The Effects of Classical Music Intervention on the Neuropsychiatric and Cognitive Mechanisms of Alzheimer's Disease Patients

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October 17, 2023

Abstract

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, presenting a profound challenge to both neuropsychiatric and cognitive well-being. As the sixth leading cause of death in the United States, AD currently lacks a cure. This concurrent drawback sheds light into both the pharmacological and nonpharmacological, therapeutic interventions that could be incorporated into an AD patient's course of treatment. Among these is the transformative promise of classical music as a nonpharmacological mediation for AD patients. The exploration between classical music and the neuropsychiatric and cognitive mechanisms of AD unveils the effects of classical music on memory, spatial reasoning, depression, sleep disorders, and other AD symptoms. Concepts such as Mozart's effect offer a source of solace for improving the quality of life of individuals diagnosed with AD. Moreover, the activation of the brain and the alteration in various brain structures give rise to the diverse effects of classical music in a healthcare and neurological setting.

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1 Introduction

The implementation of classical music into human existence traces its origins to the middle of the 18th century, serving not only as an art form but also as a wordless language of its own. Nonetheless, classical music's purpose has evolved over the years in a plethora of ways: music as a pain reliever, the beneficial role of music in exercise and sport, musical leisure activities in aging rehabilitation, etc. However, one field that often remains overlooked in this regard is the effect of classical music on the symptoms of Alzheimer's Disease (AD). Even though neuroscience remains to be a highly studied and researched field, a plethora of questions with unknown answers arise from the topic of music's effect on the brain and limbic system of an AD patient. Alzheimer's – a neurological disease resulting from neuronal degeneration – ranks among the leading causes of death worldwide. Its hallmark symptoms include memory loss, cognitive decline, disorientation, aggression, depression, and a common inability to perform everyday tasks. The likelihood of acquiring this harmful disorder is steadily increasing and is expected to worsen tremendously in the future.

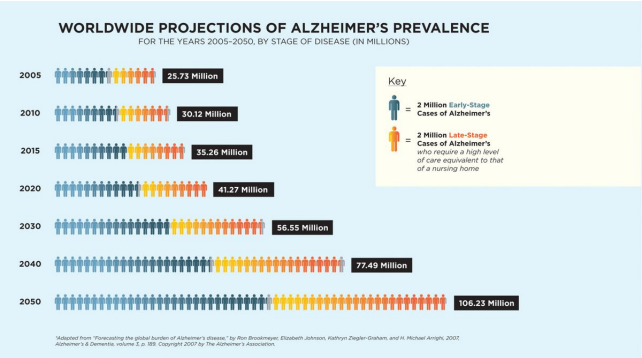

Figure 1: Worldwide Projections of AD Prevalence, 2005-2050 [D.16].

In 2020, over 40 million individuals worldwide and nearly 6 million Americans contracted AD [D.16]. These staggering figures demonstrate not just the national, per-country threat, but also the global importance and distressing impact of this disease [C.18a]. Offering a glimmer of hope amid the bleak landscape of cognitive decline, research and the associated body of knowledge indicates that classical music acts as a medium that transcends the memory loss associated with AD. In fact, classical music therapy functions as a treatment modality by improving learning, communication, mobility, and other mental and physical functions [J.17]. The aforementioned skills are all severely affected along the course of a patient with AD or other forms of dementia. This research paper aims to highlight the overall advantages and benefits derived from the application of classical music interventions to improve an AD patient's quality of life. Moreover, such a healthy inclusion possesses the potential to generate viable results during the pathogenesis and treatment of AD.

2 Alzheimer's Disease

Alzheimer's Disease (AD) – currently ranked as the sixth leading cause of death worldwide – represents a progressive neurodegenerative disorder. It lacks a definitive cure and primarily impacts a patient's cognitive functions such as memory, behavior, and thinking. AD stands as the most prevalent form of dementia, which is characterized by a gradual decline in two or more domains of cognition such as memory, language, behavior, and executive function [A.18]. The presence of neuritic plaques and neurofibrillary tangles are AD's hallmark indications – elements measured throughout the progression and regression of any disease [R.20]. This condition was first comprehensively described by Alois Alzheimer in 1906 as a "peculiar severe disease process of the cerebral cortex". Healthcare costs for AD are estimated to be approximately $500 billion yearly, ranging from the necessity for treatments to routine checkups.

