HEALING MINDS THROUGH MUSIC

by

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ABSTRACT

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In 2015, 11.6% of all recorded deaths in the world were caused by dementia ("Dementia Now Leading Cause of Death," 2016). However, the progression of dementia can potentially be slowed down by providing mental stimulation through music enrichment programs. Two distinct forms of memory have been studied in dementia patients, semantic memory and episodic memory. Semantic memory of music was found to be largely preserved, while episodic memories underwent a significant decline (Tulving, 1972). At the cellular level, symptoms of dementia include altered levels of gray and white matter, decrease in overall volume of structures within the brain, formation of neurofibrillary tangles and senile plaques, and a reduction in dopamine levels (Yang et al., 2010; Raz, 2005; Guo et al., 2016; Chui et al., 1984; Anderton, 1997; Cross et al., 1981). It was found that participation in music sessions lessened the severity of several of these processes. Thus, this research will explore how exposure to music can potentially increase memory retention, slow down neural atrophy, and as a result, have a likely effect on the progression of dementia.

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Part I: Introduction

When I first met Andrew during our music sessions, he was extremely reserved and refused to make eye contact. He barely even spoke with his family members or the staff members of the nursing home he was in. Andrew was suffering from severe Alzheimer's disease. Members of our team would approach him individually and try to find something he could relate to so we could get him engaged. We began to perform Elvis Presley's famous song, "Can't Help Falling in Love," and he instantly perked up. He looked directly at us musicians, his eyes lit up, and we could see a small sliver of a smile. By the end of the song, we could see him softly singing along to himself. We moved on to a guitar instrument demonstration, where the musician held down the strings to produce a G major chord and the participant strummed the strings. Once again, Andrew initially refused to participate. With the assistance of a staff member, we gently took his hand and had him strum the strings. We repeated this activity a few times with different chords so that together we created a chord progression. He eventually realized what he was doing, and we could tell by observing his facial expressions that he was becoming more and more present. We explained to him that he was learning how to play the guitar and doing an excellent job, and once again, we could see a small sliver of a smile appear at the corner of this mouth. After the session ended, one of the staff members told us that they had never seen him make eye contact, let alone remain focused on a single activity for several minutes and give a smile. They conveyed this instance to his family, who began to come to our sessions regularly to see this unfold for themselves. The first time they saw Andrew respond positively to our sessions, his family members were in tears. They thought there was no hope, and that Andrew's condition would continue to progress rapidly until they lost him completely. Little did they know that music had the power to heal.

There are currently about 44 million people in the world living with some sort of dementia. Dementia itself is not an actual disease, rather it is an umbrella term referring to any neurodegenerative disease causing a decline in cognitive function severe enough that it interferes with an individual's daily life. The most common form of dementia is Alzheimer's disease (AD). There are currently over five million Americans living with this disease, and it is the sixth leading cause of death in the United States. Out of the top ten leading causes of death in the United States, it is the only one with no cure. Common symptoms of dementia include memory loss, inability to communicate, and changes in behavior and personality ("2017 Alzheimer's Statistics," n.d.). At a very simplified level, this condition results from neural atrophy, or neurons dying out, which causes synapses within the brain to be lost and an overall decline in cognitive ability (Anderton, 1997).

Although there is no definitive cure for dementia, numerous studies have provided enough data to hypothesize that providing mental stimulation to the brain can affect the intensity of its progression. Mental stimulation encourages the continuing formation of synapses and prevents neurons from dying out as fast as they typically would (Anderton, 1997). Music therapy is an excellent method of providing this mental stimulation. Whether this includes learning musical terms, learning a musical instrument, singing along with musicians, or simply listening to one's favorite song, the results are just as rewarding (Thaut, 2005). These results are apparent on both the behavioral and cellular level. Typical symptoms of dementia include agitated behavior and decreased fluidity in motor movement ("What is Dementia?" 2017). At a cellular level, a reduction in several brain structures is very prominent, along with the formation of neurofibrillary tangles and senile plaques (Raz, 2005; Anderton, 1997). Dopamine (DA) is also produced at a much lower frequency (Cross, Crow, Perry, E. K., Perry, R. H., Blessed, & Tomlinson, 1981). Through this research, the effects of music therapy on reducing severity of symptoms in dementia will be examined. A literature review will be conducted to analyze various investigations and form an overall conclusion on how music therapy can be used as an effective method of treating patients with dementia and other related neurodegenerative diseases.

Part II: Memory

Semantic vs. Episodic Memory

Different types of information are recalled from different forms of memory. Each of these memory forms is affected differently with the onset of dementia. Even then, each memory form is affected differently depending on the type of dementia the individual has. Two forms of memory which have been closely studied in dementia patients are episodic memory and semantic memory. Episodic memory refers to memory for information from specific events in time, such as an individual's graduation from high school. In a musical context, this can refer to something like the name of a song heard on the radio earlier in the day. Often times, episodic memories are stored as an addition to another episodic memory which already exists. Therefore, this form of memory is extremely susceptible to modification and loss of information (Tulving, 1972). As a result, this is one of the most significantly impaired memory forms in AD patients.

Semantic memory on the other hand, refers to identifying information based on life events or inherent knowledge, which includes facts, information, how they relate to one another, and how this information can be manipulated. It can be seen as an accumulation of events that has been encountered so many times, the specific details pertaining to the occurrences can no longer be recovered. This knowledge is more ingrained within the individual and is organized in networks known as nodes, which connect to one another through associative pathways (Hultsch, Hertzog, Dizon, & Small, 1998). Once a node is activated, it spreads throughout these pathways, which in turn activate other related memories (Neely, 1991). When an individual references something from their semantic memory, it is as if they are referring to a mental encyclopedia of information. Semantic memory is much less susceptible to change and loss of information. Individuals usually have more information stored as memories in this form than they are aware of. Language and recollection of all words and symbols is an example of information stored as semantic memory. Regardless of all differences between semantic and episodic memory, it is important to note that it is often difficult to categorize memories an individual recalls on an everyday basis as semantic or episodic, since most of these memories contain characteristics of both memory forms (Tulving, 1972). However, the majority of tasks given to individuals in experiments used to study the effects of dementia on episodic and semantic memory can be distinctly categorized into one of the two memory types.

Although episodic memory is significantly impaired in AD patients, semantic memory has been found to be largely preserved during initial stages of the disease, and even in later stages in some cases. There are certain elements of music which fall explicitly under the category of semantic memory. One of the most evident is the concept of melody. In direct musical terms, this refers to "…a linear succession of musical tones that is perceived as a single entity" (Randel, 2003). However, the term can also be applied to the pattern of ascending and descending notes in a musical piece (Peretz, 1990). Still, the term "melody" can be used solely for referencing a song. Despite the precise meaning behind the use of the term, melody has been one of the most pivotal elements of study in musical semantic memory. Other elements in this category include musical instruments and their associated sounds, in addition to the emotions a piece of music conveys. The ability to recognize the emotional significance of a piece has not always been observed as a retained process in dementia patients. Research on this has garnered mixed results (Omar, Hailstone, & Warren, 2012). While this process is relatively preserved in AD patients, Matthews, Chang, De May, Engstrom, and Miller (2009) have shown that it is impaired in other forms of dementia, including frontotemporal dementia, semantic dementia (SemD), and any other diseases which are associated with degradation of the frontotemporal lobar region of the brain. However, in the case study that Matthews et al. (2009) conducted, the ability to experience pleasure while listening to music was preserved in their subject, who had auditory aphasia, which is a neurodegenerative disease characterized by damage to both temporal lobes and the inability to recognize words and familiar music (Matthews et al., 2009).

In individuals with musical knowledge, music theory and musical notation can also be included as part of semantic memory, as this information comprises the language component of music (Omar et al., 2012). A female patient with SemD demonstrated retained knowledge of information on musical structure in the Western field, such as how to compose a musical phrase. As it turns out, the patient never had any formal music training, but listened and sang along to music for several hours a day, enough to familiarize herself with its basic framework. It can be observed that this information was preserved as implicit knowledge regardless of the onset of SemD (Hailstone, Omar, & Warren, 2009). For seasoned musicians, this information is the foundation of their technique, so it is considered to be a vital part of their implicit knowledge (Omar et al., 2012). This is the same category of information that language is included in (Tulving, 1972). It is important to note that such knowledge is only considered to be a part of semantic memory if the individual has had formal musical training or extensive exposure to music.

Processing of Semantic Memory

Categorization is a key component to semantic memory processing. This is the process through which we group together and label objects or ideas with similar characteristics. For example, from a young age, we are taught that flying animals with beaks and two legs are known as "birds." For the rest of our lives, we continue to group animals with those characteristics into the category of "birds" (Koenig & Grossman, 2007). There are two processes which are fundamental to processing semantic memory: the identification of objects and ideas by their appearance, functions, definition, etc., and being able to assess this knowledge to make comparisons among different categories. The first process is similarity-based, and the second process is rule-based (Smith, Patalano, & Jonides, 1998). Similarity-based observations are instantaneous and require little effort. Rule-based processes, however, require working memory and more thought overall (Koenig & Grossman, 2007).

Koenig and Grossman (2007) provide a great example of the application of these two processes. A 45-year-old police officer is observed strictly disciplining her grandchild. The observer states that this police officer is "not what one usually thinks of as a grandmother." By using this statement, it is clear that the observer is utilizing both processes of semantic memory. They are using their physical and behavioral observations to identify the individual as a 45-year-old police officer and applying this information to make a comparison on how one would typically imagine a grandmother to be: elderly, good-natured, and eager to spoil her grandchildren. Both rule- and similarity-based observations are being made in this situation.

From this information, it can be determined that memory impairments are due to malfunctioning in either of the two components of memory processing. For instance, if an individual categorizes an apple as a vegetable, this could be a result of one of two possibilities. They could have lost information about the characteristics of an apple, thus not being able to categorize it by its similarities to other fruits, or they could have also been aware of the general characteristics of an apple, but were unable to apply this information to conclude that an apple is categorized as a fruit instead of a vegetable (Koenig & Grossman, 2007).

Memory Retention in Healthy Older Adults

Just as how certain memory forms are retained to a larger extent than others in dementia patients, the same concept applies to healthy older adults. Implicit memory forms have not been observed to have a substantial difference across different age groups. This form of memory refers to the feeling of familiarity associated with general experiences from the past, as opposed to recollection of a specific event. The experiences from the past are used as an aid to process the experience currently on hand through a process known as priming. This process relates to semantic memory processing and has been tested through various methods of examination. A very common method of testing this is through stem completion. Participants are presented with the stem of a word, such as “con_,” and asked to complete it with the first word that comes to mind. Exposure to the previous completion of a word increases the likelihood of its repeated generation over generation of a word which was not seen prior. This example demonstrates an example of the effects of priming, which in turn demonstrates an example of the use of implicit memory. Use of semantic memory is also demonstrated in this example, as all words have been seen before, and it is not the knowledge of the words themselves which are being tested, but rather the individual’s ability to complete the stem of the word with a word that was either previously seen or completely new (Hultsch et al., 1998).

Mitchell (1993) conducted a study in which a meta-analysis on aging studies indicated that younger adults performed higher on explicit memory tasks, while there was no significant difference in performance of implicit memory tasks between younger and older adults. In fact, statistical significance of age differences on the implicit memory tasks was never reached. A handful of studies have been found where younger adults perform higher when presented with verbally based implicit memory tasks (Light, LaVoie, Valencia-Laver, Owens, & Mead, 1992), but such data is not enough to draw any significant conclusions. Thus, it can be observed that information stored in implicit memory is minimally harmed as an individual ages.

Semantic memory has also been found to be relatively well preserved as an individual ages. Hultsch et al. (1998) examined different branches of research pertaining to this memory form, including word meaning and factual knowledge, and how they are each individually affected. The meaning of words, recognition of vocabulary words, and pictures of words have all demonstrated minimal deterioration when tested. Organization of nodes within the semantic memory network is extremely similar between younger and older adults. In addition, all age groups of adults have demonstrated high performance in word association tasks, such as responding with words in the same grammatical class rather than words more closely related to the stimulus.

