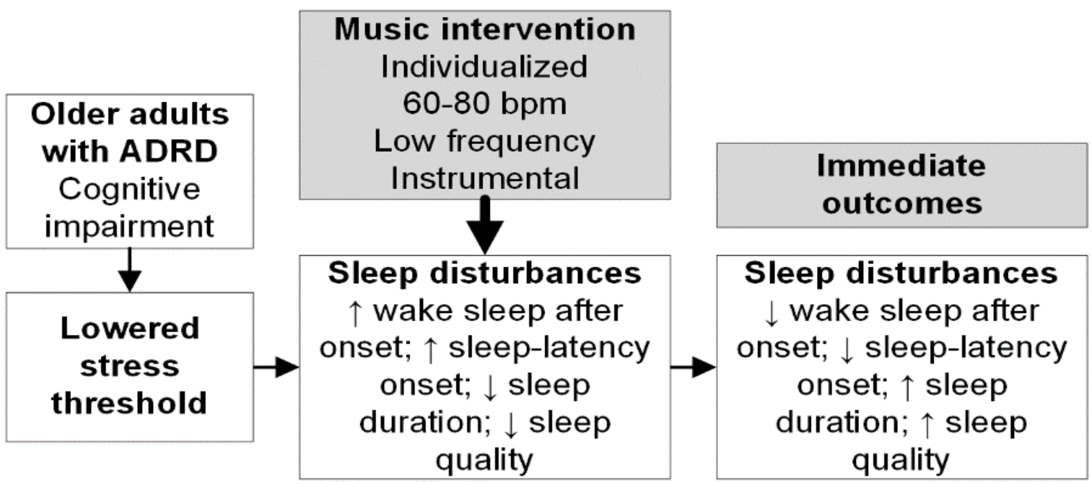
Approach

Conceptual Framework

The Progressively Lowered Stress Threshold[9] (PLST) model and the adapted mid-range theory of Individualized Music Intervention for Agitation (IMIA)[36] guided the conceptual framework for this study. The PLST model posits that older adults with ADRD accumulate stress throughout the day and due to cognitive impairment are unable to cope with stress from the environment. Their stress threshold is reduced, resulting in PLST behavior clusters, such as agitation, night awakenings, and combativeness.[9,37] Previous research has identified several stressors for older adults with ADRD, including multiple or competing stimuli. [33] In addition, sleep disturbances may contribute to increased behavioral symptoms.[38] Interventions aimed at modifying environmental stimuli right before bedtime, such as listening to soothing music, may regulate environmental stressors (i.e. noise, competing visual and audio stimuli), reduce anxious behavior and promote sleep.[37,39]

Dr. Gerdner (consultant) developed her mid-range theory IMIA from the PLST.[36] Her theory incorporates the PLST model to explain the stressors or causes associated with dysfunctional behaviors. She theorized that individualized music serves as a trigger for positive emotions associated with certain songs/artists, shifts focus of attention to more pleasant stimuli, thus decreasing agitation. [36] Previous RCTs have demonstrated the efficacy of individualized music to decrease agitation in nursing home residents with dementia.[40-43] In only 1 published quasi-experimental study individualized music was used to decrease agitation in persons with ADRD living at home.[44] Given the ability of individualized soothing music to promote sleep in healthy older adults and the evidence base of using individualized music to decrease agitation, the conceptual framework behind the proposed study is based on concepts from the PLST and IMIA models (Figure 4.1). CGs are taught to play individualized soothing music prior to bedtime for older adults with ADRD, which may elicit older adults to relax and fall asleep, shortening time to sleep onset, increasing sleep duration and improving their perceived sleep quality.

Figure 4.1 Conceptual Framework

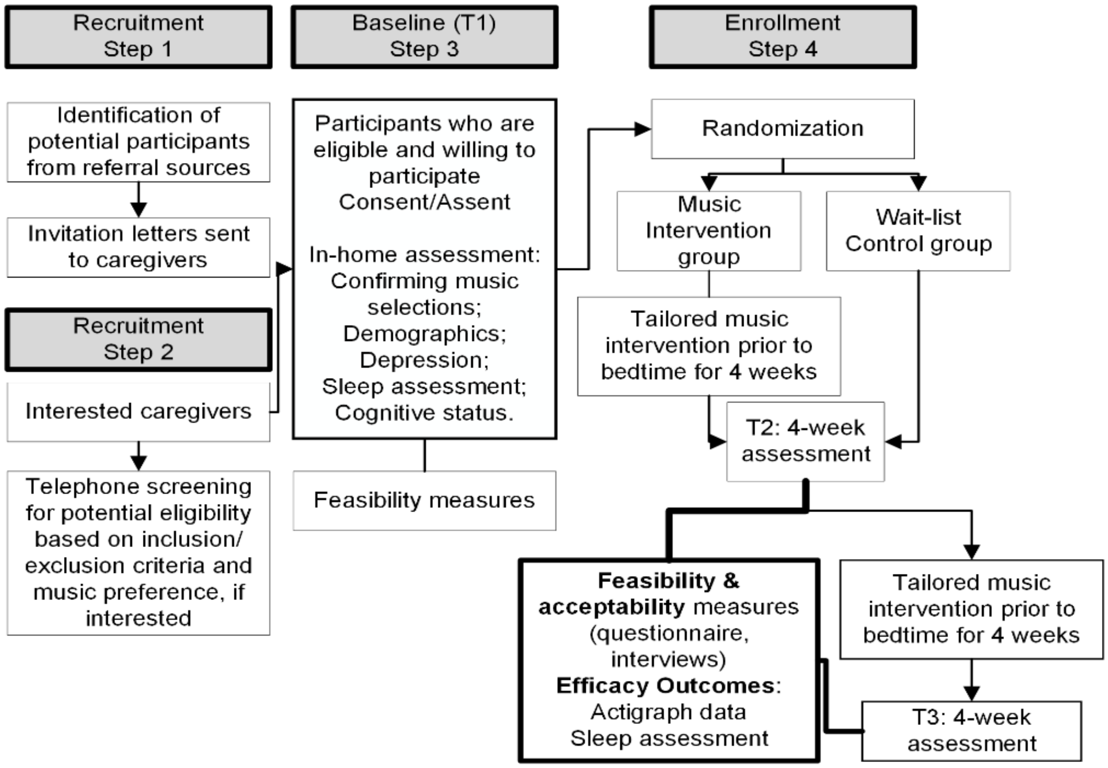


Design

Overall strategy.

A feasibility randomized wait-list controlled trial will be used. This design was chosen to examine the feasibility and acceptability (Aims 1 & 2) of a tailored 4-week home music intervention for 60 dyads across both the experimental and control groups. To provide support for a larger RCT, in Aim 3 I will examine a preliminary efficacy of the intervention in reducing sleep disturbances using actigraphy and subjective sleep measures. Figure 4.2 outlines the study flow.

Figure 4.2 Study Procedures



Participants and Setting

Participation will be offered to 60 dyads (adults over the age of 60 with a diagnosis of probable ADRD and their CGs) from Philadelphia, PA and the surrounding metropolitan area. Sites of recruitment include: A) the Penn Medicine Geriatrics clinic; B) Penn Alzheimer's disease Core Center (ADC); C) a subject registry from PennSeek which contains names of over 5,000 persons with dementia who have indicated a willingness to be contacted for future studies (see Dr. Gooneratne's, consultant); and D) control group participants from my Sponsor's ongoing R01 (R01NR015226) 4 weeks after completing the study. Table 4.1 outlines key inclusion and exclusion criteria for older adults with ADRD. CGs will be included if they provide at least 4 hours of daily care and live with the older adult, and are able to read and speak in English. Resources outlined in the Institutional Environment and Commitment training further expand on how above mentioned resources will facilitate trainee access to potential participants and resources necessary to achieve the specific aims. All study related visits (except for the brief phone calls) will be done at participants' homes at late morning or early afternoon hours.