2.1 Etiology of Alzheimer's Disease

The etiological pathway – or the set of common causes for AD – divides into both genetic and environmental factors. The predominant set of genetic risk components of AD that will be discussed include age, the presenilin mutation, Down Syndrome or Trisomy 21, and gender. A genetic factor is defined as a component that increases the likelihood of developing a particular disease depending on an individual's genetic makeup. Unquestionably, the greatest genetic risk factor for AD is advanced age, typically after the age of 65 [J.15].

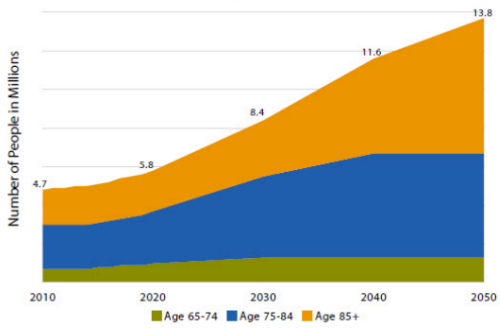

Figure 2: Projected Number of People Aged 65 or Older With Late-Onset Alzheimer's Disease, by Age Group, US, 2010-2050 [A18$_{A182A18}$].

Late-onset or sporadic Alzheimer's is the most common type of AD; signs begin to appear promptly after a person's mid-60s. Figure 2 demonstrates the prevalence of contracting late-onset AD after the age of 65. This phenomenon is relatively frequent and is estimated to increase in the mere future. On the other hand, it is important to note that early-onset or familial AD is relatively rare and is usually caused by gene changes passed down from a parent to their child. Signs first appear between an individual's 30s and mid-60s. In familial

AD, nearly half of the cases are due to mutations in three genes: amyloid precursor protein (APP), Presenilin-1 (PSEN1) and Presenilin-2 (PSEN2) [J.15]. Presenilin (PSEN) mutations will be discussed in much more detail later. It is crucial to understand that findings in early-onset familial cases will translate to the sporadic (no specific family link) late-onset AD.

Aging is the main risk factor for AD that simply cannot be explained by the popular amyloid hypothesis theory, which asserts that the amyloid-beta plaques are the major highlight of this disease. Yet, an alternate perspective to aging and AD is strongly related to the APOE$\mathcal{E}$4 allele, which remains as the most robust genetic risk factor for sporadic AD. In AD, the risk conferred by APOE$\mathcal{E}$4 is mostly observed in the 61-65 age group, which supports the statement that symptoms of late-onset AD first appear around 65 years of age [R.97]. One copy of APOE$\mathcal{E}$4 is carried by approximately 25% of individuals, but inheriting this gene does not indicate that a person will surely develop AD [21_2170_21]. It is important to note that the APOE$\mathcal{E}$4, APOE$\mathcal{E}$3, and APOE$\mathcal{E}$2 alleles all play a significant role in the onset and progression of AD, but the APOE$\mathcal{E}$4 vastly increases the risk of the disease compared to its counterparts [G.22]. Moreover, the APOE genotypes' pathogenesis has been researched way beyond just amyloid-beta plaques and the Tau neurofibrillary tangles, providing potential answers to the age-related progression of AD [T.21]. For one, APOE$\mathcal{E}$4 is associated with not only AD but also other symptoms and diseases such as age-related cognitive decline and Lewy Body Dementia (LBD) [G.22]. Secondly, the APOE Cascade Hypothesis connects the dots between an increased risk of AD and aging by stating that the biochemical and biophysical characteristics of APOE$\mathcal{E}$4 at a cellular level cause a multitude of downstream effects observed in AD [T.21].

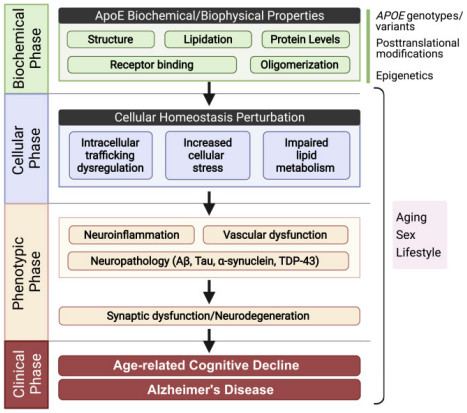

Figure 3: APOE$\mathcal{E}$4 Cascade Hypothesis Demonstrated Through 4 Phases [G.22].