More complex tasks investigating the same idea have also shown similar results. In an experiment conducted by Nebes and Brady (1988), healthy adults and AD patients were given a concrete subject and a series of words relating to the subject’s physical features and functions and told to decide whether or not the word was related to the subject. Results indicated that the AD patients were not disproportionately less accurate in assessing the words in comparison to the healthy adults. Semantic priming has also been observed to be just as strong in older adults as in younger adults. In a pronunciation task led by Balota and Duchek (1988) between older adults and younger adults, participants were given a word and then cued to pronounce the word out loud after several delays. Based on the results, it was inferred that the activation process for recalling the words was comparable between both the older adults and younger adults. Despite the retrieval process of semantic knowledge remaining intact, retrieval of this information has been found to be slower and overall more difficult in older adults. Younger adults are able to access semantic information much more quick. Older adults also frequently experience episodes where a word or fact is unavailable in the moment that they need it, but remembered at a later time (Balota & Duchek, 1988).

Episodic memory has been observed to have the most significant decline in function as an individual ages. Hultsch et al. (1998) compiled a list of all the possible explanations for decline in episodic memory. Older adults process information differently than younger adults. This includes a limited ability to initiate recollection of memories, as well as weakened ability to encode and retrieve semantic information. In addition, older adults have reductions in information processing speed and attentional capacity, which further contribute to weaker working memory. Older adults are also exposed to less stimulating environments which do not demand extensive use of memory recollection nor large-scale use of cognitive function. Lack of use of these processes may contribute to their eventual decline (Hultsch et al., 1998).

Memory Processing in Dementia Patients vs. Healthy Adults

In a study conducted by Grossman et al. (2003), differences in categorization between healthy participants and patients with AD and frontotemporal dementia (FTD) were tested. Participants were presented with the description of an object, such as “a round object three inches in diameter,” and asked to place it in one of two categories, which were “pizzas” or “quarters” in this case. One of the categories contained features which could change, such as the size of a pizza, while the other one had fixed features which would always be consistent, such as the size of a quarter. In this condition, which assessed similarity-based memory, participants were instructed to place the object description into the category which it more closely resembled, though in reality the description was an intermediate between both categories, as quarters are not three inches in diameter and a pizza is usually larger than this.

In the second condition, which assessed rule-based memory, participants were given the same descriptions as in the first condition, but with an additional phrase to provide for a more detailed description, such as “a round object three inches in diameter found in arcades.” They were also provided with two categories as in the first condition, but informed that only one of them was correct. Results indicated that the control and experimental groups performed very closely in the first condition testing similarity-based memory. In the second condition, however, judgement within the AD and FTD participants was significantly impaired. Therefore, it can be concluded from this study that the rule-based component of semantic memory requires a higher order thought process which is impaired in certain types of dementia patients (Grossman et al., 2003).

While the study conducted by Grossman et al. (2003) provided important data, further evidence is required to conclude that the dementia patients did not perform poorly on the rule-based memory tasks as a result of lack of content knowledge about the categories, which in this case were pizza and quarters. In addition, the participants may have been exposed to the categories unequal amounts of time, which would result in different levels of familiarity. The only way to counteract this issue was to expose participants to a novel category. The researchers emphasize that several previous studies testing similar ideas had participants acquire knowledge about useless information such as dot patterns and geometric figures. For this study however, it was ensured that participants would be forming categories on topics which are naturally categorized over the course of one's life.

Participants were presented with 64 realistic looking animals with different combinations of six possible features with two values each, such as straight or curly tail, and long or short snout. One animal was chosen at random to be the prototype and four of its features were chosen to be the prototypical features. If any of the remaining animals had at least three of the four prototypical features, it was classified as a member. If an animal had only one feature, it was classified as a high-distortion animal, and if an animal had exactly two features, it was classified as a low-distortion animal (see Figure 1). As in the previous experiment, participants were presented with two conditions, a similarity-based condition and a rule-based condition. They were introduced to an animal known as a "crutter," which was the prototype. For the similarity-based condition, participants were shown a pair of animals, one which was a member and one which was in the high-distortion category. The crutter was also shown in this condition, and participants were asked to select which animal more closely resembled the crutter. For the rule-based condition, participants were still shown a pair of animals with one being a member and the other being in the high-distortion category, but instead of being shown the crutter itself, they were shown outlines of the four characteristics signifying the crutter (see Figure 2). Participants were asked again which animal from the pair more closely resembled the crutter. In order to ensure that participants' responses were a result of semantic memory as opposed to episodic memory, they were shown what the prototype looked like at the end of their training session.

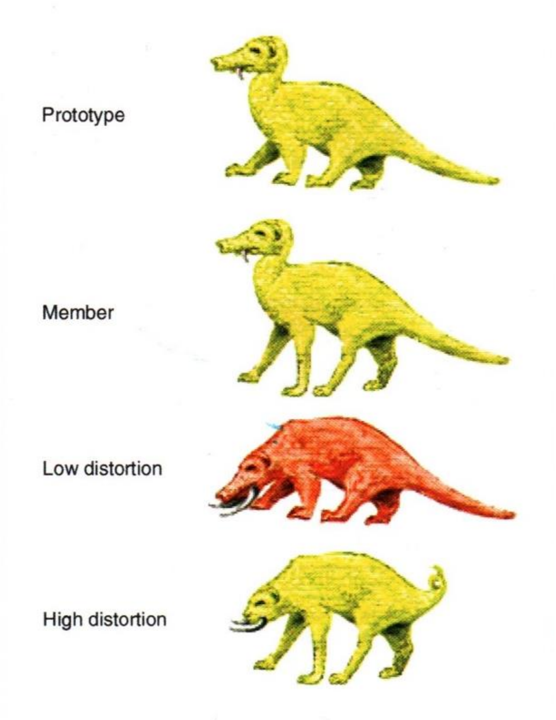

Figure 1: Samples of the stimuli presented. Reprinted from "Process and Content in Semantic Memory (pg. 253), by P. Koenig and M. Grossman, 2007, New York: Cambridge University Press.

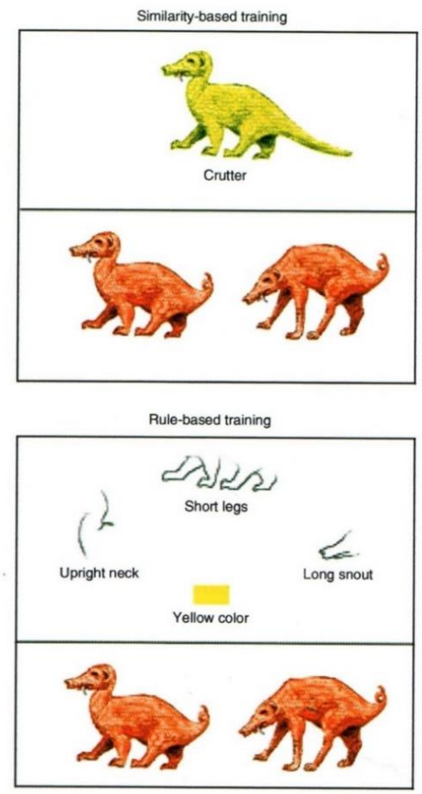

Figure 2: Samples from training trial. Reprinted from "Process and Content in Semantic Memory (pg. 254), by P. Koenig and M. Grossman, 2007, New York: Cambridge University

Participants for this study consisted of 17 patients with AD and 6 patients with SemD. The investigators further split the AD patients into two categories, one with 8 patients who demonstrated impaired semantic memory, and another with 9 patients who demonstrated average functioning of semantic memory. Results indicated that all four groups performed very closely for the similarity-based categorization. No significant differences were observed between the healthy older adult group, the SemD group, the AD group with impaired semantic memory, or the AD group with normal functioning semantic memory. With rule-based categorization however, the healthy control group demonstrated the highest scores and a proficient ability to make judgements based on rule-based categorization. SemD patients and AD patients with normal functioning semantic memory were able to apply rule-based categorization to a certain extent. AD patients with impaired semantic memory were unable to demonstrate any functioning of rule-based categorization. Thus, this study provides ample evidence to suggest that SemD patients still retain some ability to apply knowledge to information that they already know, while AD patients with impaired semantic memory do not possess the ability whatsoever.

It also provides enough information to draw conclusions on the differences in memory functioning between SemD patients and AD patients. With SemD patients, information that was once familiar can be retaught, although the information may not be retained for a long period of time (Graham, Patterson, Pratt, & Hodges, 1999). This uses mental processes similar to presenting new ideas and providing explicit ways in which they can be categorized. The key component of memory recall in SemD patients is to have content knowledge available, or background information about the concept in question. With AD patients on the other hand, individuals who performed highly on tasks measuring overall executive function, such as working memory, attention, and inhibitory control, also performed highly in identifying crutters according to rule-based categorization, but not similarity-based categorization. Therefore, even when related information to an idea is present, AD patients with deficits in categorization were unable to use the information to identify the concept, which was a crutter in this case. With episodic memory, no such correlation was found, as this is one of the most signature impairments of the disease. Overall, from this study it can be observed that in AD patients the main deficiency lies in lack of function of executive abilities, and in SemD patients the main deficiency lies in inability to access knowledge from the past (Grossman et al., 2003).

Part III. Effects of Music Therapy on Memory

It is apparent that semantic memory is overall better preserved than episodic memory in dementia patients. However, there are certain forms of cognitive stimulation which dementia patients can engage in to further increase their memory retention. One of these is music therapy and exposure to familiar pieces of music. It has been hypothesized that music provides dementia patients with enough mental stimulation to potentially alter the progression of their disease. In fact, it is when dementia patients do not actively exercise their mental capabilities that the disease rapidly progresses. In this section, the effects of different forms of music therapy will be assessed to observe how they affect different memory tasks in patients with varying forms of dementia and differing levels of severity.

Models for Assessing the Effects of Music Therapy

A model has been developed in order to organize all the levels of ways in which music can alter behavior and possess therapeutic applications. It highlights the linkage between music and therapy. This model is known as the Rational-Scientific Mediating Model (R-SMM) of music in therapy and medicine. This model does not provide insight on the specific mechanisms needed to extract the therapeutic qualities from music, but rather gives information on how to uncover the precise information needed and knowledge required to theorize music as a form of medicine. The R-SMM was established based on the idea that the physiological, neurological, and psychological foundations of the perception of music are what comprise the scientific basis of music as a form of therapy. As a result, the model is structured around four primary steps for investigation. The first step is musical response models, which involves studying the physiological, neurological, and psychological effects derived from music. The second step involves the same ideas as the first step, but focuses on parallel models of nonmusical areas, including the physiological, neurological, and psychological processes which occur as a result of nonmusical influences. Step three involves the exploration of the effects on the nonmusical brain and overall behavior function taking place because of the processes studied in step two. The final step involves the comparison of all data collected from the three previous steps to form general conclusions on how music can provide therapeutic effects for individuals. The R-SMM is relevant because it is the first scientific model demonstrating the potentially beneficial role of music therapy, which has allowed researchers to compare the effects of rhythm and music on the nonmusical brain and study it as a form of rehabilitation. This model is extremely dynamic, enabling the establishment of novel ideas and for the physiological and psychological effects of music perception to be generalized to the overall workings of brain (Thaut, 2005).

All forms of music therapy can be categorized into one of four categories of neurologic music therapy (NMT), which is a concept derived from conclusions made from the R-SMM. The first category is neuroscience-guided rehabilitation, which consists of rehabilitation plans created from data and research on the workings of the brain and clinical trials. The second category involves learning and training models, which provides methods for therapeutically enhancing cognitive function, speech, and language, in addition to improving rhythmic motor skills. The third category focuses more on the intricate foundations of music, including its rhythmic organization, diverse language network, and information on how these work together to create complex neural patterns which are depicted through cortical plasticity models. The final category of this system examines the multimodal sensory information perceived through all forms of the senses to create motor, speech, language, and cognitive function. This information is organized into neurological facilitation models, which are then tested in experiments (Thaut, 2005).