Table 4.1 Inclusion and Exclusion Criteria for Older Adults with ADRD

Inclusion	**Exclusion**
Age 60 and older	Planned transition to another residential or institutional care setting in less than 3 months *to decrease attrition rates*
Physician diagnosis of probable ADRD using standard assessments and diagnostic criteria	Hearing impairment (defined as inability to hear a normal speaking voice at a distance of 1-1/2 feet)[11] *to exclude those who cannot hear the music intervention*
Presence of sleep problems determined first during phone screening using NPI sleep disorders item,[45] then using proxy-rated Sleep Disorders Inventory (SDI)[46] (presence of at least one sleep disturbance symptom of moderate severity)	Presence of extrapyramidal symptoms affecting non-dominant hand which may include persons with the following diagnoses: schizophrenia, bipolar disorder, Huntington's disease, Parkinson's disease, Lewy Body dementia due to REM sleep disorders *affecting actigraphy measurement of sleep disturbances*[47]
Stable dose of psychotropic medications, sedatives/hypnotics, anti-dementia or opioids in the past 90 days (typical time frame in clinical trials) prior to enrollment *to minimize confounding effects of medications*	Currently enrolled in an interventional clinical trial for ADRD aimed to improve sleep *as to not to confound the efficacy results*
Tolerates and agrees to wear wrist actigraph	Acute sleep disturbances within 2 weeks of screening *as it may indicate sleep disorders not related to ADRD or delirium*[47]
Responsive to their environment (e.g., able to understand short commands)	End stage disease (i.e. cancer, bed bound) *to minimize factors affecting actigraphy measurement*
Sufficient English to complete questionnaires	

Procedures and Randomization Process

I will seek IRB approval from the University of Pennsylvania prior to recruitment. As outlined in the letters of support, I will have full access to patient databases at three of the recruitment sources (Penn Geriatrics Clinic, ADCC and PennSeek). Dr. Gooneratne (consultant) will facilitate my access to the PennSeek database. To access my sponsor's control group participants, the research staff will first seek permission from CGs to contact them via mail. I will send invitation letters to all potential dyads (addressed to CGs) from four recruitment sources detailing the purpose of the study with information on how to contact me. CGs interested in participating will be screened by telephone for key inclusions/exclusion criteria (Table 1) and for music preferences, if interested. After the initial screening and confirmed willingness of CGs to participate in the research project, I will set a time to meet with the dyad at their home for a consent/baseline assessment. Prior to completing the assessment, I will review study purpose/procedures and obtain written consent (see Human Subjects section). If older adult with ADRD is unable to provide informed consent then I will seek proxy consent and older adult's assent. The inability to provide informed consent will be determined by asking older adults with ADRD specific questions to evaluate their understanding of the study purpose, risks and benefits. We will also collect baseline demographic data (if not available in the medical records), screen for depression, and assess sleep quality. Following the baseline assessment, dyads will be randomized to either the music intervention or wait-list control group. The CGs will learn about the dyad assignment 72 hours following the randomization. The intervention group will be retested at 4 weeks (T2) from baseline (T1), and wait-list control group will be retested at 4 weeks (T3) following the intervention (T2). We will collect feasibility information at screening, T1, T2, and T3 as well as acceptability measures (T2 & T3) for all dyads (Figure 4.2).

Determining Music Preferences

Previous research has shown the following music characteristics as efficacious in reducing sleep disturbances[31-33] - music selections should be at least 30 minutes in length,[30] between 60-80 beats per minute (bpm), slow stable rhythm, low frequency tones, and absence of lyrics or strong percussion.[33,48] Investigator selected music with soothing properties, disregarding personal preferences and background, has not been beneficial in promoting sleep.[48] Familiarity with music may improve adherence to the music intervention and several studies have shown the efficacy of music is affected by the listener's enjoyment with preferred genre having the most beneficial effect.[48,49] Gerdner and others used individualized music, including specific songs and artists selections, to evoke pleasant memories associated with these songs in nursing home residents with ADRD.[15,41] Specific songs might not have the soothing properties previously reported as effective in promoting sleep in older adults. Consequently, in this trial I propose that soothing music selections should be based on preferred genre of music to maximize treatment adherence and participant's enjoyment, but should not contain specific songs/selections familiar to older adults with ADRD because of a possible stimulatory, rather than sleep-inducing, effect. To assess for individualized music genre I will use Gerdner's (consultant) Assessment of Personal Music Preference during the screening telephone prior to the baseline in-home visit.[11]

Following the assessment, I will consult with Drs. Bradt and Gerdner to choose music according to older adults' preferred genre that includes music properties known to induce sleep. I will then return to the dyad's home at baseline (T1) with a portable music player to play and discuss selection of 6 pieces of music. I chose the number of selections based on previous clinical trials that used music to induce sleep.[33] If older adults with ADRD show signs of distress (i.e. grimacing, crying) or excitement I will reassess musical selections with the consultants and return a week later with new music selections. If at that point, older adults are not satisfied with the selection or appear to be in distress while listening to music, the dyad will be excluded, and will be considered a drop out, since the dyad has already consented to be randomized. Older adults' discontent will be documented. Given the acceptability of Dr. Gerdner's individualized music protocol in nursing home residents with ADRD, we do not expect more than 10% of the sample to be dissatisfied with the music selection. If at half way enrollment point more than 10% of the recruited sample has shown dissatisfaction, I will reassess the music preference protocol with Drs. Bradt and Gerdner.

Music Intervention Protocol.

The music intervention consists of listening to preferred soothing music at bedtime every night for four weeks (28 sessions total). I chose the length of intervention based on previous studies that recommend the duration of the music intervention to be at least three weeks[49] and based on a minimum length required to see changes in sleeping patterns.[50] Dyads will receive 4 weekly phone calls in a four week period in addition to the baseline and post-intervention home visits. Length and frequency of each contact will be documented. This theory based (Fig. 1a) CG-assisted intervention builds on the evidence-based protocol of using personalized music to decrease agitation in older adults with ADRD. It also accounts for sleep-inducing properties of music. After finalizing music selections, the dyads will be instructed to play music for at least 30 minutes via the speaker before bedtime and go to sleep following the end of music selection. I chose the length of 30 minutes based on previous studies showing that at least 30 minutes of listening to music was required to reach the desired soothing effect.[30] The dyads may choose to listen to all six selections or only listen to one, repeatedly. CGs will be instructed to encourage participants to listen to music following bedtime routine, laying down with their eyes closed, wearing nighttime clothes, and room lights dimmed. I will then follow up with the dyads 1 day after the start of the 4 week intervention, ensuring that there are no issues in listening to music.

Wait-list Protocol

The control group will receive music intervention 4 weeks following the baseline assessment (T1). Similarly to the music intervention group, I will assess the appropriateness of music selections based on the method described above.

Treatment Fidelity Monitoring.

To ensure treatment fidelity I will use strategies outlined in the NIH Behavior Change Consortium.[51] Specifically, I will create a treatment manual for consistency of delivery of the intervention, have regular contact with the dyads, keep written records of home sessions/phone calls by date and duration. I will include a brief checklist in the sleep diary for the CGs to document music selection and any missed music sessions by the participants. I will place 4 weekly phone calls (or via preferred method of communication) to CGs with reminders to fill out the sleep diary. As part of post-doctoral training and the MHealth internship with Dr. Gooneratne (consultant) I will explore the possibility of using remote mobile monitoring as means to decrease the CG burden, track music selection, and adherence to the intervention.

Instrumentation for Aim 1: Feasibility Measures.

The feasibility measures in Table 4.2 are the recommended measures to estimate important parameters for the subsequent study.[52,53]

Table 4.2 Feasibility Measures

Measures (role in analysis)	**Operational definition**	**Data sources**
Adherence to the study protocol and completion of the study measures (primary)	Number (and %) of subjects following the study protocol and completing the study measures.	Field notes, records in the sleep diary, verification by study staff
Recruitment rate (secondary)	Number (and %) of subjects recruited per month	Documentation in the written study records
Participant attrition (secondary)	Number (and %) of subjects who dropped out in the course of the study (and reasons for dropping out)	Dyad, documentation in the written study records
Reasons for excluding or declining (secondary)	Explanations for why subjects were not recruited or declined to be in the study	Dyad
Willingness to be randomized (secondary)	Subjects who are not willing to be randomized to either an intervention or control group	Verbal (YES or NO by phone) or written statements from the subjects 48 hours following the disclosure of the randomization assignment
Appropriateness of the eligibility criteria (secondary)	Number (and %) of subjects who were turned away due to not meeting the inclusion/exclusion criteria	Documentation in the written study records

Instrumentation for Aim 2

To assess acceptability of the study components I will first evaluate CG satisfaction with study benefits using a validated 11-item survey developed by my co-sponsor,[54,55] which examines satisfaction with participation and perceived benefits. The

CG perceived benefits include four categories: overall benefit, dementia understanding, confidence managing care, enhanced skills, and life easier. The perceived benefits for older adult with ADRD include: improved daily life and helped keep loved one at home. Second, I will capture the general level of enjoyment from older adults with ADRD derived from listening to music by asking them a single question – "How enjoyable did you find listening to selected music?" I will record their responses using a 7-point Likert scale (1 - not at all enjoyable …to 7- extremely enjoyable …). I will use this score as a covariate in the analysis, given previous research has shown that general level of enjoyment listening to soothing music correlates with its efficacy.[48,49,56] Third, I will elicit qualitative data from the dyads. Gathering qualitative data in addition to quantitative information is helpful in optimizing the results from a feasibility or a pilot study.[52] Interviews will take no longer than 20 minutes and include prompts to expand on dyads' responses in the survey.