The cascade – or the successive progression of APOE$\mathcal{E}$4 – begins at the biochemical and cellular phase as demonstrated in Figure 3. Properties of the allele such as lipidation and receptor binding have harmful impacts on some cell processes, which could accumulate into cellular stress and eventually lead to the onset of age-related cognitive decline and AD. Aging and AD are interconnected but are distinct in nature. The number of neurons do not severely increase or decrease in aging, but neuronal and synapse loss is a key indication of AD. Nevertheless, aging and the increased risk of contracting AD with the APOE$\mathcal{E}$4 gene is a predominantly researched topic within the field, proving to hold a major connection to sporadic AD.

Another genetic factor for AD that is widely discussed is the PSEN1 gene mutation, encoding the Presenilin-1 (PS1) protein. In early-onset AD or familial Alzheimer's Disease (FAD), PSEN1 mutations account for nearly 90% of all mutations recorded in FAD, illustrating the significance of this gene and its protein products [rSJ17]. The presenilin hypothesis proposes that these deleterious mutations result in a decrease of the needed presenilin functions in the brain, triggering both neurodegeneration and dementia in FAD [rSJ17]. Another component to discuss – with regard to PSEN1 and PS1 – is the $\mathcal{Y}$-secretase enzyme whose catalytic subunit is PS1. More specifically, $\mathcal{Y}$-secretase cleaves different types of transmembrane proteins attached to the plasma membrane of a cell, which includes the amyloid precursor protein (APP) – a central element of AD. $\mathcal{Y}$-Secretases produce two types of amyloid-beta proteins in AD: A$\mathcal{B}$42 and A$\mathcal{B}$40. The only difference between the two is that A$\mathcal{B}$42 has two extra residues at its C-terminus end [Z.13]. It has been proposed in the past that A$\mathcal{B}$42 and A$\mathcal{B}$40 are heavily responsible for AD since they accumulate into one of the hallmark pathological indications for this disease – A$\mathcal{B}$ plaques. However, PSEN1 mutations did not increase both of the proteins; instead, the proteins both decreased in number (especially A$\mathcal{B}$40) which elevated the A$\mathcal{B}$42/A$\mathcal{B}$40 ratio [rSJ17]. This A$\mathcal{B}$42/A$\mathcal{B}$40 ratio is a useful diagnostic marker of AD since the ways in which PSEN1 mutations affect APP and A$\mathcal{B}$-plaques is complex and not yet properly acknowledged [C.06]. It is clear that $\mathcal{Y}$-secretases produce the final A$\mathcal{B}$ proteins involved in AD, but they also regulate Notch signaling, which regulates cell proliferation, cell fate, differentiation, and cell death [R.12]. Therefore, pharmacological interventions such as drug therapy attempt to alter A$\mathcal{B}$ protein production without interfering with $\mathcal{Y}$-Secretases' ability to perform Notch signaling [S.12].

The next genetic factor for AD that will be discussed is Down Syndrome (DS) or Trisomy 21: a genetic disorder caused by the presence of an extra copy of Chromosome 21 or a part of it. It is distinguished based on craniofacial abnormalities, heart defects, cognitive impairments, and neurological alterations [M.20]. With over 200,000 cases in the United States alone, DS is one of the leading genetic risk factors for FAD. Furthermore, clinical and biomarker changes in DS associated FAD demonstrate that many of the same cortical regions are affected in both diseases such as the hippocampus and the prefrontal cortex [M.21a]. As they progress, both diseases share similar cellular dysfunctions such as impaired autophagy, reduced and/or damaged lysosomal

activity, and mitochondrial dysfunction [M.20].