Different Forms of Memory

It is often assumed that the music presented to dementia patients should be simplistic in nature, especially in later stages of the disease when cognitive abilities begin to decline. This is not the case though, as certain aspects of music which are already present will not be lost, particularly those which are stored as semantic knowledge, since this form of memory is retained even into the later stages of dementia. Some of this semantic musical knowledge may include intact lyrics and harmonies which the dementia patient grew up listening to. Measurement of response is another significant method of assessing the effects of music therapy. In early stages of dementia, most patients are able to garner a verbal response. As patients move into the later stages of the disease, their responses may become more symbolic in nature. Even in the most severe stages, symbolism is still relevant, although in some cases, lack of response can still be very meaningful (Halpern, 2012).

Vanstone et al. (2012) investigated retention of the musical lexicon in early- to middle-staged AD patients. The musical lexicon is comprised of semantic memories. It was found that this is largely retained in the participants they investigated, unlike episodic memories. This experiment very closely resembled another experiment previously conducted by Halpern and O'Connor (2000). Participants consisted of three groups: a control group of 40 older adults (OA) and 35 younger adults (YA), and an experimental group of 10 AD patients with mild to moderate severity. The younger adults were 18-23 years in age, the older adults were 65-88 years in age, and the AD patients were 58-89 years in age. Both control groups were screened for depressive symptoms and no participants in either group revealed any significant symptoms.

Participants were given two tests, the first of which tested recognition memory and pleasantness ratings for studied unfamiliar memories. Sixteen melodies were shortened to about five seconds long and rearranged so that they still had the same style but were not recognizable. The melodies were split into List A and List B, both of which contained eight melodies. Participants were randomly assigned to List A or B. The melodies in each list were presented to the individual being tested three times, with each time being referred to as a block. The melodies in each block were presented in one of three different orders, and each participant received a different order of the three blocks. Participants were instructed to listen to the melodies very carefully, as they would be tested on their ability to recognize them. A test trial was presented with 16 melodies total, eight from the list they studied and eight foils from the list they did not study. Participants were asked to rate the pleasantness of the melody on a scale of 1-5 and answer with "yes" or "no" on whether they had heard the melody before.

Participants were also tested on their familiarity with traditional melodies through the Familiarity Decision Test (FDT). Through this test, they were presented with 10 familiar melodies and 10 unfamiliar melodies and were instructed to assess whether the melody was familiar or not with a "yes" or "no." Familiar melodies were selected from a repertoire of melodies popular in North America and unfamiliar melodies were manually distorted versions of familiar melodies created specifically for this experiment. The unfamiliar melodies differed from the ones used in the previous test, ensuring that it was the first time all participants had heard the melodies. Procedures were conducted in a quiet room at the university or at the participant's place of residence. Through these methods, three different types of memory were targeted. Explicit memory was studied with the recognition tasks, which refers to memory that an individual works to consciously recall. Implicit memory was studied with the pleasantness rating, which refers to melodies which an individual can recall subconsciously with minimal effort, and semantic memory was tested with the FDT (Tulving, 1972; Vanstone et al., 2012).

When participants were tested on stating whether or not a melody had been presented before, the number of correct answers varied greatly among all three groups. The young adults scored highest, followed by the older adults, followed by the AD patients. Results from the pleasantness rating test showed that participants gave higher ratings to melodies they had heard before. Scores between AD patients and older adults were similar but scores from the young adults group varied significantly. For the FDT, which the younger adults were not tested on, the AD participants and older adults scored very closely. Relations between prior music experience and test scores were investigated, but only one significant correlation was found.

Results indicated that the AD group performed the poorest on the explicit memory tasks, followed by the OA group and the YA group, which performed the highest. On the implicit memory tasks, the OA and AD groups performed very similarly, but still far below the YA group. All three groups demonstrated strong recognition of traditional melodies with very comparable scores. Therefore, it can be observed that dementia patients and healthy older adults all demonstrate relative retention of semantic memory in comparison to episodic memory. They are able to recall songs which are embedded into their memory and do not have a specific spatiotemporal context, but are unable to recall details from specific events. In addition, the study implies that musical knowledge and nonmusical knowledge follow a similar trajectory with regard to the dissociation between episodic and semantic memory.

Another study conducted by Cuddy et al. (2012) provides further evidence that musical semantic memory is better preserved over episodic memory for music in AD patients. Participants consisted of 50 individuals with AD who were categorized into three groups: mild, moderate, and severe, according to medical evidence, caregiver interviews, and Mini-Mental State Examination (MMSE) scores. Most of the participants were considered to be "pure" cases of AD, though there were a few cases with minor vascular involvement, indicating the presence of another disease. The control group consisted of 50 young adults, mainly university students, and 100 healthy older adults, all with healthy cognitive and physical health. Tests were conducted either in a quiet room at the participant's home, or in a room at Queen's University. Sessions were distributed over as many days as needed for the participant's optimum comfort, which was usually 2-4 sessions. For the experimental procedures, participants took a variety of tests, listed below.

1. Familiarity Decision Test (FDT): Ten-second long excerpts from 10 familiar and 10 unfamiliar songs were presented to participants and they had to identify which ones were familiar.

2. Familiar Lyrics Test (FLT): Participants were presented with 10 familiar lyrics and 10 unfamiliar lyrics and asked to decide which ones were familiar.

3. Distorted Tunes Test (DTT): This test consisted of excerpts from 26 popular melodies, 17 of which had pitch distortions, meaning the pitches presented were one or two semitones higher or lower than the original pitches of the melodies.

The contour of the original tune, or pattern of ups and downs, was preserved. Participants were to assess whether the melody sounded correct or not.

4. Distorted Lyrics Test (DLT): This test contained 30 lyrics, 20 of which had basic grammar mistakes. Participants had to decide whether the lyrics were correct or incorrect.

5. Lyrics Prompt Test (LPT): Participants were instructed to sing the melody that corresponded to the lyrics deemed familiar in the FLT. They were assured that the quality of their singing was not being judged, rather, the idea that they actually remembered the melody.

6. Proverbs Completion Test (PCT): This test contained 21 proverbs which 80% of a group of 60 healthy older adults was able to accurately remember. The first half of the proverb was read aloud, and participants were required to complete it by stating the second half.

Participants were scored on each test based on percentage correct, with the exception of the LPT. Each singing response was scored as 0, 0.5, or 1 based on whether the participant could not sing the melody at all, sang the melody with errors, or sang it so that it was recognizable, respectively. The total score was divided by the number of lyrics in the FLT correctly recognized by the participant and converted to a percentage. No significant differences were found between sexes, age, or general education. Music experience accurately predicted test results in only certain situations. Within the AD groups, no significant differences were found between participants receiving or not receiving medication or mixed versus pure diagnoses. Performance within the control groups was very high, with 11 out of the 12 median scores being above 85%. For the FDT, FLT, DTT, and LPT, severe AD patients struggled significantly. For the DLT and PCT, all three AD groups had difficulty.

All six of the tests reveal that severity in AD is the most accurate predictor of performance. Demographics such as age and gender had very little effect. Still, severity in AD affected each test differently. Long-term familiarity for melody and lyrics was found in all cases of AD, even in some severe cases. This was also true for the ability to sing when prompted with lyrics. In addition, mild and moderate AD patients were able to identify melodic distortions in the same performance ranges as the control group participants. However, grammatical distortions within lyrics were difficult for all three AD groups to recognize. Thus, it is apparent that the ability to recognize music is spared in mild and moderate AD patients, as well as in some severe AD patients, and formal music training has no effect on this. This study provides evidence that semantic musical memory is spared in most dementia patients, which significantly differs from the effects of dementia on episodic memory, which is impaired even in mild AD patients.

Immediate recall with music as a memory enhancer was further investigated in patients with AD in an experiment conducted by Simmons-Stern, Budson, and Ally (2010). The purpose of this study was to determine whether AD patients are able to learn new information with music as a stimulant. Researchers sought to test memory for the lyrics of children's songs in order to see whether it would maximize the benefit of music. Participants consisted of 13 patients with a clinical diagnosis of AD along with 14 healthy older adults. They were presented with four-line excerpts from 80 different children's songs which they were unfamiliar with. A sung and spoken version of each of the 80 excerpts was recorded by an experienced vocalist. During the study phase, participants were presented with lyrics to 40 of the songs. Of those, 20 were presented with their spoken recording and the other 20 were presented with their sung recording. Participants were informed that their memory would be tested for the lyrics. During the test phase, participants were presented with the lyrics to all 80 songs without any audio recording and asked if it was "old or new."

Results indicated that healthy, older adults performed higher than AD patients on the recognition tasks. Accuracy was greater for AD patients in the sung condition as opposed to the spoken condition, but this was not the case with the healthy adults. Mean recognition accuracy in the control group for the spoken set was 0.77 and 0.74 for the sung set. For the experimental group, mean recognition accuracy for the spoken set was 0.28 and 0.40 for the sung set. This study provides evidence that music plays a role in enhancing the memory of AD patients. This can be attributed to how the parts of the brain associated with music processing are affected at a slower rate in AD patients in comparison to other parts of the brain associated with memory. Music processing involves all lobes of the brain with these structures in particular: the basal ganglia, cortical and subcortical motor areas, cerebellum, and amygdala. As a result, complex neural circuits throughout the entire brain can be formed (Grahn, 2009; Levitin & Tirovolas, 2009). On the contrary, memory processing is limited to very specific parts of the brain which specialize in processing and consolidating different memory forms

(“Where are memories stored in the brain?” 2018). However, the article still offers the question of why music did not enhance the ability to recall in healthy participants. The article presents lots of information and theories on how AD patients encode new information, how this differs from healthy individuals, and how both groups of individuals respond to different types of stimuli.

Most studies investigating the effects of music therapy on memory recall in dementia patients only look into immediate recall. Samson, Baird, Moussard, and Clément (2012) took a new perspective on this subject and investigated how immediate recall in dementia patients differed from delayed recall. Participants consisted of 17 individuals with mild to moderate AD and 17 healthy individuals as a control group. Test subjects were presented with 32 familiar melodies and 32 unfamiliar melodies which were all 4-10 seconds in duration. During the first study phase, participants were presented with 8 familiar and 8 unfamiliar melodies and asked whether they were familiar or not and told to try and remember them. Participants then underwent two recognition tests (R1 and R2) in which they were given 8 familiar melodies mixed with 8 unfamiliar melodies and asked whether they had heard the melody before. During the second recognition test, the melodies were given in a different order. A delayed recognition test (DR) of the 16 melodies was given 24 hours later to test long-term retention. Different unfamiliar melodies were given during each test.

In the first test of familiarity judgement, both groups were very accurate. Both control groups had a mean of 97.4% correct responses and the AD groups had a mean ranging from 87.5% - 100% in accuracy. Both control groups demonstrated an increase in percentage correct between R1 and R2, as expected, and only a slight decline in percentage correct during the DR. They were also better able to recognize the familiar melodies over the unfamiliar melodies. The AD groups, however, performed very poorly in recognizing both familiar and unfamiliar melodies. It was also found that across the three recognition tests, the number of false alarms increased for the familiar melodies with the AD patients, but not for unfamiliar melodies.

The main ideas investigated in this experiment are explicit memory and how the musical lexicon is affected by the progression of AD. Even though AD patients were unable to recognize both familiar and unfamiliar melodies during both tests, they were still able to make sound decision-made judgements, suggesting preservation of the musical lexicon. The researchers bring up a valid point regarding prior experiments completed on similar topics. When unfamiliar melodies are presented to participants for them to assess whether they are familiar or not, it is the feeling of familiarity which is really being assessed. When this feeling is tested for without prior exposure to a study phase, the same memory forms are not being tested. Without the opportunity to study the melodies in question, participants are actually being tested on the strength of their musical lexicon as opposed to recognition memory. As a result, these studies claim that AD patients retain their ability to engage in recognition memory tasks, when in reality, they are just referring to their musical lexicon, which is minimally affected by the onset of dementia. In this study, participants in the experimental group proved themselves to be capable of partaking in familiarity decision-based judgements at the same level as the control group. Even in advanced stages of AD, patients are still able to recognize melodies as familiar. Thus, it can be concluded that the musical lexicon is spared in AD patients, even as the disease progresses into its most severe stages.