Table 4.3 Sleep Measures

<table>
<tr><th>Name (Definition)</th><th>Role in analysis</th><th>Psychometric properties</th></tr>
<tr><td colspan="3">Objective actigraphy outcomes</td></tr>
<tr><td>Sleep latency (Time it takes a person to fall asleep starting from first intention to sleep)</td><td>Primary (efficacy)</td><td rowspan="3">Correlation with polysomnography (r=0.81-0.91) in adults with ADRD;[57] Intra-device reliability (r >98%)[6]; Sensitivity 0.97; specificity 0.33; accuracy 0.86)[58] when compared to polysomnography in adults.</td></tr>
<tr><td>Wake after sleep onset (Time awake during the night, beginning from the time person falls asleep)</td><td>Secondary (efficacy)</td></tr>
<tr><td>Total sleep duration (Actual time person is asleep)</td><td>Secondary (efficacy)</td></tr>
<tr><td colspan="3">Self-report</td></tr>
<tr><td>Sleep diary[59]</td><td>Reconciliation with actigraphy data (Efficacy)</td><td>In nursing home residents with ADRD – sensitivity of 87% and specificity of 90%[57]</td></tr>
</table>

Name (Definition)	Role in analysis	Psychometric properties
Neuropsychiatric Inventory sleep item[45]	Screening	Inter-rater reliability: (0.926-1.00); concurrent validity with BEHAVE-AD ($p<0.05$)[45]
PROMIS sleep related impairment – SF 8a[60]	Efficacy outcome	Convergent validity with PSQI ($r=0.68$); reliability 0.90[60]
Sleep disorders inventory (SDI)[46]	Screening, Efficacy	Content validity with NPI sleep subscale ($r=0.34$, $p<0.05$)[46]

Instrumentation for Exploratory Aim 3.

Sleep measures in this study include both objective (actigraphy) and subjective measures (Table 4.3). Older adults with ADRD will be provided instructions on how to wear actigraphs (AMI Motion logger) on their non-dominant hand in order to monitor their sleep patterns for four weeks. Wrist actigraphy was chosen because it has been shown to be a sensitive and accurate method for measuring sleep latency, wake after sleep onset and total sleep duration in clinical populations, when compared to the gold standard – polysomnography.[58] Wrist actigraphy monitoring has been shown to be tolerated well by older adults with ADRD[47,61,62] and provide a reliable way to objectively monitor sleep-wake cycles in this population.[47] CGs will be asked to complete a sleep diary, documenting the older adults with ADRD's daily sleep patterns. Using a sleep diary[59] in addition to actigraphy provides a more reliable representation of sleep-wake cycles in older adults with ADRD.[61] Furthermore, pairing actigraphy data with the sleep diary is the recommended approach by the American Academy of Sleep Medicine for home-dwelling older adults.[62] Sleep diary questions are kept to a minimum to increase compliance and adherence to the protocol. Actigraphy data analysis will be completed using validated scoring algorithms from my sponsor's R01 (R01NR015226; e.g. 60-

second epochs).[47] Differences between actigraphy data and sleep/wake record data will be reconciled on an individual basis with the dyad using an established protocol from my sponsor. Previous research has shown that, although widely acceptable, older adults with severe ADRD may remove actigraphs.[47] Dyads will receive check in calls to ensure that older adults with ADRD are wearing the actigraphs and the CGs are not experiencing issues when completing the sleep diary.

Additional Instrumentation for Aim 3

We will collect the following baseline demographic information (either through the medical records or from the dyad): age, sex, race/ethnicity, marital status, income, nature of the dyadic relationship, and years of education. We will also screen for depression in older adults via proxy CG using a validated questionnaire (Patient Health Questionnaire, PHQ-9).[63] There is evidence of the association between sleep disturbances and depression in older adults with AD.[64] Scores greater than 10 indicate presence of major depression. Mini Mental State Examination[65] will be used to estimate cognitive status at baseline and as a covariate in the analysis.[47]

Analyses

Sample Size Calculation

The sample size and power calculation for this feasibility trial relies on the estimated confidence intervals width for parameter estimates of interest (feasibility outcome) and is powered sufficiently for these descriptive purposes. By design, this study was not powered to determine the efficacy of music intervention in reducing sleep disturbances. I will answer this important question in a future RCT (K99/R00 application). The primary feasibility outcome is participant adherence to the protocol. I will conclude that this study is feasible if at least 85% of the dyads complete the study components and measures. A value accurate within 10-15 percentage points for adherence mean is sufficient to identify a problem that would justify modification of the intervention.[66] In a RCT comparing relaxation program and music listening in older adults with mild cognitive impairment, adherence rate exceeded 93% at 12 weeks.[67] Therefore, with an observed adherence rate of 85% in the proposed study with 50 dyads, we can be 95% confident that the estimate is accurate within 10% points. I will call this study acceptable if the average score is at least 80% (% responding "Yes" or a "Great deal"). With 50 dyads, we can be 95% confident that the estimate is accurate within 12% points (see Table 4 for additional parameters of interest). Group sample sizes of 25 dyads each achieve 80% power to detect an effect size of 0.8 between 2 groups, assuming the attention control group achieves a sleep latency time of 38.28 mins[68] with a SD of 48.31, and the music intervention group achieves a sleep latency time of 77.3 mins (increase of 39.1 mins). Previous related studies detected comparable treatment effects using subjective sleep outcomes in healthy older adults[33,69] and we realize that effect sizes in pilot/feasibility studies may be overly large. I plan to recruit ten additional dyads for a total of 60 dyads (30 dyads per group) to allow for 16% attrition. One-month attrition in my sponsor's project Touch was 5% (the intervention consisted of providing relaxing sensory cues in the form of brief massage for older adults with ADRD living at home). Four-month attrition in my co-sponsor's pilot Tailored Activity Program and COPE trials, both aimed at home-dwelling persons with ADRD and their CGs, were 7%[70] and 11.8%,[55] respectively.

Table 4.4 Confidence Intervals (CI) for each Parameter of Interest (N=50)

Outcome	Estimated proportion	CI_{95}

Adherence to the protocol	0.85	0.75, 0.95
Attrition rate	0.16	0.07, 0.29
Willingness to be randomized	0.80	0.68, 0.92
Acceptability survey	0.80	0.68, 0.92

3.2 Analysis Aims 1 and 2

Aim 1: Examine the feasibility of processes that are key to the success of the subsequent study including rates of: adherence to the protocol, completion of the study measures, recruitment, attrition and refusal.

Aim 2: Examine the acceptability of the intervention using survey and qualitative data.

We will provide descriptive statistics of rates of adherence to the study components, recruitment, participant attrition, reasons for excluding or declining, willingness to be randomized, appropriateness of the eligibility criteria, and acceptability survey results (Table 4.4). The study will be considered feasible with 85% protocol adherence and study measures completion. Qualitative data from the dyad interviews will be recorded using field notes with major themes extracted related to the satisfaction and the acceptability of the study components.

Analysis of Exploratory Aim 3

Aim 3: Provide preliminary efficacy of the intervention on four sleep quality outcomes: 1) wake time after sleep onset (WASO), 2) sleep-latency onset, 3) total sleep duration, and 4) perceived sleep quality.