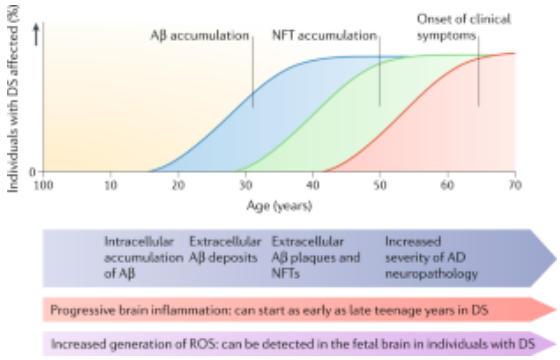

Figure 4: Pathological Indications of DS Common in AD [E.19].

By the age of 40, NFT and A$\mathcal{B}$ accumulation are present in the brains of individuals with DS, which is sufficient enough to confirm a pathological diagnosis for AD [C.18b]. In Figure 4, evidence demonstrates that progressive brain inflammation can emerge as early as the late teenage years in DS based on recorded intracellular accumulations of A$\mathcal{B}$. The early appearance of AD's hallmark indications in individuals with DS can be explained by the presence of neuron-derived exosomes, which are tiny extracellular vesicles that contain elevated levels of both A$\mathcal{B}$ peptides and the hyperphosphorylated Tau protein [C.18b]. Since exosomes are blood biomarkers, their progression and development can be monitored, which informs future AD diagnostics, preventions, and potential treatments in the DS population as well as the general population.

Finally, sex is an important genetic risk factor for contracting AD, with almost two thirds of the late-onset AD population being women [dLMJBRD18]. It cannot simply be stated that women are more likely to develop AD since they have a greater life longevity compared to men. This is because AD pathology starts many years prior to the appearance of most clinical symptoms [L.18]. However, there is increasing evidence that the perimenopause to menopause transition (PTMT) – a midlife neuroendocrine transition specific to women – is heavily responsible for the sex-observed pathophysiological mechanisms underlying AD [dLMJBRD18]. PTMT is strongly neurological in nature; it disrupts and alters the systems and mechanisms regulating estrogen and impacts thermoregulation, circadian rhythm, sleep, depression, and even cognition [dLMJBRD18]. During PTMT, estrogen, progesterone, pituitary, hypothalamic, and ovarian hormone levels fluctuate and decrease. Estrogen, specifically, is unique to females and is found in a plethora of areas in the brain controlling memory and cognitive function, indicating its neurological significance [E.18]. When the brain's estrogen network disconnects from other brain areas, the resulting hypometabolic state serves as a major site for neurological dysfunction [L.18]. In fact, perimenopausal (PERI) and postmenopausal (MENO) women show major declines in estrogen-dependent memory tests compared to men, which

is the first indication that PTMT can trigger cognitive decline in the female population [dLMJBRD18]. Secondly, the MENO and PERI groups disclosed higher rates of cerebral metabolic rate for glucose consumption (CMRglc) decline compared to males and premenopausal (PRE) women. Glucose is necessary to provide the precursors for neurotransmitter synthesis and fuel adenosine triphosphate (ATP) production, which is the source of energy and storage at the cellular level [A.13]. With a noticeable decrease in glucose levels, the neurological workings of the body are severely disrupted in PERI and MENO individuals. In essence, decreased estrogen levels and the deterioration of the pathway that affects CMRglc explain the higher percentage of women developing AD.

In addition to genetic risk factors, various environmental, predisposing contributors pertain to AD such as Type 2 diabetes (T2D)/Type 2 diabetes mellitus (T2DM), obesity, and cerebrovascular disease.