Emotion

It is widely accepted that exposure to any sort of music is useful in alleviating stress and elevating moods in most individuals. Similarly, music therapy has been found to reduce anxiety and depressive symptoms in AD patients. A pilot study conducted by Guétin et al. (2009) used 30 individuals with mild to moderate AD and split them into two groups to form a control group and an experimental group. The experimental group participated in individualized music therapy sessions while the control group participated in individualized reading sessions. Sessions were held once a week for 16 weeks, although the researchers continued to follow up with the participants for an additional 8 weeks. The Hamilton Scale was used to measure anxiety and the Geriatric Depression Scale was used to measure depression. Significant improvements in both anxiety and depression were observed in the experimental group from week 4 until week 16, and these improvements lasted all the way until the end of the observatory period.

Clément, Tonini, Khatir, Schiaratura, and Samson (2012) found coinciding results when they measured emotional well-being following participation in music therapy sessions. Participants for this study included 14 individuals with severe AD who took part in eight music therapy sessions over the course of four weeks. There were two components to the sessions, a receptive component where tasks were very passive, such as listening to music, and a productive component, where tasks were much more inclusive, such as playing a musical instrument. Both short-term and long-term benefits were apparent after participation in music therapy sessions, as indicated by facial expressions and mood.

A case study conducted by Gagnon, Gosselin, Provencher, and Bier (2012) on a woman referred to as MD with early AD also revealed similar results. MD was tested on her ability to recognize the emotions conveyed by music as well as facial expressions, and it was found that she was able to recognize all emotions except anger, thus further providing empirical data to indicate that musical emotional judgements are relatively preserved even with AD.

Language and Communication

In addition to enhancing certain forms of memory, music therapy has also been proven to be effective on language functioning and communication, as indicated by research conducted by Brotons and Koger (2000). The study included 26 participants, half of which had been receiving music therapy treatment for a minimum of three months, twice a week. The other half served as the control group and had conversational sessions with a caregiver without any form of music therapy. One week prior to the study, all participants took the MMSE to test cognitive function and the Western Aphasia Battery (WAB) to test language ability. Different aspects of language functioning were tested through the WAB, including spontaneous speech, auditory verbal comprehension, repetition, and naming. Music therapy sessions were administered twice a week for four weeks for a total of eight sessions. Both tests were given at the end of every four sessions. It was observed that significant improvements were seen in the speech content and fluency subtests of the WAB, as well as in MMSE scores of individuals receiving music therapy treatment, while such improvements were not observed in the control group. Although these findings present promising data, they were collected from only 10 of the 26 participants, which severely affects their validity. This information still provides evidence for the effectiveness of a technique for increasing ease of communication in dementia patients, though further investigation on this topic is still necessary before any associated actions can be taken.

Behavior

It is evident that music therapy has a beneficial effect on recalling certain forms of memory and enhancing language and communication, but it has also been recognized as a useful method for improving negative behaviors common to dementia patients. Brotons and Pickett-Cooper (1996) conducted a study in which they assessed the effects of music therapy on agitated behavior in AD patients, which consisted of restlessness, hyperactivity, and subjective distress, which were assessed by the Agitation Behavior Scale and dosages of PRN medication. Subjects included 20 AD patients who participated in five music therapy sessions of 30 minutes each. Caregivers of the patients rated agitative behavior of the participants according to the scale the morning prior to beginning music therapy. The actual music therapy sessions were videotaped in order to accurately observe behavior and come up with a reflective score. Behavior was also assessed for 20 minutes after the sessions. Additionally, participants' medical charts were monitored to keep track of PRN medication intake. After conducting a two-factor analysis of variance and a Fisher PLSD, it was indicated that agitation scores were highest prior to the start of music therapy sessions.

Another study conducted by Clark, Lipe, and Bilbrey (1998) studied the effects of using music to decrease aggressive behaviors in AD patients during bathing episodes. Participants consisted of 18 adults with severe AD who were randomly placed in the experimental group, which received music, or the control group, which did not receive music. After observing behavior during 10 bathing episodes, it was found that 12 out of the 15 identified aggressive behaviors were decreased. Caregivers also reported that overall cooperation during the bathing task was increased during the music condition. A very similar study was conducted by Thomas, Heitman, and Alexander (1997) where the effects of music on bathing cooperation was assessed in dementia patients. Bathing cooperation consisted of different categories, including hiding and hoarding, verbally agitated behavior, and aggressive behavior. Participants for this experiment consisted of a convenience sample of 14 individuals with moderate to severe dementia. Each participant received three pretreatment observations, three treatment observations, and three posttreatment observations. Significant improvement in results were only observed in the aggressive behavior category.

Part IV: Cellular Effects of Dementia

Gray Matter and White Matter

The process of aging is a combination of significant alterations throughout the body, both physically and mentally. The changes which occur in the central nervous system (CNS) are especially dramatic, though all organs are impacted by aging. Modifications in white and gray matter are some of the most definitive indications of aging (Raz, 2005). White matter refers to collections of neuron somas, while gray matter refers to the myelinated axons of the neurons. In the spinal cord, gray matter is more concentrated towards the middle of the spine with white matter surrounding it, while in the brain, white matter is more concentrated towards the middle with gray matter surrounding it (Jensen, 2014). After consulting several postmortem investigations, it is apparent that the amount of white matter in the brain declines as an individual ages, though it increases from young adulthood to the middle ages. On the contrary, gray matter in the brain remains roughly constant from age 20 to age 50 and reaches a plateau around the age of 50 (Miller, Alston, & Corsellis, 1980). The effects of aging on gray and white matter in the brain were further explored in *in vivo* investigations on participants from infancy to 70-80 years of age. The course of the decline in white matter follows a route much different than the continuous decline of gray matter. It follows a trajectory of steady increase up until an individual's early to mid-20s. This increase is followed by a plateau in one's middle years, which can be anywhere from late 30s to early 60s. After this plateau, the volume of white matter in the brain begins to decline up until the end of the individual's life (Pfefferbaum et al., 1994).

These trajectories of white and gray matter degradation over time are altered once an individual is overcome with dementia. Most dementia forms are characterized by an abnormally high volume of white matter in the brain and a lower than average volume of gray matter in the brain. In more severe stages, these volumes have these same proportions but are more extreme. However, the amounts of both types of matter vary depending on the form of dementia being evaluated. In AD, it is primarily the volume of gray matter which is reduced, while in subcortical ischemic vascular dementia (SIVD), the volume of white matter is significantly increased (Stout, Jernigan, Archibald, & Salmon, 1996).

In an experiment with 15 healthy functioning older adults, 15 AD patients, and 14 SIVD patients, measurements of gray and white matter volumes in the temporal lobe were taken using an MRI scanner and assessed using ANALYZE software. Between the AD and SIVD patients, there were minimal differences in gray and white matter volumes. Most differences were observed between either of the two experimental groups and the control group. Cortical gray matter amounts were smaller in SIVD patients while whole brain white matter volumes were smaller in AD patients. Within the temporal lobe, gray matter amounts were lower on both sides of the brain in AD patients in comparison to the control group. These results indicate that white matter damage throughout the brain has much more severe consequences than damage within the temporal lobes. In addition, atrophy of gray matter affects the severity of dementia and overall cognitive function of the individual more significantly than white matter atrophy (Yang et al., 2010).

Changes in Different Structures of the Brain

Aging in healthy older adults is also characterized by shrinkage in volume of metencephalic structures of the brain, which includes the cerebellum, vermis, pons, and basal ganglia. It was found that all of these structures undergo a reduction in size as an individual ages, although this process occurs at a different rate in each structure. The cerebellar hemispheres and basal ganglia demonstrate the most significant reduction in size, followed by the vermis, while the cerebellum and pons demonstrate the most minimal change in size. In addition, a significant reduction was observed in the corpus callosum, with the average annual shrinkage rate from numerous longitudinal studies being at 0.90% (Raz, 2005). Raz (2005) summarizes the longitudinal changes occurring in all metencephalic structures and the corpus callosum based on nine studies in Tables 1 and 2. Table 1 examines changes in the basal ganglia alone, while Table 2 examines all other structures. It is important to note that eight of these studies were conducted on population sizes with very limited age ranges of either young adults or older adults.

Table 1: Longitudinal Changes in the Volume of Basal Ganglia

Study	***N***	**Age (years)**	**Interval**	**Caudate Nucleus**	**Putamen**	**Globus Pallidus**
Lieberman et al., 2001	15	31	2.1	1.52		
Lang et al., 2001	17	28	1	1.10	0.20	+4.22
Tauscher-Wisniewski et al., 2002	10	29	4.9	1.90		
Raz et al., 2003	53	52	5.25	0.83	0.73	0.51
DeLisi et al., 1997	20	28	4.3	0.37		

Note. Adapted from *Cognitive Neuroscience of Aging* edited by Cabeza et al. Copyright 2005 by Oxford University Press

Table 2: Longitudinal Changes in the Volume of Metencephalic Structures and Corpus Callosum

Study	***N***	**Age (years)**	**Interval**	**Cerebellum**	**Vermin**	**Corpus Callosum**	**Pons**
Tauscher-Wisniewski et al., 2002	10	29	4.9	1.86			
Raz et al., 2003	53	52	5.25	0.64	0.41		0.16

Cahn et al., 2002	36	24	1.1	+1.0			
Tang et al., 2001	66	79	4.4	1.2			
Liu et al., in press	90	38	3.5	0.13			
Ho et al., 2003	23	27	3	1.71			
DeLisi et al., 1997	20	28	4.3	0.49		0.18	
Sullivan et al., 2002	215	72	4			0.90	
Teipel et al., 2002	10	65	2			0.90	

Note. Adapted from *Cognitive Neuroscience of Aging* edited by Cabeza et al. Copyright 2005 by Oxford University Press

In an experiment conducted by Guo et al. (2016), scans conducted by an MRI revealed that the cerebral cortex and cerebellum undergo atrophy in dementia patients, though the rate and exact locations of this vary depending on the neurodegenerative disease being tested. In AD and FTD, the overall volume of these two brain regions is decreased. These results are similar to results observed in atrophy of brain regions in healthy older adults. Much of the ideas presented are based on Hebbian theory, which is the idea that cells which are activated at the same time are connected to one another. In a similar manner, these cells will also die out at the same time. Thus, when any form of dementia sets in, these connectivity networks of neurons within the brain experience a spread of toxic agents throughout several neural pathways, which results in the degeneration of several neurons at the same time, causing a drastic decrease in overall volume (Schmahmann, 2016).