Descriptive statistics and univariate comparisons will describe the intervention and control groups. To explore differences between the groups, we will use Chi-square, Wilcoxon rank-sum tests, and independent t-tests, as appropriate, and we will adjust for the statistically significant variables accordingly in the multivariate analysis. To provide the preliminary efficacy and to estimate the effect size, we will use adjusted mean differences in treatment effects on the primary sleep outcome (sleep latency) and secondary outcomes (WASO, total sleep duration and sleep quality). The following data will be used as covariates: baseline cognitive status of the person with ADRD (MMSE), age, sex, education, general enjoyment of music and depressive symptoms. Sex will be incorporated as a biological variable following the NIH notice NOT-OD-15-102. To examine whether wait-list control group participants experienced the same sleep benefits as the intervention group we will compare four (T2) to eight (T3) week scores of control group dyads to baseline (T1) to four (T2) week scores of experimental group participants on statistically significant outcomes from the main analyses, using the same methods as described.

Potential Problems and Alternative Strategies.

Aim 1: Based on previous studies in this population, I predict that the majority of dyads will adhere to the music intervention protocol and complete the study measures. I will re-examine trial procedures with my Sponsor/Co-Sponsor, if the rate drops below 85%. Qualitative data will be sought following the intervention and may help explain the extraneous factors not accounted for in the quantitative data to improve adherence rates in a future trial. Participant payment will be offered to incentivize the participants. Adherence to wear the actigraph might be lower compared to rates of listening to music, since older adults with ADRD might forget to put on the actigraph after changing clothes. To circumvent any missing data from the actigraphs I will call CGs reminding them to complete sleep diaries, encourage older adults to listen to music and wear the actigraphs.

I expect older adults with ADRD may not enjoy listening to music. To circumvent this issue, we will determine tailored music using the evidence based protocol[11] matching person's preference and background to maximize enjoyment.

Aim 2: I predict that the music intervention will be well received by the dyads. If participants are dissatisfied with the music intervention, I will prompt them for additional details on the cause of their dissatisfaction during qualitative interviews and modify the protocol accordingly in future studies.

Aim 3: Since the primary aims of this RCT are to examine the feasibility and acceptability of the music listening intervention, I predict a trend towards improving objective and subjective sleep measures, as evidenced by shorter sleep latency, WASO, increased total sleep duration and improved sleep quality. The baseline and post-intervention assessments might be too tiresome for some participants, in which case I will reassess the number and the possible alternative less time consuming assessments still appropriate for this population. I would also consider breaking the baseline visit into 2 consecutive days. Despite these caveats, the results of this work will inform future efficacy RCTs, potentially adding to the number of non-pharmacologic approaches available.

Protection of Human Subjects

Risk to Human Subjects

Human Subjects Involvement, Characteristics and Design

Proposed study is a randomized, wait-list controlled clinical trial investigating the feasibility and acceptability of a tailored music intervention aimed to reduce sleep disturbances in older adults with Alzheimer's disease and related dementias (ADRD) living at home. Participation will be offered to 60 dyads (120 participants total, adults over the age of 60 with a diagnosis of probable ADRD and their CGs) from Philadelphia, PA and the surrounding metropolitan area. Participants may be of any gender, race or ethnicity. I expect the age range of the potential older adults with ADRD to be between 60 and 96 years old since this age range is predominant in adults with ADRD living at home.[70] I expect caregivers to be, on average, younger than adults with ADRD[71] and to be predominantly female.[8,54] I expect 65% of older adults with ADRD to be women since almost two-thirds of Americans with Alzheimer's disease are women.[1] In terms of education, I expect participants recruited from Penn's Alzheimer's disease Core Center (ADCC) to be more highly educated, compared to participants recruited from the other 3 sources described below, given published sample characteristics[72] and results from my dissertation (see preliminary dissertation results in the applicant's background section).

Key inclusion and exclusion criteria for enrolling older adults with ADRD in the proposed study are outlined in Table 4.1 Inclusion and Exclusion Criteria for Older Adults with ADRD. Caregivers will be included if they provide at least 4 hours of daily care, live with the older adult, and are able to read and speak in English.

Sites of recruitment include: A) the Penn Medicine Geriatrics clinic; B) Penn Alzheimer's disease Clinical Core (ADCC); C) a subject registry from PennSeek which contains names of over 5,000 persons with dementia who have indicated a willingness to be contacted for future studies; and D) control group participants from my Sponsor's ongoing R01 (R01NR015226) 4 weeks after completing the study. As outlined in the letters of support, I will have full access to patient databases at three of the recruitment sources (Penn Geriatrics Clinic, ADCC and PennSeek). Dr. Gooneratne (consultant) will facilitate my access to the PennSeek database.

Following the baseline assessment, dyads will be randomized to either the music intervention or wait-list control group. I will randomly assign each dyad using www.randomizer.org. I will contact each dyad via phone to let them know of their group assignment. The caregiver will learn about the dyad assignment 72 hours following the randomization. The intervention group will be retested at 4 weeks (T2) from baseline (T1), and wait-list control group will be retested at 4 weeks (T3) following the intervention (T2). We will collect feasibility information at screening, T1, T2, and T3 as well as acceptability measures at T2 and T3 for all dyads. Music intervention involves listening to individualized soothing music daily for 30 minutes at bedtime for 4 weeks. The wait list group will receive a comparable 4 week program, but will do so 4 weeks following the baseline assessment.

Parent Study Approval

Dr. Hodgson and her study team (which includes the applicant) received approval from the University of Pennsylvania (Penn) Institutional Review Board (IRB). Penn IRB has approved the ongoing collection of data for Dr. Hodgson's R01 (NR015226) study investigating a timed activity intervention to reduce symptoms of circadian rhythms disorders compared to an attention control condition in older adults with ADRD living at home. Penn IRB has also approved the ongoing collection of data for the ADCC (P30-AG010124).

Proposed Study Approval.

I will work with my sponsors to obtain IRB approval the University of Pennsylvania IRB for the proposed study in this research training application.

Source of Materials

Proposed Study. The primary sources of data will be a combination of subjective (self-report) and objective (actigraphy) data from the dyads. I will collect demographic information from the study records, if available. Screening may take place over the phone or during dyad's scheduled clinic visit to the ADCC or the Geriatrics Clinic. Prospective data will be collected at the dyad's home.

To accomplish specific aim 1 (the feasibility of the intervention) I will collect the following information about enrollment of the dyads: rates of recruitment, participant attrition, reasons for excluding or declining, willingness to be randomized, appropriateness of the eligibility criteria, adherence to the intervention protocol and completion of study measures. To complete specific aim 2 (the acceptability of the intervention) I will ask caregivers to fill out satisfaction questionnaires and prompt the dyad with additional questions related to the intervention acceptability using short (less than 20 minutes) interviews. In addition, I will capture the general level of enjoyment from older adults with ADRD derived from listening to music by asking them a single question – "How enjoyable did you find listening to selected music?" I will record their responses using a 7-point Likert scale (1 - not at all enjoyable …to 7- extremely enjoyable …). I will use this score as a covariate in the analysis, since previous research has shown that general level of enjoyment listening to soothing music correlates with its efficacy.[48,49,56]

To accomplish specific aim 3 (providing preliminary efficacy of the intervention) I will collect the following demographic information at baseline (either through the medical records or from the dyad): age, sex, race/ethnicity, marital status, income, nature of the dyadic relationship, and years of education. Older adults with ADRD will be asked to wear an actigraph (AMI Motion logger) on their non-dominant hand to monitor their sleep patterns for 4 weeks. Data from the actigraphs will be downloaded after they are returned to me. To assess for individualized music genre I will use Gerdner's (consultant) Assessment of Personal Music Preference during the screening telephone prior to the baseline in-home visit.[11] I will use the answers from this form to choose music selections in consultation with Drs. Bradt and Gerdner.

Table 4.5 summarizes each measure, source, expected time for completion and timing in relation to the trial (screening, baseline, post intervention). Total time commitment at the screening is approximately 30 minutes, 1 hour at baseline, 1 hour and 30 minutes during post intervention.