Firstly, the interplay between diabetes, obesity, and AD highlights the complex relationship between lifestyle factors and the risk of cognitive decline. It should be noted that obesity is characterized by an excessive accumulation of body fat, which is measured using the Body Mass Index (BMI). Obesity can, in turn, trigger the development of T2D, and the risk of acquiring this disease linearly grows with an increase in BMI [E.22b]. T2D – representing 90-95% of diabetic cases – can be defined as a disease affecting metabolic activity, characterized by the presence of chronic hyperglycemia due to pancreatic cell failure [C.21]. Just by itself, hyperglycemia or high blood glucose, can contribute to molecular, biochemical, and histopathological lesions in AD [ML14]. Yet, the main focus when researching the connection between T2D and AD is insulin resistance – the body's reluctance to the insulin hormone, subsequently resulting in an increase of blood sugar. The hyperglycemic status of T2D patients due to insulin resistance affects neuronal homeostasis and affects K-ATP channels, which increases A$\mathcal{B}$ peptide levels [C.21]. Also, an increased level of glucose in the blood and the dysregulation of glucose molecules drives an unregulated non-enzymatic reaction between many carbohydrates (such as sugars) and lipids and between free amino groups (-NH2) of several proteins and nucleic acids, which results in advanced glycation end-products (AGEs) [C.21]. High levels of AGEs elicit inflammatory reactions in the brain and develop symptoms leading to poorer memory and higher hippocampal levels of insoluble A$\mathcal{B}$42 [M.16b]. AGEs promote A$\mathcal{B}$ plaques and neurofibrillary tangle formation more in AD patients with T2D than in non-diabetic AD patients [C.21]. The two main hallmark indications of AD – A$\mathcal{B}$ plaques and neurofibrillary tangles – will be discussed in detail in the pathology section.

Another environmental risk factor for AD is cerebrovascular disease (CVD) – a type of cardiovascular disease that harms the blood vessels supplying the brain. CVD is the most frequent type of life-threatening injury to the brain and is the fifth most common cause of death. CVD and AD share many of the same risk factors such as the APOE$\mathcal{E}$4 gene, T2DM, obesity, and age [S.16]. These account for some of the genetic and environmental risk factors of AD previously discussed, which demonstrates that CVD's origin is pathologically and environmentally similar to that of AD. A$\mathcal{B}$ plaques in AD accumulate in the

extracellular part of a neuron; in cerebral arterioles and blood vessels supplying to the brain, A$\mathcal{B}$ builds up in the capillaries of CVD patients. Most AD patients have A$\mathcal{B}$ angiopathy resulting from CVD, which predominantly affects the cerebral leptomeninges, cortex, cerebellum, and the brain stem [S.16]. The capillary A$\mathcal{B}$ angiopathy is detected in almost 35-45% of AD cases, which provides robust evidence supporting the hypothesis that CVD can contribute to the symptoms distinct to AD due to the synergistic relationship of the diseases [G.21].

2.2 Pathology of Alzheimer's Disease

The principal pathological indications of AD include the presence of amyloid beta (A$\mathcal{B}$) plaques, neurofibrillary tangles containing an aggregation of the Tau protein, neuroinflammation, and oxidative stress [S.18]. The entirety of neurodegenerative diseases involves the eventual degradation of neurons in the brain, and this trend is especially evident in the progression of AD. The exact path in which neuronal death occurs is obscure, yet there are many theories driven around the same question. Apoptosis, the process of programmed cell death to eliminate unwanted cells, is the most extensively studied topic regarding neuronal loss in AD due to its unique cellular nature. Yet, the A$\mathcal{B}$ peptide known to be responsible for driving neuronal apoptosis is not recorded in many post-mortem tissue specimens of AD patients [R.22]. Even though there are other researched explanations for neuronal death such as necrosis, necroptosis, and/or pyroptosis, the pathological mechanisms underlying neuronal death and dysfunction in AD continue to elude full comprehension. Nevertheless, the loss of neurons undoubtedly constitutes the basis of progression for this disease.

Regarding neuronal loss, there has been an elevated degree of focus on cholinergic neurons that release the neurotransmitter acetylcholine (ACh), which has a crucial role in both the peripheral and central nervous system [M.16a].

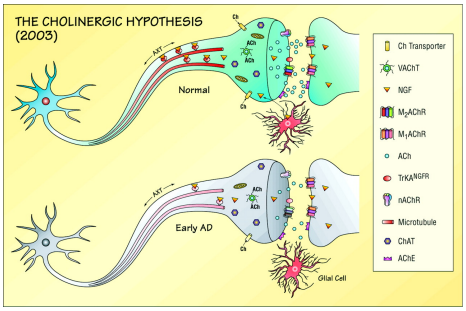

Figure 5: The Cholinergic Hypothesis & Release of ACh [J.03]