Additionally, alterations in the Purkinje cells of the cerebellar cortex have been observed as a result of AD. These are inhibitory cells found in the cerebellar cortex responsible for releasing the neurotransmitter GABA, which reduces the transmission of nerve impulses. This inhibitory action helps coordinate and regulate motor movement (Sinha & Rogers, 2015). Imprialos and Baloyannis (1998) studied the postmortem cerebellar cortexes of five AD patients and found that the morphology of Purkinje cells was significantly altered from what they typically look like. Purkinje cells are known for their flask-like shape and large number of surrounding dendrites (Minai, 2014). They also have a thick axonic network at the location where the axon meets the cell body. One of the most obvious differences in the Purkinje cells of the AD patients was the deterioration of dendritic branches. The majority of dendritic spines were also completed degraded, in addition to the thick axonic network. Loss of dendritic spines leads to a decrease in the establishment of synapses within the cerebellum, which negatively impacts motor movement within the individual (Imprialos & Baloyannis, 1998). Thus, this investigation provides evidence to support the notion that the overall degradation of Purkinje cells and the

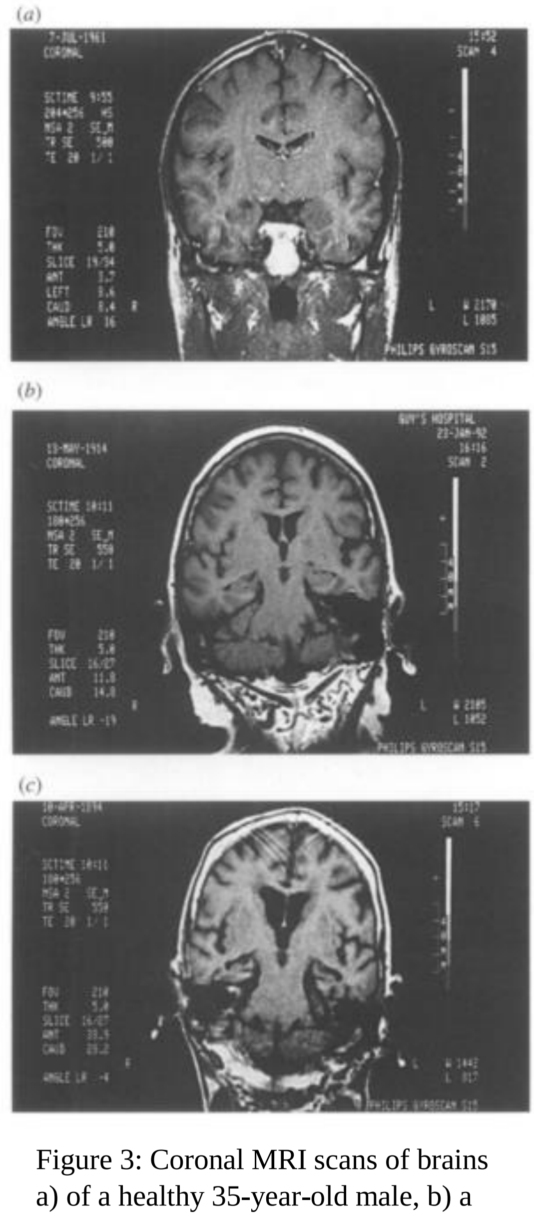

Figure 3: Coronal MRI scans of brains a) of a healthy 35-year-old male, b) a healthy 82-year-old female, and c) a 99-year-old female with AD. From "Changes in the Ageing Brain in Health and Disease," by B. Anderton, 1997.

alterations which occur in synapse formation as a result are an additional factor relating to the pathology of AD and its associated impairments.

Volume of the brain has been observed to decrease in non-pathological aging as a result of changes in other structures as well. After the age of 50, changes are observed in sulci, gyri, and ventricles of the brain. Following this, every decade consists of a progressive 2-3% loss in overall brain weight (see Figure 3). Sulci widen, gyri begin to atrophy, and ventricles expand (Anderton, 1997). In addition, it is widely accepted that neuronal numbers in certain brain regions are altered as aging occurs. The hippocampus, amygdala, and cerebral cortex are impaired the most from loss of neurons. Within the hippocampus alone, neuronal loss can be reduced by up to 50% of what the individual's initial neuronal volume was in their early teens (West, 1993). Meanwhile, other neurons within the cerebral cortex demonstrate shrinkage but no loss. The nucleus basalis is almost completely spared from both neuronal shrinkage and loss (Chui, Bondareff, Zarow, & Slager, 1984).

With regard to dendrites and synapses, contrasting evidence has been found on whether these formations are lessened in volume or experience growth. Regardless of how they are modified, any sort of change in neurons and their connections between one another results in altered neuronal function and altered behavior and cognitive function as a result. Some evidence suggests that synapses are reduced by up to 20% in some cortical regions, while other research indicates that synapses within the hippocampus are actually increased as a result of neuronal sprouting by remaining neurons due to overall reduction in neuronal volume (Masliah, Mallory, Hansen, DeTeresa, & Terry, 1993; Lippa, Hamos, Pulaski-Salo, DeGennaro, & Drachman, 1992). Although the nucleus basalis is relatively spared in terms of shrinkage with aging, this region of the brain is involved in AD and demonstrates signs of degradation with progression of the disease (Chui et al., 1984).

Neurofibrillary Tangles and Senile Plaques

Furthermore, the presence of neurofibrillary tangles and senile plaques in the brain are signature characteristics of AD. Neurofibrillary tangles are highly phosphorylated forms of the protein tau (See Figure 4a.). This protein is involved in the composition of microtubules and accumulates in its phosphorylated form as a result of an imbalance in the activity between the protein kinases and phosphatases acting on it. Several of the protein kinases involved in the phosphorylation of tau are involved in signaling, suggesting a defect in signaling pathways as an additional reason for the buildup of phosphorylated tau. Since the tau protein is associated with microtubules, highly phosphorylated versions of this protein result in defects within the microtubule network (Brion, 1998). Neurofibrillary tangles are mainly composed of paired helical filaments (PHF) and straight filaments, though mainly PHF. Gray, Paula-Barbosa, and Roher (1987) observed the frontal cerebral cortex of four biopsies from individuals with advanced AD. They found that in neurons with especially large amounts of PHF, the cytoskeleton is completely distorted, as the microtubules it is composed of are distorted due to overly phosphorylated tau. As a matter of fact, the area of the PHF was so large that the beginning and end were unable to be seen in one glimpse through the electron microscopes that were used (Gray et al., 1987). Neurons, or any cell for that matter, cannot function properly without a sturdy cytoskeleton, which is why large numbers of neurons die out. As a result, it can be observed that the presence of neurofibrillary tangles in AD results in significant neuronal degeneration, while this same effect does not occur to the same degree in healthy aging (Anderton, 1997).

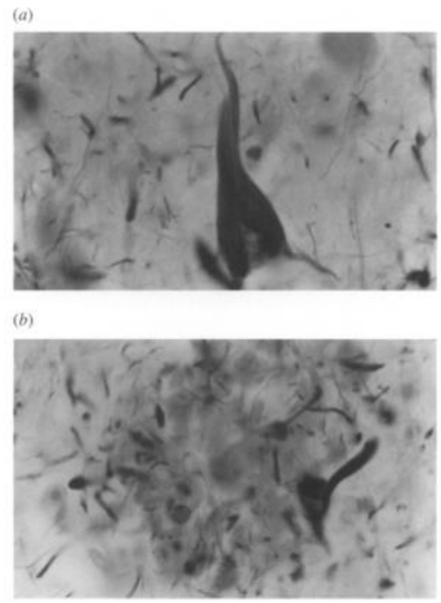

Figure 4: Light microscopy a) revealing a neurofibrillary tangle in a pyramidal cell and b) a senile plaque with a β-amyloid core and swollen neuronal processes. From “Changes in the Ageing Brain in Health and Disease,” by B. Anderton, 1997.

Neurofibrillary tangles increase in quantity as AD progresses through its stages. Any changes observed in stages I and II are not considered to be associated with the disease. Once the individual surpasses stage II, changes are much more widespread and severe, and are found throughout the transentorhinal region, entorhinal cortex, amygdala, and hippocampus, which causes the most cognitive impairment. When the brains of healthy individuals in later stages of their life were examined, it was found that neurofibrillary tangles were found in the transentorhinal region and entorhinal region, though not to the extent that they were found in severe AD patients. The presence of these formations in the hippocampus was one of the most notable differences between healthy aging and aging with AD, which explains why memory loss is one of the most prominent symptoms of AD, since formation and consolidation of memories is the primary function of the hippocampus (Anderton, 1997).

Hyperphosphorylated forms of the protein tau have also been observed in the cerebrospinal fluid (CSF) of AD patients. Molina, Touchon, Pau, and Mourton-Gilles (1998) conducted an experiment in which tau protein levels in CSF were tested in AD patients, patients with other forms of dementia though mainly FTD, and patients with neurological diseases besides dementia, such as amyotrophic lateral sclerosis without dementia, polyneuropathy, and tension headaches. CSF samples were taken from all three groups of participants and tested for the presence of the tau protein using a commercial immunoassay. Out of all the 57 CSF samples analyzed, the mean concentration of tau protein in the AD group was 543.6 pg/mL, 284.5 pg/mL for other dementia patients, and 326.2 pg/mL for all other patients without any form of dementia. It is strongly evident that tau protein levels in the AD participants were significantly higher than tau protein levels in both other groups, between which the levels were more or less similar. The authors do make an important point that there were significant variations between other studies testing similar ideas. For example, Molina et al. (1998) was unable to find any correlation between tau protein levels and the age of the participant. In addition, the overall tau protein levels in Molina et al.'s (1998) study were higher than those observed by Jensen, Basun, and Lannfelt (1995), which is probably a result of biological differences between each individual participant. Overall, it can be observed from this study that tau protein levels are higher in the CSF of AD patients, but further investigation is still required in order to draw any additional definitive conclusions.

Senile plaques are another characteristic signature of AD which are still found in healthy aging individuals, though not in as large a quantity. These structures are portions of gray matter up to 200 μm in length. Senile plaques are surrounded by swollen or abnormally shaped neuronal processes and have an extracellular core of β-amyloid protein (see Figure 4b.). Several different proteins compose the core, but the primary one is β-amyloid protein. A correlation has been found between abnormally high levels of β-amyloid and declines in cognitive abilities. In addition, the neuronal processes surrounding this core do not have a sturdy cytoskeletal structure, resulting in their inability to function appropriately (Anderton, 1997).

Dopamine-Beta-Hydroxylase Activity

Structural variations within the brain are a significant characteristic in dementia patients, but varying levels of enzymes and neurotransmitters are also a natural effect of any neurodegenerative disease. Cross et al. (1981) examined how dopamine-beta-hydroxylase (DBH) activity is reduced in AD patients. This enzyme is responsible for catalyzing the hydroxylation reaction of the neurotransmitter dopamine into norepinephrine, in addition to serving as a marker for the study of noradrenergic nerve and cell function (Rush & Geffen, 2008). Deficiency of this enzyme can cause defects in autonomic functions of the body, such as regulation of blood temperature and body temperature (“Dopamine beta-hydroxylase deficiency,” 2019). In their experiment, Cross et al. (1981) collected postmortem brain tissue and measured DBH levels in AD patients and in healthy older adults. They found that DBH levels were significantly lower in AD patients in all three areas of the brain that were studied: the frontal cortex, temporal cortex, and hippocampus. It was ensured that enzyme activity remained unaffected by additional variables such as sex, age, or cause of death. This information suggests that noradrenergic neurons may be degenerating in AD patients as a result of onset of the disease, which coincides with previously found data indicating that noradrenaline neurons have decreased concentrations in postmortem investigations of AD patients.

Part V: Effects of Music Therapy on the Neuroscientific Basis of Dementia

Neural Connectivity

It is apparent that dementia interferes with the formation of connections within the brain due to the deterioration of several structures. Wilkins, Hodges, Laurienti, Steen, and Burdette (2014) observed that after listening to music of their preferred genre, individuals often report deeply emotional experiences, such as personal thoughts and certain memories being triggered. An experiment was conducted aiming to investigate why listening to different types of music triggers similar experiences across different individuals. Researchers studied whether differences in certain brain patterns of functional connectivity might be associated with the type of music an individual prefers. Functioning imaging data was collected while participants listened to classical, country, rap/hip-hop, rock, Chinese opera, and a participant's favorite song. The investigators analyzed how listening to preferred music as opposed to music that was not preferred affected functional brain connectivity patterns.

The study included 21 young adults based on their most preferred musical genre. The distribution among the four genres of classical, country, rap/hip-hop, and rock was almost even. None of the participants had any neurological disorders. Before starting the experiment, participants were asked what genre of music they preferred, if they had any formal music training, and their favorite song. Six musical selections that were each five minutes long we presented to each of the participants in an MRI scanner while blood oxygen level dependent (BOLD) functional mRI data were collected. The music selections included four pieces that were famous within their genre, one unfamiliar selection, and the participant's favorite song. Participants were presented with the songs with no interruptions and with their eyes closed. After random presentation of the music selections, participants rated their preference for each piece on a scale of 1-10 using a visual analog scale (VAS). The highest and lowest VAS scores were used to determine the participant's favorite and least favorite selections.