Table 4.5 Schedule of Data Collection / Measures

Domain	**Measure(s)**	**Exp. Time to complete (mins)**	**Tested when**	**Source(s)**
Feasibility	Rates of recruitment, participant attrition, reasons for excluding or declining, willingness to be randomized, appropriateness of the eligibility criteria, adherence to the intervention protocol	Integrated throughout the study timeline	Baseline Post intervention	Dyad
Acceptability	Satisfaction questionnaire (caregiver),[54,55] qualitative interviews (dyad), enjoyment question	5 (questionnaire) 20 (exit interview)	Post intervention	Dyad
Cognitive status	Mini Mental State Examination (MMSE)[65]	10	Baseline	P

Demographic characteristics	Age, sex, race/ethnicity, marital status, income, nature of the dyadic relationship, years of education	10	Baseline	Dyad, medical records (if applicable)
Depressive symptoms	Patient Health Questionnaire-9 (PHQ)[63]	10	Baseline	CG
Personalized music	Assessment of personal music preference[11]	15	Screening	P or CG
Sleep quality in dementia	Sleep disorders inventory (SDI)[46]	10	Screening, Baseline, Post intervention	P (via proxy)
Pattern of sleep/wake	Sleep diary[59]	5 per day (140 total)	Post intervention	CG
Presence of sleep disturbances	Neuropsychiatric Inventory sleep item[45]	2	Screening	CG
Sleep quality in dementia	PROMIS sleep related impairment – SF 8a[60]	10	Baseline, Post intervention	P

Notes: P- participant with ADRD, CG – caregiver

I will be responsible for the quality control of the data in collaboration with my co-sponsors. The following steps are currently in place to ensure data quality: accurate and complete instructions for completing the questionnaires, double data entry, and data auditing. Additionally, I will meet regularly with my sponsors (Hodgson & Gitlin) and Dr. Hanlon (a biostatistician and a consultant), and my mentoring team to ensure the quality of the data collected.

Potential Risks

Potential risks for the dyads who participate in this study are related to participant burden, fatigue and/or stress in response to self-report instruments or interviews, and loss of confidentiality. In addition, older adults with ADRD may experience discomfort from sleeping with the wrist actigraph. A list of the potential risks in this study and the protection against these risks are addressed below. The risks of participation in this study should be no more than minimal with effective confidentiality measures in place. There are no physical risks associated with filling out self-report measures. Some participants may get tired or feel anxious while responding to the questions. Additionally, there is a risk for failing to maintain the confidentiality of data.

Ethics of Participant Payment

Dyads will receive a $50 gift card for completing the intervention or the wait-list control condition. To calculate reimbursement, I used the Wage Payment model which operates on the notion that participation in research requires little skill but does require time and effort.[73] The payment of $50 is not sufficient to be considered coercive.

Adequacy of Protection against Risks

Recruitment and Informed Consent

Participant Recruitment. As indicated, I will use four potential sources for participant recruitment: A) the Penn Geriatrics clinic, B) Penn Alzheimer's disease clinical core (ADCC), C) a participant registry from PennSeek which contains names of over 5,000 individuals with dementia who have indicated a willingness to be contacted for future studies, and D) control group participants from my Sponsor's ongoing R01 (R01NR015226) 4 weeks after completing the study.

For the Geriatrics clinic I will have access to the patient database with address information of all potentially eligible participants (those diagnosed with ADRD) and family members/legal representatives to send them an introductory letter. The purpose of this letter is twofold. First, the letter informs the patient that he/she is a possible candidate for this study. Second, the letter provides my contact information (telephone and email) in addition to a pre-paid post card. If caregivers are interested in hearing more about the study, they may indicate their willingness to hear more about the study by calling, emailing me or returning the pre-paid post card. Once I hear back from the caregivers I will schedule a telephone call screening assent to screen for inclusion/exclusion criteria.

For the in-person clinic introductions, following verbal approval from the geriatrician and being introduced to the potential participants at the Geriatrics clinic, I will be able to screen participants prior to or after their clinic visit for inclusion/exclusion criteria. Since clinic visits may take longer than expected, I will offer the potential dyad to schedule a telephone screening phone call at a more convenient time. If the dyad is eligible and interested in participating, I will set up a time for a screening telephone assent call. Similar to the Geriatric clinic, I already have access to Penn ADCC database, where I completed my dissertation work in which I successfully enrolled 60 older adults with mild cognitive impairment using similar recruitment strategy (sending out a letter describing the purpose of my study prior to first contact with interested participants).

In order to recruit from the participant registry, which contains names of over 5,000 individuals who have indicated a willingness to be contacted for future studies, I will work to send out an introductory letter (described below) to these potential participants. Dr. Gooneratne will facilitate my access to the database. A fourth source of recruitment will come from control group participants from my Sponsor's ongoing R01 (R01NR015226) 4 weeks after completing the study. To access my sponsor's control group participants, the research staff will first seek permission from caregivers to contact them via mail. I will send invitation letters to all potential dyads (addressed to caregivers) from 4 recruitment sites detailing the purpose of the study with information on how to contact me.

Enrollment procedures.

Screening telephone assent call. During my initial telephone call with a potential dyad who expressed interest in participating, I will obtain assent for a telephone screen from the dyad. If older adult with ADRD is too cognitively impaired, I will ask to speak with the legal authorized representative (LAR) to obtain a proxy phone screening assent. I will explain to the dyad the purpose, risks and benefits, and ways to withdraw from the study. I will ask the caregiver about the presence of sleep disturbances in person with ADRD. The presence of at least one sleep disturbance of moderate severity occurring in the two weeks prior to assessment will be used as a cut-off for potential eligibility. I will ask for permission to retain the information collected during the call in a recruitment database. I will also ask questions regarding music preferences over the phone. I will reinforce with the dyad that they have the right to cancel the authorization at any time, and should do so using the contact information that I will provide. This information will aid in establishing the feasibility of the proposed study (Specific Aim 1).

Written consent. Once potential dyads express their willingness to participate and are eligible based on the screening telephone call, I will schedule an in-person meeting with the dyad. I will screen the dyad for inclusion/exclusion criteria (see Table 1). I will review the consent form with the dyad and answer any questions they have about the proposed study. The consent form will include a brief description of the study, including risks and benefits, principal investigator's contact information, and ways to withdraw from the study. The consent forms also contain Health Insurance Portability and Accountability Act (HIPAA) statements of authorization of release of medical records, thus facilitating collection of a limited clinical dataset. I will then determine older adult's ability or inability to provide informed consent. Both the CG and the person with ADRD will be asked the following five questions based on the consent form: What is the purpose of the study? What are the risks to the study? What are the benefits of the study? How to contact me, the principle investigator? How to withdraw from the study?

Ability to give consent. Assessing older adults' capacity to provide consent is an important step in the informed consent process. Older adults who can verbally provide 4 out of 5 answers correctly will be considered capable of providing their own consent.[74] I will again answer any questions they may have about the study. If they continue to agree to participate, then they will be asked to sign the last page of the consent form designating their consent to participate in the study. The dyad will receive a copy. Older adults who are eligible and agree to participate in the study will be made aware that the care that they receive from the ADCC or the Geriatrics clinic will not be affected by their participation or if they wish to withdraw from the study at any time.

Inability to give consent. For older adults who have given oral assent to participate in the study but cannot verbally provide 4 answers correctly (demonstrating the lack of cognitive ability to provide consent), I will ask for proxy consent from their LAR.

Protection against Risks

Potential risks for the dyads who participate in this study are related to burden, fatigue and/or stress in response to self-report instruments or interviews, anxiety related to music intervention, and loss of confidentiality. In addition, older adults with ADRD may experience discomfort from sleeping with the wrist actigraph. A list of the potential risks in this study and the protection against these risks are addressed below. The risks of participation in this study should be no more than minimal with effective confidentiality measures in place. There are no physical risks associated with filling out self-report measures for this study. Some participants may get tired or feel anxious while responding to the questions. Additionally, there is a risk for failing to maintain the confidentiality of data.

Risk associated with questionnaires or interviews. Dyads may get tired, fatigued and/or feel anxious while completing the questionnaires. There are no physical risks associated with completing the questionnaires or answering satisfaction questions during interviews.

Protection against risk. To avoid fatigue and distractions I will inform the dyad that they may request a break between the questionnaires if they become tired. The testing is divided into several small sections, so there will be frequent rest periods, and the testing can be continued during a follow up session. The dyad may request additional rest periods at any time. Prior to each task, the nature of the task is discussed. The study is voluntary so dyads can choose not to answer any question and have the right to withdraw if desired. Home visits will be scheduled at the most convenient time to the participants and will not take place late in the evening, when persons with ADRD may experience increased agitation and Sundowning. Interview questions are designed so that the interview will be no longer than 20 minutes in length. In the event that a negative emotional response occurs when filling out the questionnaires, the dyads will be reminded that they do not have to answer any question that they do not feel uncomfortable with and they will be provided with a break. Using standard protocol older adults will be referred to a psychiatric provider at the University of Pennsylvania Hospital experienced in treating patients with cognitive impairment and depression if older adult scores greater than 10 on the PHQ-9, indicating major depression. Importantly, if he/she expresses suicidal thoughts I will make sure that the person is safe, notify the PCP and follow up with the psychiatric provider.

Risk associated with music intervention. Some older adults with ADRD may become more agitated in response to listening to soothing music.

Protection against risk. The PI trainee in collaboration with the consultants will chose music according to older adult's preferred genre and account for music properties that are known to induce sleep (30 mins in length, 60-80 bpm, low pitch, no lyrics). Specific songs/artists indicated by older adults will not be used, as to not introduce a confounding factor of music familiarity and memories evoked by the specific song/artists which may stimulate older adults instead of having a sedative effect. The PI will then return to the home with a portable music player to play and discuss selection of 6 pieces of music. The PI will receive feedback from the dyad on the selection. If the PI receives positive feedback regarding the selection of musical pieces, the PI will demonstrate to the dyad proper instructions on how to listen to soothing music at bedtime. If older adult with ADRD shares a negative experience while listening to selected music (i.e. grimacing, crying, looking excited), the PI will reassess musical selections with the consultant and return to the home a week later with new music selections. Previous studies that used music to improve sleep did not report any adverse reactions to the music presented.[33,48]

Risk associated with the loss of confidentiality and accidental disclosure of health related information. Some health related information may be disclosed accidentally through paper records or breaches in the electronic data servers.

Protection against risk. To protect against breaches in confidentiality, identifiers will be removed from study-related information and dyads will be given a unique identification number (e.g. 001, 002). Information linking the number to the dyad will be kept in a separate locked file cabinet at the University of Pennsylvania School of Nursing, accessible only to me, and destroyed at the end of this project. For the paper based questionnaires I will place unique identification numbers, rather than participants' names, on the appropriate questionnaires. Completed questionnaires will be placed in separate, coded, and sealed envelopes and kept in a separate locked file designated for this study at the University of Pennsylvania School of Nursing. Once this data is uploaded to the secure server and double entered, paper copies will be securely destroyed. De-identified data will be encrypted and stored on a dedicated server that is log-in accessible only to the investigators and key study personnel. All de-identified data abstracted from study tools will be entered into a password protected and encrypted internet-based data management system known as REDCap (Research Electronic Data Capture). Only de-identified data (without names or medical record numbers of participants enrolled) will be entered into REDCap system. Data that are brought onto a computer for analysis purposes will be reviewed on a dedicated server that is password protected. If portable media is required (e.g. a USB drive; external hard drive), only de-identified, coded data will be entered on this drive. It will also be password protected and accessible to me and my mentors. File will be destroyed once data analysis is complete.

Risk associated with wearing an actigraph. Some participants may experience discomfort from sleeping with the wrist actigraph.

Protection against risk. Initial discomfort usually subsides after the first night. If the participant cannot tolerate the watch, he/she will be instructed that removal of the watch for short periods of time is allowed.

Potential Benefits of the Proposed Research to Human Subjects and Others

Caregivers may find the individualized music listening intervention is helpful at reducing sleep disturbances in older adults with ADRD. It is possible that while these results may benefit older adults with ADRD and their caregivers in the future, participants in this study will not realize an immediate or direct benefit from enrolling in the study. Given the minimal risks associated with this study, and the general benefit to older adults with ADRD, their families, and the research community, the overall risk to benefit ratio is favorable.

Importance of Knowledge Gained

The overall goal of this interdisciplinary research study is to examine the feasibility and acceptability of a tailored music intervention aimed to improve sleep in older adults with ADRD. Additionally, I plan to examine the preliminary efficacy of the intervention to reduce sleep disturbances in this population. This study will lead to a greater understanding of how music interventions can be delivered to older adults with ADRD living at home. Results from this study will inform future larger studies using music interventions to reduce sleep disturbances. Given the limited efficacy of pharmacological approaches to address behavioral and psychological symptoms of ADRD, which includes sleep disturbances, the results will inform the development and future testing of a widely available potentially low cost music intervention aimed to decrease sleep disturbances in the largest group living with ADRD – home-dwelling older adults and their caregivers.

Data and Safety Monitoring Plan

Trial monitoring will be done by the PI trainee and the sponsor (Dr. Hodgson). This will accompany the Trainee's fellowship goal of understanding and mastery of research ethics and the responsible conduct of research (see section B. Training Goals and Objectives included in the Applicant's background and Goals for Fellowship).

The following information will be monitored: adverse events (AEs), including serious adverse events (SAEs), unanticipated problems (UPs). SAEs in this population include, but not limited to death, hospitalization, evidence of abuse, suicidal ideation, and medical emergencies. The PI trainee (or the sponsor) will notify the IRB within 48 hours of any serious possible or potentially study-related AEs. The report will include the description of the AEs and any actions taken by the PI trainee. The PI trainee will also keep a log of all AEs. Any deviations related to the protocol will be reported to the IRB using a deviation form immediately upon the discovery of the deviation. Given the non-invasive nature of the music intervention my sponsor and I do not anticipate AEs beyond the average rate of these events in this population.

ClinicalTrials.gov requirements

Not applicable because this is a feasibility and acceptability study aimed to enrolled 60 persons with ADRD.

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CHAPTER 5: CONCLUSION

Introduction

We know little about the nature of musical abilities in persons with mild cognitive impairment (MCI), a high risk group of individuals who are more likely to convert to dementia compared to the general population (Petersen, 2004). Major gaps exist in the literature regarding the relationships between musical and cognitive abilities in persons with MCI and how musical abilities may compensate for deficits in cognitive abilities driven by the underlying pathology. The purpose of this dissertation was to examine musical abilities in persons with MCI and elucidate the role musical abilities may play in preserving cognitive abilities. In addition, based on my passion for music and a desire to expand my expertise into intervention studies, I have written and submitted a post-doctoral application to the National Institutes of Health exploring how a music intervention may help alleviate one of the most distressing behavioral and psychological symptoms of dementia – sleep disturbances.

The specific aims of purpose one of this dissertation were to: 1) determine the association between musical and cognitive abilities in older adults with MCI; 2) determine whether musical abilities moderate the relationship between hippocampal volume and cognitive abilities in persons with MCI;

To address the second purpose I developed and submitted a post-doctoral application, the purpose of which was to examine the feasibility and acceptability of an individualized music intervention to improve sleep disturbances in older adults with dementia. The specific aims of the post-doctoral application were to: 1) Examine the feasibility of processes that are key to the success of the subsequent study including rates of: adherence to the protocol, completion of the study measures, recruitment, attrition and refusal; 2) Examine the acceptability of the intervention using survey and qualitative data; and 3) Provide preliminary efficacy of the intervention on four sleep quality outcomes: a) wake time after sleep onset, b) sleep-latency onset, c) total sleep duration, and d) perceived sleep quality. This final chapter summarizers the principal findings of this research, outlines research plan for the proposed post-doctoral project, discusses the implications for clinical practice and future research.