A fundamental measurement of brain activity is degree (K), which represents the number of edges, or functional links for each node within the brain network. Results indicated that high degree nodes, or hubs, were located within the default mode network (DMN), as well as within the precuneus, regardless of song preference. The DMN is responsible for processing memories and introspective thoughts. The degree of the hubs in each location did not vary across different conditions. Increased stimulation was also found in the auditory cortex and hippocampus. Thus, it can be concluded that functional connectivity is determined by the participant's preference towards music, and not by the type of music specifically or by the presence or absence of lyrics. In addition, listening to preferred music alters areas of the brain which in turn triggers emotion. These results provide information which can serve as a foundation for individuals with neurological impairments, such as different forms of dementia. It was clearly evident that listening to preferred music had positive effects on the connectivity of different neural networks, which is one of the most significant areas of decline in dementia patients. Therefore, this experiment provides a resource for further investigation on the use of different forms of music therapy as a method of mental stimulation.

DA Levels and Blood Pressure

In addition to increasing mental stimulation within the brain, music has also been found to have an effect on blood pressure by regulating dopamine (DA) levels. Sutoo and Akiyama (2004) found that calcium increases brain dopamine synthesis through a calmodulin (CaM)-dependent system, and increased DA levels are known to reduce blood pressure. In this study they researched the effects of music on this pathway on spontaneously hypertensive rats (SHR). Male SHR which were 12 weeks old were kept at room temperature in a designated animal center one week prior to being used in the experiment. They received proper care, such as getting food and water within a timely manner and being exposed to a 12-hour light/dark schedule. A cannula was implanted in the lateral cerebral ventricle and experiments were started four days after this was done. The rats were placed in a cage with a speaker and taped music playing Mozart’s Adagio from Divertimento No. 7 in D Major, K. 205 on repeat for 120 minutes. Changes in blood pressure were analyzed during and after treatment. Calcium levels were also measured in addition to DA levels after being exposed to music and after not being exposed to music. The immunohistochemical staining procedure was performed in order to analyze the distribution of DA levels. A brain mapping analyzer was used to observe differences in fluorescence intensity.

Systolic blood pressure in SHR did significantly decrease during exposure to music and after cessation of music. It began to decrease gradually after the start of the music. Blood pressure levels were lower by 13 to 24 mmHg than the non-music control group after exposure to music for 120 minutes. Increases in calcium levels were also observed during music exposure. These levels increased slightly and then remained level during the exposure period. With regard to DA levels, fluorescence was strongest in the lateral area of the neostriatum of the experimental SHR by 18%. No other significant differences were observed in DA levels between the control and experimental groups of mice.

This experiment provided enough data to conclude that calcium promotes synthesis of DA through a CaM-dependent system within the brain. These increased DA levels inhibit sympathetic activity which in turn reduces blood pressure. This reduction in systolic blood pressure in the SHR during and after exposure to Mozart’s music, and the disappearance of this effect upon inhibition of the calcium-dependent DA-synthesizing pathway through injection, suggests that calcium levels are increased in the brain, which causes an increase in DA production, which reduces blood pressure as a result. Thus, the authors have inferred that listening to certain forms of music can be beneficial for diseases which alter DA levels and blood pressure in the brain, such as AD, as portrayed in the study conducted by Cross et al. (1981). This experiment can be used as a guide for performing similar studies to test differences in DA levels in normal functioning older adults and individuals with AD.

Takahashi and Matsushita (2006) performed a similar experiment where the effects of music therapy on systolic blood pressure were observed in individuals with moderate to severe dementia. This experiment specifically focused on observing long-term effects as opposed to immediate effects. Participants consisted of 43 older adults with a mean age of 83 years diagnosed with a form of dementia which had progressed to a moderate or severe stage. They were split into two groups, an experimental group of 24 individuals who received music therapy treatment, and a control group of 19 individuals who did not receive any music therapy treatment. Music therapy sessions were administered once a week over the course of two years. The researchers were observing three characteristics: systolic blood pressure, intelligence levels, and changes in cortisol levels in saliva. Blood pressure typically increases with age, and this was observed in the control group of participants who did not receive any music therapy treatment. In the experimental group, however, a significant decrease in blood pressure was observed, although no significant effects were observed on intelligence levels or cortisol levels in saliva.

These results provide valuable data on not only the effects of music therapy, but on how these effects can persist with continuous exposure to music even as the individual progresses into severe stages of dementia. Improvements in mental and physical health were observed in all participants in the experimental group despite their severity level, while these effects were not observed in the control group. Prevention of cerebral and cardiac diseases was also a lasting effect observed in the experimental group. Although several novel ideas were presented in this study regarding long-term effects of music therapy treatments, the study is lacking in its vagueness. Specifics were not given on the types of cerebral and cardiac diseases which were prevented and how these effects were measured. Regardless, it can be observed from the studies conducted by Sutoo and Akiyama (2004) and Takahashi and Matsushita (2006) that continuous participation in music therapy sessions has a lasting effect on lowering systolic blood pressure in dementia patients.

Sympathetic Activity

Recent studies have indicated that salivary chromogranin-A (sCgA) co-released with catecholamines can be an accurate method of determining sympathetic activity. Chromogranin A is a secretory protein stored in vesicles with other types of neurotransmitters. It is released along with other catecholamines when activity in the sympathetic nervous system increases and is therefore used as a marker of sympathetic activity and stress levels. This protein can be found in saliva as well as neuroendocrine tissues ("Salivary Chromogranin A," 2019). Sympathetic activity is often used as a method of measuring stress response, which can be altered through exposure to certain musical stimuli. The rhythm, harmony, and melodies of music all work together to stimulate cognitive and psychological functions and trigger emotional reactions (Suzuki et al., 2004). Suzuki et al. (2004) discusses in their experiment how certain experiences, including emotions, memories, and images, are evoked upon presentation of certain aspects of music. They examined how sCgA can be used for stress evaluations in dementia patients after participation in music therapy sessions. Changes in problematic behavior were also observed in order to assess any cognitive and behavioral changes.

Participants consisted of 23 individuals with senile dementia, 4 males and 6 females, with a mean age of 82 years. The music therapy group consisted of 10 individuals with either AD or vascular dementia, and the control group consisted of 13 individuals from the same dementia care unit who did not participate in the music therapy sessions. The music therapy group participated in sessions twice a week for 8 weeks, totaling 16 sessions. Three music therapists and three nurses came up with the therapy program. Music therapy consisted of singing songs, playing percussion instruments, making personal references such as using the participants' names, while continuously reinforcing social interaction. The same protocol was used for all 16 sessions. To observe cognitive function and mental status, patients were given the MMSE, N type Mental States Scale (NM scale), and N type Activities of Daily Living (N-ADL). To rate behavior in participants, the Multidimensional Observation Scale for Elderly Subjects (MOSES) was used. Endocrinological stress was evaluated using sCgA, which coexists and is co-released with catecholamines and thus has a direct relationship with it. Therefore, testing for catecholamines provides direct information about CgA levels. All tests were administered before and after the intervention at precise timings.

The MMSE showed a significant change in the music therapy group, but not in the control group. Scores for the N-ADL did not show any significant changes. The MOSES test indicated that the mean score for irritability significantly decreased in the music therapy group but not in the control group. It was also reported that individuals who participated in the music therapy demonstrated decreased levels of salivary cortisol and CgA. These results indicate that music therapy had positive effects in decreasing stress levels in participants, which decreases irritable behavior, thus slowing down sympathetic activity. The authors of the study suggest that music therapy should be incorporated into the daily lives of dementia patients, although the small number of participants calls for further data to be gathered before any definite conclusions can be drawn, as only 10 participants received the music therapy treatment. Overall, the endocrinological measurement of CgA levels appears to be a useful supplementary evaluation for investigating changes in stress levels of individuals with dementia over short-term periods, as levels always decreased following a music therapy session. The endocrinological measurement of CgA, behavioral evaluation, and functional assessment methods, including the MMSE and MOSES, were all useful in evaluating the effects of music therapy in persons with senile dementia. The study did an excellent job of assessing and analyzing both behavioral and cognitive effects of music therapy on dementia, however, it should be noted that the MMSE is a very basic cognitive test and additional investigations should be conducted to assess the effects on different aspects of cognitive function.

A similar study conducted by Valdiglesias et al. (2017) revealed different results. The researchers sought to determine whether musical intervention or exposure to a multisensory stimulation environment (MSSE) would alter sCgA levels in older individuals with severe dementia, and if there would be a significant difference in results between the two groups. The participants were randomly assigned to one of the two groups in either of the interventions in weekly 30-minute sessions for 16 weeks. Levels of sCgA were measured before and after the sessions and compared. No significant differences were observed after analyzing sCgA levels before and after either of the interventions. Moreover, no significant correlations were found between severity of dementia, agitation, anxiety, stress, or cognitive function and sCgA levels. The authors concluded that even though music therapy and MMSE may be effective methods of increasing overall wellbeing in dementia patients, measuring this through sCgA levels is not the most effective method. Since these results contradict those of Suzuki et al. (2004), evidence from further investigations is needed in order to determine whether or not sCgA levels should continue to be used as a determinant of stress levels.

In addition to decreasing sympathetic activity, music therapy sessions were used to observe whether parasympathetic activity would be affected, which included observation of other aspects such as cerebrovascular disease (CVD) and heart rate variability (HRV). These factors are associated with psychological stress and aging in the average individual (Okada et al., 2009). Okada et al. (2009) performed an experiment in which 87 participants with CVD and advanced dementia were split into a group receiving music therapy and a group not receiving music therapy. Music therapy sessions were once a week for 45 minutes, over the course of 10 weeks, and facilitated by licensed music therapists. They consisted of well-known Japanese nursery rhymes, folk songs, hymns, and recent Japanese popular music. HRV parameters indicated that parasympathetic activity was increased, and sympathetic activity was decreased, revealing that overall psychological stress was reduced. In addition, it was observed that symptoms of CHF, including tachycardia, tachypnea, and overall agitated behavior, were reduced following music therapy treatment. Adrenaline and noradrenaline levels were also regulated and protected from symptoms of CHF. Therefore, it can be concluded that music therapy is an effective resource for increasing parasympathetic activity in not only dementia patients, but also in CHF patients. The authors go as far as to claim that music therapy treatments can be used to stabilize dementia symptoms and entirely prevent CHF in very elderly patients. While further evidence is needed to validate these results, this study definitely provides empirical data to provide a strong foundation for further study on economically advantageous methods of treating the elderly population.

Gray and White Matter

Loss of overall brain volume and altered amounts of gray and white matter are significant effects of aging in the elderly population, however, Tabei et al. (2017) conducted a study in which they examined the effects of exercising in conjunction with musical accompaniment and how this affected structural volume in the brain. It is apparent that exposure to music provides cognitive stimulation to the brain, but combining this with physical activity makes for an extra source of mental stimulation, thus inducing increased brain activity. Additionally, the rhythm of music often triggers physical movement, as demonstrated by patients with Parkinson's disease who showed improved gait and stride length after participating in music therapy sessions (McIntosh, Brown, Rice, & Thaut, 1997). The rhythmic components of music have a powerful impact on enhancing connections between the auditory and motor systems of the brain, which ultimately enhances movement. Sound in general possesses the ability to arouse and prime the motor system in such a manner that it becomes more responsive (Thaut, 2005). The authors cite an excerpt from the Joint Commission on Guideline for

Dementing Disorder, describing music therapy as a "…recommendation to be done as prevention of cognitive decline in elderly adults…" (2010).

Participants consisted of 51 individuals in the exercise and music group (ExM), 61 individuals in the group which only exercised (Ex), and 32 individuals in the control group of participants who did not partake in either activity. All individuals were over the age of 65 and were considered to be physically and mentally healthy. Participants took part in 40 sessions over the course of one year, and the intensity of the exercise routine increased gradually with each session. Routines for the ExM and Ex groups were the same and facilitated by professional instructors. The ExM group had dance pop music with heavy use of a synthesizer played loudly over speakers, while the Ex group just had a percussive sound playing over the speakers to keep beat. MRIs and various neuropsychological evaluations were given before and after the study. The MMSE was given to assess cognitive ability, Raven's Colored Progressive Matrices (RCPM) was used to assess intellectual function, the Logical Memory (LM)-I/-II subtests were used from the Rivermead Behavioral Memory Test (RBMT) to assess memory function, and two tasks were given to assess function of the frontal lobe: word fluency (WF) and Trail-Making Test (TMT)-A/-B.

Significant improvements were observed in the MMSE and both subtests of the RBMT for both experimental groups. The Ex group showed significant improvement in the WF test and the control group showed significant improvements in the LM-II and TMT-B tests after one year. Significant differences were seen in visuospatial assessment between both experimental groups and the control group. With regard to gray matter volume, no significant differences were observed between any of the groups, however, a gradual decline in overall volume was observed between all three groups of participants. There were a few select structures in the ExM and Ex groups which showed an increase in gray area volume, signifying preservation, when compared to the control group (see Figure 5). These structures included the frontal, temporal and cingulate gyri, insula, parahippocampal gyrus, hippocampus, uncus, thalamus, and cerebellum. After calculating the volume differences in pre- and post-interventional MRI scans, it was found that Ex and ExM brain volumes were actually preserved significantly in comparison to the control group. The right superior frontal gyrus was the only structure which showed preservation in the ExM group alone as opposed to both experimental groups. Similar calculations were made to observe differences in white matter volume pre- and post-intervention and it was observed that white matter increased in the Ex and ExM groups, whereas it was reduced in the control group. For the visuospatial assessments, significant differences were only observed between the ExM and control groups.

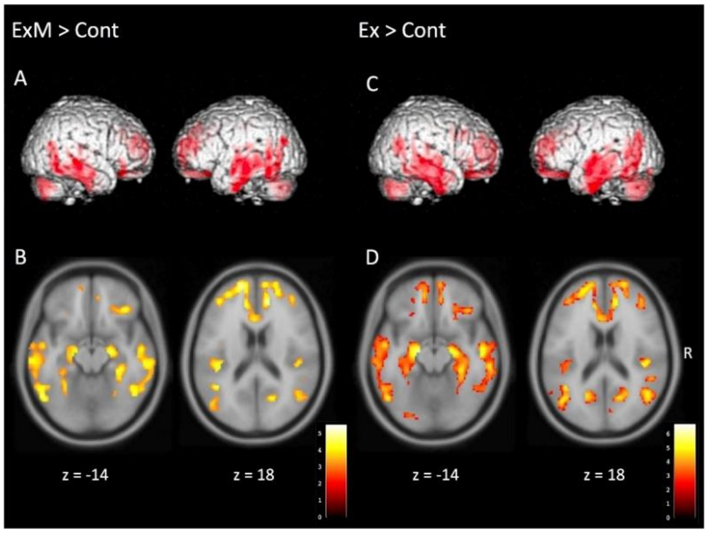

Figure 5: A,B: Gray matter volume was larger in ExM group as opposed to control group. C,D: Gray matter volume was larger in Ex group as opposed to control group. From “Physical Exercise with Music Reduces Gray and White Matter Loss in the Frontal Cortex of Elderly People: The Mihama-Kiho Scan Project,” by Tabei et al., 2017.

Overall, this study effectively portrayed how exercise in conjunction with exposure to music was the best method for increasing neuroplasticity of the brain and increasing cognitive function. Several structures within the brain were actually preserved in volume in comparison to the control group. The authors previously conducted a study investigating the same topic (Satoh et al., 2014) with a sample size with half the number of individuals. This experiment yielded very similar results, which further validates Tabei et al.'s (2017) results. They also state that their results aligned very closely with those garnered from mouse models with AD. The mice exhibited altered synaptic function and overall pathology in the brain very similar to that of AD. They were split into two groups, one which received exercise and music and one which did not. Results demonstrated that synapses were protected and oxidative stress was reduced in the group which received exercise and music (García-Mesa et al., 2011). Furthermore, the effects of a music-based exercise regime on dementia patients as opposed to healthy patients has been investigated to further validate the results of Tabei et al.'s (2017) study. Fifteen women with dementia took part in music-based exercises for 30 minutes a day while a control group of 10 women received the same amount of attention through daily conversation. The experimental group demonstrated a significant improvement in cognition, as indicated by the MMSE. Their mean score increased from 12.87 to 15.53, while the control group's average only increased from 10.80 to 11.00 (Van de Winckel, Feys, De Weerdt, & Dom, 2004). All three experiments provide evidence that such a form of mental stimulation can be effective in preventing neurodegeneration to a certain extent, which in turn enhances cognition. This information can potentially be expanded to conduct experiments on individuals with varying forms of dementia and observe how it affects their symptoms on a broader level.

Part VI: Conclusion

As can be observed, exposure to music plays an influential role in affecting the memory and brain structure of individuals with dementia. This can be recognized at the behavioral level after studying several memory-related tasks, and also at the cellular level after studying several brain scans and looking at different structures within the brain. With respect to memory, semantic memories are retained much more accurately than episodic memories. This is a result of the method through which these memories are consolidated. Hence, music therapy interventions should focus on providing exercises to trigger semantic memories as opposed to episodic memories. The ability to recall specific details about events in a spatiotemporal context may be lost, but recall of ideas deeply embedded within an individual's knowledge is well preserved even in later stages of dementia. Often times, dementia patients are unaware that they still remember certain concepts until these memories are triggered, which supports the idea that individuals with neurodegenerative diseases are in consistent need of mental stimulation.

This concept is further supported at a neuroscientific level after observing what goes on in the brain as an individual ages and during the onset of dementia. One of the most significant symptoms of aging in all individuals, regardless of whether they have any form of dementia, is neural atrophy and a resulting decline in the ability to form synapses and consolidate new information. This symptom is amplified with the onset of any neurodegenerative disease. With the mental stimulation provided by continuous exposure to music, the formation of connections within the brain is strengthened. This results in a reduction of the intensity of other structural deficits which occur in the brain, including senile plaques, neurofibrillary tangles, and reduction in volume of different structures within the brain. This implies that the individual may potentially experience an overall decline in health at a slower pace. Although empirical data has been provided to support the notion that exposure to music in differing forms serves as a foundation for enhanced behavioral and cognitive health within dementia patients, further evidence is necessary in order to draw specific conclusions on how the actual progression of dementia will be affected by exposure to music therapy.

This study provides insight on how dementia patients can potentially be treated. Although this study focused solely on dementia, specifically AD, future studies should expand and assess the effects of music therapy on other neurodegenerative diseases. Assisted living facilities in the United States are currently lacking in their ability to provide their residents with activities which actively engage their mental processes. Music therapy sessions are an excellent way of providing an individual with both cognitive and behavioral involvement. Aside from facilitating recall of semantic memories and preventing cognitive decline, it is widely accepted that music possesses the ability to allow individuals to express and enjoy themselves. This factor is present in individuals despite the severity of their condition. I have observed this effect firsthand on numerous occasions from facilitating and participating in music enrichment sessions myself. Music promotes communication and interaction between the dementia patient and others and allows the individual to connect with something in a way that they cannot connect with anything else. This statement is accurate for all levels of severity in the majority of dementia cases. Individuals are able to experience genuine happiness despite any diagnosis that they might have. Mild or severe, old or young, American or Non-American, male or female, music possesses the power to heal in a way that nothing else can.

REFERENCES

2017 Alzheimer's Statistics. (n.d.). Retrieved April 21, 2019, from https://www.alzheimers.net/resources/alzheimers-statistics/

Anderton, B. H. (1997). Changes in the ageing brain in health and disease. *Philosophical Transactions of the Royal Society B: Biological Sciences. 352*(1363), 1781-1792. doi:10.1098/rstb.1997.0162

Balota, D. A. & Duchek, D. M. (1988). Age-related differences in lexical access, spreading activation, and simple pronunciation. *Psychology and Aging*, *3*(1), 84-93. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Brion, J. P. (1998). Neurofibrillary tangles and Alzheimer's disease. *European Neurology*, *40*(3), 130-140. doi:10.1159/000007969

Brotons, M. & Koger, S. M. (2000). The Impact of Music Therapy on Language Functioning in Dementia. *Journal of Music Therapy*, *37*(3), 183-195. Retrieved from https://academic.oup.com/jmt/

Brotons, M. & Pickett-Cooper, P. K. (1996). The Effects of Music Therapy Intervention on Agitation Behaviors of Alzheimer's Disease Patients. *Journal of Music Therapy, 33*(1), 2-18. Retrieved from https://academic.oup.com/jmt/article/

Chui, H. C., Bondareff, W., Zarow, C., & Slager, U. (1984). Stability of neuronal number in the human nucleus basalis of Meynert with age. *Neurobiology of Aging*, *(5)*2, 83-88. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Clark, M. E., Lipe, A. W., & Bilbrey, M. (1998). USE OF MUSIC to Decrease Aggressive Behaviors in People With Dementia. *Journal of Gerontological Nursing*, *24*(7), 10-17. Retrieved from https://www.healio.com/nursing/journals.jgn

Clément, S., Tonini, A., Khatir, F., Schiaratura, L., & Samson, S. (2012). Short and Longer Term Effects of Musical Intervention in Severe Alzheimer's Disease. *Music Perception: An Interdisciplinary Journal*, *29*(5), 533-541. doi:10.1525/mp.2012.29.5.533

Cross, A. J., Crow, T. J., Perry, E. K., Perry, R. H., Blessed, G., & Tomlinson, B. E. (1981). Reduced dopamine-beta-hydroxylase activity in Alzheimer's disease. *British Medical Journal: Clinical Research Edition*, *282*(93), 282-293. Retrieved from https://www.bmj.com/content/

Cuddy, L. L., Duffin, J. M., Gill, S. S., Brown, C. L., Sikka, R., & Vanstone, A. D. (2012). Memory for Melodies and Lyrics in Alzheimer's Disease. *Music Perception: An Interdisciplinary Journal*, *29*(5), 479-491. doi:10.1525/mp.2012.29.5.479

Dementia now leading cause of death. (2016, November 14). Retrieved April 22, 2019, from https://www.bbc.com/news/health-37972141

Dopamine beta-hydroxylase deficiency. (2019, April 16). Retrieved from https://ghr.nlm.nih.gov/condition/dopamine-beta-hydroxylase-deficiency

Gagnon, L., Gosselin, N., Provencher, V., & Bier, N. (2012). Perception and Emotional Judgments of Music in Dementia of the Alzheimer Type: A Short Case Study. *Music*

Perception: An Interdisciplinary Journal, 29(5), 509-519. doi:10.1525/mp.2012.29.5.509

García-Mesa, Y., López-Ramos, J. C., Giménez-Llort, L., Revilla, S., Guerra, R., Gruart, A., LaFerla, F. M., Cristòfol, R., Delgado-García, J. M., & Sanfeliu, C. (2011). Physical Exercise Protects Against Alzheimer's Disease in 3xTg-AD Mice. *Journal of Alzheimer's Disease, 24*(3), pp. 421-454. doi:10.3233/JAD-2011-101635

Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (1999). Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. *Neuropsychology, 13*(3), 359-380. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Grahn, J. A. (2009). The role of the basal ganglia in beat perception: neuroimaging and neuropsychological investigations. *Annals of the New York Academy of Sciences, 1169*, 35-45. doi:10.1111/j.1749-6632.2009.04553.x

Gray, E. G., Paula-Barbosa, M., & Roher, A. (1987). Alzheimer's disease: paired helical filaments and cytomembranes. *Neuropathology and Applied Neurobiology, 13*(2), 91-110. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Grossman, M., Smith, E. E., Koenig, P. L., Glosser, G., Rhee, J., & Dennis, K. (2003). Categorization of object descriptions in Alzheimer's disease and frontotemporal dementia: Limitation in rule-based processing. *Cognitive, Affective, & Behavioral Neuroscience, 3*(2), 120-132. Retrieved from https://link.springer.com/content/

Guétin, S., Portet, F., Picot, M., Pommié, C., Messaoudi, M., Djabelkir, L., Olsen, A. L., Cano, M. M., Lecourt, E., & Touchon, J. (2009). Effect of Music Therapy on Anxiety and Depression in Patients with Alzheimer's Type Dementia: Randomised, Controlled Study. *Dementia and Geriatric Cognitive Disorders, 28*(1), 36-46. Retrieved from https://www.karger.com/Article/

Guo, C. C., Tan, R., Hodges, J. R., Hu, X., Sami, S., & Hornberger, M. (2016). Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. *Brain, 139*(5), 1527-1538. doi:10.1093/brain/aww003.