Summary and Discussion of Principle Findings

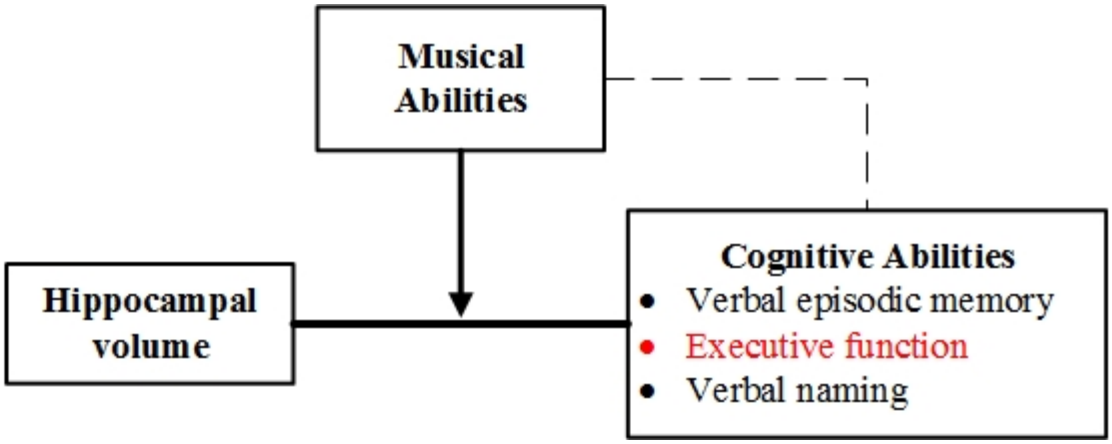
We addressed the first purpose of this dissertation in a prospective cross-sectional study with persons with MCI recruited from the University of Pennsylvania Alzheimer's Disease Core Center (ADCC). The first aim was to determine the association between musical and cognitive abilities in older adults with MCI. We defined musical abilities and operationalized musical abilities using a musical sophistication index (General Musical Sophistication Subscale) as "musical skills, expertise, achievements and related behaviors" (Müllensiefen, Gingras, Musil, & Stewart, 2014, p. 2). We found that participants who had higher scores on the index of musical abilities had lower scores on the measure of verbal naming (Boston Naming Test). Additionally, musical abilities predicted 18% of the variance in the verbal memory recognition performance. The second aim was to determine whether musical abilities moderate the relationship between hippocampal volume and cognitive abilities in persons with MCI. Musical abilities did moderate the relationship between hippocampal volume and one of the cognitive abilities – executive function (Trail Making Test B). To address the second purpose of the dissertation I developed and submitted a post-doctoral application, the purpose of which is to examine the feasibility and acceptability of an individualized music intervention to improve sleep disturbances in older adults with dementia. We present principle findings pertaining to the first and second aims as well as specific aims of the post-doctoral research application in Table 5.1.

Table 5.1 Principle Findings of Specific Aims

Purpose 1	**Chapter**	**Principle Findings**
Aim 1: Determine the association between musical and cognitive abilities in older adults with MCI	II	The participants, on average, scored lower on the index of musical abilities compared to published norms. Musical abilities were negatively associated with verbal naming. Musical abilities were not associated with age, intelligence, years of education, depressive symptoms or cognitive function. Musical abilities predicted scores on the episodic memory recognition task.
Aim 2: Determine whether musical abilities moderate the relationship between hippocampal volume and cognitive abilities in persons with MCI	III	Musical abilities negatively correlated with executive function. The higher musical abilities were the better participants scored on the executive function measure. Musical abilities modified the relationship between hippocampal volume and executive function.
Purpose 2: Post-doctoral application	**Chapter**	**Specific Aims**
Develop and submit a post-doctoral application, the purpose of which is to examine the feasibility and acceptability of an individualized music intervention to improve sleep disturbances in older adults with dementia.	IV	Aim 1: Examine the feasibility of processes that are key to the success of the subsequent study including rates of: adherence to the protocol, completion of the study measures, recruitment, attrition and refusal. Aim 2: Examine the acceptability of the intervention using survey and qualitative data. Aim 3: Provide preliminary efficacy of the intervention on four sleep quality outcomes: 1) wake time after sleep onset, 2) sleep-latency onset, 3) total sleep duration, and 4) perceived sleep quality.

Based on these findings we modified the original conceptual model (Figure 5.1). We separated executive function (Aim 2) from cognitive abilities, since musical abilities moderated the relationship between hippocampal volume and executive function, only. In the box pertaining to Aim 1 we highlighted cognitive abilities associated with musical abilities (Chapter II).

Figure 5.1 Revealed Relationships between Cognitive Abilities and Hippocampal Volume Moderated by Musical Abilities



Notes: Solid arrow represents a moderating effect of musical abilities. Dotted line denotes possible associations between musical and cognitive abilities.

We found that enhanced musical abilities may emerge as an important compensatory mechanism for persons with MCI struggling with cognitive deficits. Musical abilities, although related to some cognitive abilities, did not correlate with most cognitive measures. We also found that although musical abilities did moderate the relationship between hippocampal volume and executive function, it was not in the direction that we expected. Instead, in participants who did not report themselves as musical, executive function was negatively correlated with hippocampal volume. For participants who scored in the 90^{th} percentile on the index of musical abilities, greater hippocampal volume was associated with higher executive function. Additionally, these participants scored above the population average on the GMSS. Musical abilities not only weakened the relationship between hippocampal volume and executive function, but eventually reversed it. Taken together, the findings from this dissertation contributed to the body of scientific knowledge in four ways. First, these results added to our understanding of musical abilities in persons with MCI, where previous research efforts primarily targeted people with dementia. Second, the findings helped elucidate the relationship between musical and cognitive abilities in this population. Third, to our knowledge this was the first study to suggest that musical abilities modified a relationship between a biological disease marker and executive function. Lastly, the findings from this dissertation increased my interest in developing music interventions for older adults with dementia. Therefore, I have submitted a post-doctoral application to the National Institute of Health to examine the efficacy of music interventions in older persons with dementia.

Prior to this dissertation, musical abilities in persons with MCI were largely unexplored. Previous research found that persons with MCI do not differ from older adults with early AD and normal cognition in assigning emotion expressions (happy, sad, or unsure) to musical experts (Kerer et al., 2014). On the other hand, compared to cognitively normal older adults, persons with MCI did worse on the measures of verbal music memory (Kerer et al., 2013). These findings are not surprising, since verbal music memory relies heavily on episodic memory and language, cognitive abilities that are often impaired in MCI (Petersen, 2004). In our study, persons with MCI scored lower on musical abilities (general musical sophistication subscale) compared to the published norms (Müllensiefen, Gingras, Stewart, & Musil, 2014). We cannot definitively conclude that less musical skills in persons with MCI are unique to MCI. As discussed earlier (see Chapter II), activities contributing to enhanced musical abilities may decline as one ages (Müllensiefen, Gingras, Musil, et al., 2014). Alternatively, persons with MCI may disengage from music due to the self-awareness of their cognitive deficits. This dissertation provided additional knowledge on the nature of musical abilities in persons with MCI.

Our findings suggest that musical abilities are negatively associated with verbal naming (Chapter II). At first, these results may seem contradictory to previous studies of music training benefits in older adults (Gooding, Abner, Jicha, Kryscio, & Schmitt, 2014; Hanna-Pladdy & Gajewski, 2012; Hanna-Pladdy & MacKay, 2011). The differences may be due to the measurement differences of musical abilities. In our study we chose to use a self-report questionnaire aimed to gauge a broad spectrum of musical abilities. Gooding et al. (2014) examined musical training using a non-validated self-reported musical experience questionnaire and an objective test of musical knowledge in healthy older adults. The team found that formal musical training is associated with enhanced episodic memory, but not improved verbal naming (Gooding et al., 2014). Previous studies also used an arbitrary chosen marker for being a musician (Hanna-Pladdy & Gajewski, 2012; Hanna-Pladdy & MacKay, 2011). Instead, our study used a continuous measure of musical abilities, general musical sophistication subscale, in persons with MCI with diverse music experiences. Our findings suggest that older adults with MCI may compensate for their deficits in memory by engaging in activities that are less reliant on memory and language. For some individuals, these activities may involve music. The body of work reported here expanded on the relationship between musical and cognitive abilities in persons with MCI across the continuum of musical abilities.

The findings from the second aim (Chapter III) suggested that musical abilities modified a relationship between hippocampal volume and executive function taking into account age, gender, years of education, intelligence, depression and comorbidities. As described in Chapter III, previous research has shown the moderating effects of education (Bennett, Schneider, Wilson, Bienias, & Arnold, 2005; Bennett et al., 2003), social networks (Bennett, Schneider, Tang, Arnold, & Wilson, 2006), perceptual speed (Boyle, Wilson, Schneider, Bienias, & Bennett, 2008) and purpose in life (Boyle et al., 2012) on the relation between the underlying disease pathology and cognitive function. The findings of this dissertation not only added insight to this line of research, but also contributed to our understanding of the relationship between musical abilities and executive function in older adults with MCI.