Hailstone, J. C., Omar, R., & Warren, J. D. (2009). Relatively preserved knowledge of music in semantic dementia. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*(7), 808–809. doi:10.1136/jnnp.2008.153130

Halpern, A. R. (2012). Dementia and Music: Challenges and Future Directions. *Music Perception: An Interdisciplinary Journal, 29*(5), 543-545. doi:10.1525/mp.2012.29.5.543

Halpern, A. R. & O'Connor, M. G. (2000). Implicit memory for music in Alzheimer's disease. *Neuropsychology, 14*(3), 391-397. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Hultsch, D. F., Hertzog, C., Dixon, R. A., & Small, B. J. (1998). *Memory Change in the Aged.* Cambridge, England: Cambridge University Press.

Imprialos, P. & Baloyannis, S. (1998). The Purkinje Cell of the Cerebellar Cortex in

Alzheimer’s Disease. In B. Vellas, J. Fitten, & G. Frisoni (Eds.), *Research and Practice in Alzheimer’s Disease 1998* (pp. 89-100). New York: Springer Publishing Company.

Jensen, M. B. (2014, April 24). *Gray and white matter | Organ Systems | MCAT | Khan Academy.* Retrieved from https://www.youtube.com/watch?v=ZZQzMeFoZY0

Jensen, M., Basun, H., & Lannfelt, L. (1995). Increased cerebrospinal fluid tau in patients with Alzheimer's disease. *Neuroscience Letters, 186*(2-3), 189-191. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Koenig, P. & Grossman, M. (2007). Process and content in semantic memory. In J. Hart, Jr. & M. A. Kraut (Eds.), *Neural Basis of Semantic Memory* (pp. 247-264). Cambridge, England: Cambridge University Press.

Levitin, D. J. & Tirovolas, A. K. (2009). Current Advances in the Cognitive Neuroscience of Music. *The Year in Cognitive Neuroscience, 1156*, 211-231. doi: 10.1111/j.1749-6632.2009.04417.x

Light, L. L., LaVoie, D., Valencia-Laver, D., Owens, S. A., & Mead, G. (1992). Direct and indirect measures of memory for modality in young and older adults. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *18*(6), 1284-1297. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Lippa, C. F., Hamos, J. E., Pulaski-Salo, D., DeGennaro, L. J., & Drachman, D. A. (1992). Alzheimer's disease and aging: effects on perforant pathway perikarya and synapses. *Neurobiology of Aging, 13*(3), 405-411. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Masliah, E., Mallory, M., Hansen, L., DeTeresa, R., & Terry, R. D. (1993). Quantitative synaptic alterations in the human neocortex during normal aging, *Neurology, 43*(1), 192-197. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Matthews, B. R., Chang, C. C., De May, M., Engstrom, J., & Miller, B. L. (2009). Pleasurable emotional response to music: a case of neurodegenerative generalized auditory agnosia. *Neurocase, 15*(3), 248–259. doi:10.1080/13554790802632934

McIntosh, G. C., Brown, S. H., Rice, R. R., & Thaut, M. H. (1997). Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 62*(1), pp. 22-26. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/

Miller, A. K., Alston, R. L., & Corsellis, J. A. (1980). Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. *Neuropathology and Applied Neurobiology, 6*(2), 119-132. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Minai, M. (2014, August 12). *Purkinje Cells.* Retrieved from https://embryo.asu.edu/pages/purkinje-cells

Mitchell, D. B. (1993). Implicit and explicit memory for pictures: Multiple views across the lifespan. In P. Graf & M. E. J. Masson (Eds.), *Implicit memory: New* *directions in cognition, development, and neuropsychology* (pp. 171-190). Hillsdale, NJ: Erlbaum.

Molina, L., Touchon, J., Pau, B., & Mourton-Gilles, C. (1998). Detection of Tau Proteins in Cerebrospinal Fluid from Patients with Dementia of the Alzheimer Type. In B. Vellas, J. Fitten, & G. Frisoni (Eds.), *Research and Practice in Alzheimer's Disease 1998* (pp. 115-122). New York: Springer Publishing Company.

Nebes, R. D. & Brady, C. B. (1988). Integrity of semantic fields in Alzheimer's disease. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior, 24*(2), 291-299. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Neely, J. H. (1991). Semantic priming effects in visual word recognition: A selective review of current findings and theories. In D. Besner & G. W. Humphreys (Eds.), Basic processes in reading: Visual word recognition (pp. 264-336). Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.

Okada, K., Kurita, A., Takase, B., Otsuka, T., Kodani, E., Kusama, Y., Atarashi, H., & Mizuno, K. (2009). Effects of music therapy on autonomic nervous system activity, incidence of heart failure events, and plasma cytokine and catecholamine levels in elderly patients with cerebrovascular disease and dementia. *International Heart Journal*, *50*(1), 95-110. Retrieved from https://www.jstage.jst.go.jp/article/ihj/

Omar, R., Hailstone, J. C., & Warren, J. D. (2012). Semantic Memory for Music in Dementia. *Music Perception: An Interdisciplinary Journal, 29*(5), 467-477. doi:10.1525/mp.2012.29.5.467

Peretz, I. (1990). Processing of local and global musical information by unilateral brain-damaged patients. *Brain: A Journal of Neurology, 113*(4), 1185-1205. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Pfefferbaum, A., Mathalon, D. H., Sullivan, E. V., Rawles, J. M., Zipursky, R. B., & Lim, K. O. (1994). A Quantitative Magnetic Resonance Imaging Study of Changes in Brain Morphology From Infancy to Late Adulthood. *Arch Neurol., 51*(9), 874–887. doi:10.1001/archneur.1994.00540210046012

Randel, D. M. (2003). The Harvard dictionary of music. Cambridge, MA: Belknap Press.

Raz, N. (2005). The Aging Brain Observed in Vivo: Differential Changes and their Modifiers. In R. Cabeza, L. Nyberg, & D. Park (Eds.), *Cognitive Neuroscience of Aging* (pp. 19-57). New York, New York: Oxford University Press, Inc.

Rush, R. A. & Geffen, L. B. (2008). Dopamine β-Hydroxylase in Health and Disease. *CRC Critical Reviews in Clinical Laboratory Sciences, 12*(3), 241-277. Retrieved from https://www.tandfonline.com/doi/abs/

Salivary Chromogranin A. (2019). Retrieved from https://www.salimetrics.com/analyte/salivary-chromogranin-a/

Samson, S., Baird, A., Moussard, A. & Clément, S. (2012). Does Pathological Aging Affect Musical Learning and Memory? *Music Perception: An Interdisciplinary Journal*, *29*(5), 493-500. doi:10.1525/mp.2012.29.5.493

Satoh, M., Ogawa, J., Tokita, T., Nakaguchi, N., Nakao, K., Kida, H., & Tomimoto, H. (2014). The Effects of Physical Exercise with Music on Cognitive Function of Elderly People: Mihama-Kiho Project. *PLOS One*, *9*(4). doi:10.1371/journal.pone.0095230

Schmahmann, J. D. (2016). Cerebellum in Alzheimer's disease and frontotemporal dementia: not a silent bystander. *Brain, 139*(5), pp. 1314-1318. Retrieved from https://academic.oup.com

Simmons-Stern, N. R., Budson, A. E., & Ally, B. A. (2010). Music as a memory enhancer in patients with Alzheimer's disease. *Neuropsychologia, 48,* 3164-3167. doi: 10.1016/j.neuropsychologia.2010.04.033

Sinha, S. & Rogers, K. (2015, May 15). *Purkinje cell.* Retrieved from https://www.britannica.com/science/Purkinje-cell

Smith, E. E., Patalano, A. L., & Jonides, J. (1998). Alternative strategies of categorization. *Cognition*, *65*, 167-196. Retrieved from https://wesscholar.wesleyan.edu/cgi/

Stout, J. C., Jernigan, T. L., Archibald, S. L., & Salmon, D. P. (1996). Association of dementia severity with cortical gray matter and abnormal white matter volumes in dementia of the Alzheimer type. *Archives of Neurology, 53*(8), 742-749. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

Sutoo, D. and Akiyama, K. (2004). Music improves dopaminergic neurotransmission: demonstration based on the effect of music on blood pressure regulation. *Brain Research, 1016*(2), 255-262. Retrieved from https://www.sciencedirect.com/science/article/

Suzuki, M., Kanamori, M., Watanabe, M., Nagasawa, S., Kojima, E., Ooshiro, H., & Nakahara, D. (2004). Behavioral and endocrinological evaluation of music therapy for elderly patients with dementia. *Nursing and Health Sciences, 6*(1), 11-18. Retrieved from https://onlinelibrary.wiley.com/

Tabei, K., Satoh, M., Ogawa, J., Tokita, T., Nakaguchi, N., Nakao, K., Kida, H., Tomimoto, H. (2017). Physical Exercise with Music Reduces Gray and White Matter Loss in the Frontal Cortex of Elderly People: The Mihama-Kiho Scan Project. *Frontiers in Aging Neuroscience*, *9,* pp. 174. doi:10.3389/fnagi.2017.00174

Takahashi, T., & Matsushita, H. (2006), Long-Term Effects of Music Therapy on Elderly with Moderate/Severe Dementia. *Journal of Music Therapy*, *43*(4), 317-333. Retrieved from https://academic.oup.com/jmt/

Thaut, M. H. (2005). *Rhythm*, *Music*, *and the Brain: Scientific Foundations and Clinical Applications.* New York, NY: Routledge.

Thomas, D. W., Heitman, R. J., & Alexander, T. (1997). The Effects of Music on Bathing Cooperation for Residents with Dementia. *Journal of Music Therapy*, *34*(4), 246-259. Retrieved from https://academic.oup.com/jmt/

Tulving, E. (1972). Episodic and Semantic Memory. In E. Tulving & W. Donaldson (Eds.) *Organization of Memory.* (pp. 382-402). London, United Kingdom: Academic Press, Inc.

Valdiglesias, V., Maseda, A., Lorenzo-López, L., Pásaro, E., Millán-Calenti, J. C., &

Laffon, B. (2017). Is Salivary Chromogranin A a Valid Psychological Stress Biomarker During Sensory Stimulation in People with Advanced Dementia? *Journal of Alzheimer's Disease, 55*(4), 1509-1517. doi:10.3233/JAD-160893

Van de Winckel, A., Feys, H., De Weerdt, W., & Dom, R. (2004). Cognitive and behavioural effects of music-based exercises in patients with dementia. *Clinical Rehabilitation, 18*(3). Retrieved from https://journals.sagepub.com/doi/abs/

Vanstone, A. D., Sikka, R., Tangness, L., Sham, R., Garcia, A., & Cuddy, L. L. (2012). Episodic and Semantic Memory for Melodies in Alzheimer's Disease. *Music Perception: An Interdisciplinary Journal, 29*(5), 501-507. doi:10.1525/mp.2012.29.5.501

West, M. J. (1993). Regionally specific loss of neurons in the aging human hippocampus. *Neurobiology of Aging, 14*(4), 287-293. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

What Is Dementia? (2017). Retrieved from https://www.nia.nih.gov/health/what-dementia

Where are memories stored in the brain? (2018). Retrieved from https://qbi.uq.edu.au/brain-basics/memory/where-are-memories-stored

Wilkins, R. W., Hodges, D. A., Laurienti, P. J., Steen, M., & Burdette, J. H. (2014). Network Science and the Effects of Music Preference on Functional Brain Connectivity: From Beethoven to Eminem. *Scientific Reports, 4*(6130). Retrieved from https://www.nature.com/articles/

Yang, D. W., Hong, Y. J., Cho, A. H., Yoon, B., Shim, Y. S., Cho, J. H., Kim, J. Y., & Kim, B. S. (2010). Differences of gray matter and white matter volume in

Alzheimer's disease and subcortical ischemic vascular dementia. *The Journal of the Alzheimer's Association, 6*(4), S10-S11. Retrieved from https://www.alzheimersanddementia.com/article/