Another immediate outcome of this dissertation work was the development and submission of a post-doctoral application to the National Institutes of Health. Sleep disturbances are common amongst older adults living with dementia (Deschenes & McCurry, 2009; Vitiello & Borson, 2001). Sleep disturbances are associated with dementia pathology (Spira, Chen-Edinboro, Wu, & Yaffe, 2014), poor cognitive function (Scullin & Bliwise, 2015) and may worsen behavioral symptoms in dementia (Garcia-Alberca et al., 2013; Porter, Buxton, & Avidan, 2015) contributing to increased institutionalization (Pollak, Perlick, Linsner, Wenston, & Hsieh, 1990). Given the relationship between musical and cognitive abilities, music may be an effective intervention for reducing sleep disturbances in older adults with dementia. Although this post-doctoral work will not focus on musical abilities in persons with MCI, the findings of the first two aims of this dissertation plus my passion for music and building my expertise in intervention research, directly influenced the direction for future research and training related to clinical trial methodology. A feasibility clinical trial proposed in

Chapter IV will serve as a first step in a career trajectory focused on the efficacy of music in improving the well-being of older adults with dementia and their caregivers.

Implications for Clinical Practice

This body of work has important implications for clinical practice and public health. Given recent emphasis on tailoring non-pharmacological interventions for older adults with cognitive impairment (Gitlin, Hodgson, & Choi, 2016; Kolanowski, Litaker, & Buettner, 2005), music has several characteristics that can be individualized to persons' likes and dislikes, racial and ethnic background. These characteristics include the genre of music, tempo, and the presence or absence of lyrics. Our work highlights the range of musical abilities in older adults with MCI. Nearly 40% of the sample in our study have played or currently play an instrument, indicating that music activities may be an appropriate activity for these individuals. What about individuals with no prior musical interests? Although music can be an effective intervention even for those older adults with dementia who had no prior musical training (Sarkamo et al., 2016), music interventions can be particularly helpful for older adults with some prior music background because of the match with the individual's background. Persons with MCI pursuing cognitively stimulating activities may be able to reduce their risk of progressing to dementia (Wilson, Scherr, Schneider, Tang, & Bennett, 2007). Music interventions have the potential to be an effective personalized therapy for these individuals.

Given the associations between music and cognitive abilities, the question remains as to which music activity is the most effective at maintaining cognition in persons with MCI. Our findings suggest that musical abilities moderates a relationship between the underlying hippocampal changes in the brain and executive function.

Musical training is a major contributor to enhanced musical abilities, therefore we can hypothesize that musical training had the biggest influence in moderating this relationship. If this is true, encouraging older adults with MCI to pursue music experiences in any capacity later in life is a worthy pursuit.

Implications for Future Research

The results of this body of work demonstrated the need for further research in the area of musical abilities in persons with MCI and dementia. Larger longitudinal studies in well-described samples of older adults with MCI will be required to determine the course of musical abilities in these individuals. Examining the changes in musical abilities will confirm previous studies suggesting the preservation of musical abilities in dementia. Furthermore, this knowledge may contribute to a more accurate MCI diagnosis and risk of conversion to dementia.

Future studies should delineate which of the musical activities outside of musical training are beneficial for persons with MCI and dementia. For example, it could be the case that participating in community-based music activities may be just as beneficial at maintaining cognition as playing a musical instrument. Furthermore, exploring the mechanism(s) behind the benefits of engaging in music should be explored.

Lastly, music interventions aimed at persons with MCI are needed to improve the well-being and maintain cognitive function of older adults with MCI. Individuals with MCI face uncertainty regarding their diagnosis and the trajectory of the disease progression. Music interventions may be helpful in maintaining cognitive function and compensating for memory deficits. Music interventions have the ability to be highly individualized to the person's background and interests.

APPENDIX A: FREQUENCY OF RESPONSES ON THE MUSICAL SOPHISTICATION INDEX (GOLD-MSI; N=60)

Question	**Response frequency (%)**		
	Disagree	**Neither Agree nor Disagree**	**Agree**
1. *I spend a lot of my free time doing music-related activities.	26.0	20.0	**53.3**
2. I sometimes choose music that can trigger shivers down my spine.	**60.0**	15.0	25.0
3. *I enjoy writing about music, for example on blogs and forums.	**76.7**	15.0	8.3
4. *If somebody starts singing a song I don't know, I can usually join in.	**50.0**	23.3	26.7
5. I am able to judge whether someone is a good singer or not.	13.3	6.7	**80.0**
6. I usually know when I'm hearing a song for the first time.	8.3	8.3	**83.3**
7. *I can sing or play music from memory.	41.7	5.0	**53.3**
8. I'm intrigued by musical styles I'm not familiar with and want to find out more.	38.3	20.0	**41.7**
9. Pieces of music rarely evoke emotions for me.	21.7	10.0	**68.3**
10. *I am able to hit the right notes when I sing along with a recording.	30.0	23.3	**46.7**
11. I find it difficult to spot mistakes in a performance of a song even if I know the tune.	27.1	15.3	**57.6**
12. *I can compare and discuss differences between two performances or versions of the same piece of music.	28.3	20.0	**51.7**
13. I have trouble recognizing a familiar song when played in a different way or by a different performer.	10.0	18.3	**71.7**
14. *I have never been complimented for my talents as a musical performer.	**60.0**	8.3	31.7
15. *I often read or search the internet for things related to music.	**60.0**	10.0	30.0
16. I often pick certain music to motivate or excite me.	18.3	13.3	**68.3**
17. *I am not able to sing in harmony when somebody is singing a familiar tune.	**46.7**	13.3	40.0
18. I can tell when people sing or play out of time with the beat.	15.0	15.0	**70.0**
19. *I am able to identify what is special about a given musical piece.	21.7	15.0	**63.3**
20. I am able to talk about the emotions that a piece of music evokes for me.	10.0	11.7	**78.3**
21. I don't spend much of my disposable income on music.	**65.0**	11.7	23.3
22. I can tell when people sing or play out of tune.	8.3	15.0	**76.7**
23. *When I sing, I have no idea whether I'm in tune or not.	35.0	8.3	**56.7**
24. *Music is kind of an addiction for me - I couldn't live without it.	33.3	10.0	**56.7**
25. *I don't like singing in public because I'm afraid that I would sing wrong notes.	**46.7**	21.7	31.7
26. When I hear a piece of music I can usually identify its genre.	26.7	16.7	**56.7**
27. *I would not consider myself a musician.	**80.0**	6.7	13.3

28. I keep track of new music that I come across (e.g. new artists or recordings).	**58.3**	15.0	26.7
29. *After hearing a new song two or three times, I can usually sing it by myself.	**51.7**	23.3	25.0
30. I only need to hear a new tune once and I can sing it back hours later.	**78.3**	10.0	11.7
31. Music can evoke my memories of past people and places.	3.3	1.7	**95.0**
32. *I engaged in regular, daily practice of a musical instrument (including voice) for _____ years.	0 year 1-9 years 10+ years	**48.3** 35.0 16.7	
33. *At the peak of my interest, I practiced ________ hours per day on my primary instrument.	0 year 0.5-1 year 1.5-5+ years	**41.7** 35.0 23.4	
34. I have attended _______ live music events as an audience member in the past twelve months.	0-1 2-3 4-6 7-11+	**36.7** 13.4 15.0 35.0	
35. I have had formal training in music theory for ______ years.	0 year 0.5-7+ years	**78.3** 21.7	
36. I have had _______ years of formal training on a musical instrument (including voice) during my lifetime.	0 year 0.5-2 years 3-10+ years	**45.0** 21.6 33.4	
37. *I can play _______ musical instruments.	0 1 2-3 6+	**70.0** 18.3 10.0 1.7	
38. I listen attentively to music for _________ per day.	0-15 min 15-30 min 30-60 min 60-90 min 2 hours 2-3 hours 4+ hours	28.3 15.0 **33.3** 11.7 3.3 5.0 3.3	
39. The instrument I play best (including voice) is_____ a. None b. Piano c. Voice d. Guitar e. Others (Drums, percussion, snare drum, trombone, whistle)	 **63** 15 8 5 10		

Notes: Original index responses for questions 1-31 are: Completely Disagree; Strongly Disagree; Disagree: Neither Agree nor Disagree; Agree; Strongly Agree; Completely Agree. Bolded are the most frequent response for each question. The total percentage for each question is greater than 100% due to rounding error. * denotes 18 items on the index belonging to general musical sophistication subscale.

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