The alterations in choline uptake, negatively affected ACh release, deficits in the nicotinic (nAChR) and muscarinic (M2AChR and M1AChR) receptors and their functions, and deficits in transport through the axon are exhibited in the early AD neuron above in Figure 5. The decrease in the number of

symbols and the reduced color intensity in the legend illustrate that many proteins, enzymes, and essential cell structures in AD turn defective or are missing all together, which essentially kills the whole neuron. Nearly all brain regions are innervated by cholinergic neurons, which are responsible for processes related to learning, memory, and attention. The progressive degeneration of the basal forebrain cholinergic neurons (BFCNs), for instance, is correlated with the harmful symptoms and memory deficits that AD impedes on a patient [M.16a]. In fact, BFCNs provide the main cholinergic information to prefrontal cortices in the brain along with other crucial structures such as the amygdala (responsible for evoking emotions) and the hippocampus, which plays a significant role in long term memory function and memory consolidation [M.22]. Pathologically, there have been major depletions of the cholinergic synthetic enzyme named choline acetyltransferase (ChAT) and the cholinergic hydrolytic enzyme acetylcholinesterase (AChE) in and around BFCNs [MM21]. ChAT is interconnected with the process of synthesizing or polymerizing ACh, whereas AChE breaks down ACh into its component parts. Together, these enzymes along with the ACh neurotransmitter play an essential role in the nervous system due to their ability to regulate cell signaling and host effective communication amongst neighboring neurons. A dramatic loss of ChAT and AChE activity in a considerable number of AD cases strongly supports the claim that the BFCN's degeneration is a strong foundation for the cholinergic theory of AD.

Onto the more prominent hallmarks of AD (ones that contribute to the loss of neurons and their synapses) are the extracellular neuritic plaques containing the amyloid-beta ($A\mathcal{B}$) protein and the intracellular neurofibrillary tangles (NFTs) carrying the hyperphosphorylated Tau protein.

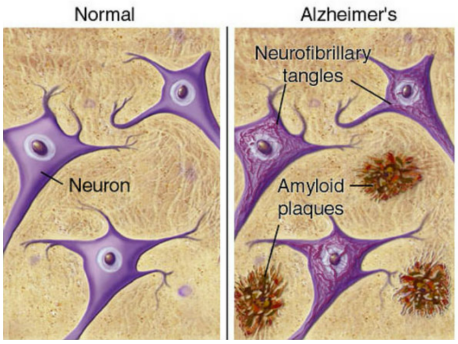

Figure 6: $A\mathcal{B}$ plaques and NFTs in Healthy vs. Affected Neuronal Cavity [$A15_{A153_A15}$]

In a healthy neuron, there are visibly almost no $A\mathcal{B}$ plaques in the exterior of the cell, and there are no NFTs present either. This allows for the cell to effectively communicate with surrounding neurons and also operate intracellularly. On the other hand, the neurons in a brain with Alzheimer's contain $A\mathcal{B}$ plaques surrounding the cell, and NFTs present in the soma/cell body of the neuron.

As a result, neuronal function is disrupted, which eventually contributes to the cell's death.

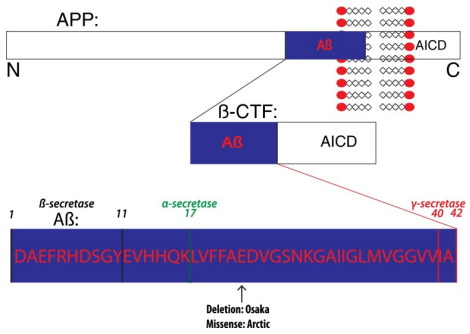

Figure 7: A schema of amyloid precursor protein (APP) cleaved to form A$\mathcal{B}$ plaques [O.14]

It is important to note that A$\mathcal{B}$ is a regular peptide produced in the body, but A$\mathcal{B}$ plaques – specifically – indicate a neuropathological hallmark of AD [O.14]. The precursor protein (APP) – located on a cell's plasma membrane – undergoes cleavage by $\mathcal{B}$-secretases and y-secretases to produce insoluble A$\mathcal{B}$ fibrils. All mutations in APP linked to AD are within the A$\mathcal{B}$ peptide, $\mathcal{B}$-cleavage, or y-cleavage sites. As seen in Figure 7, APP is cleaved by the $\mathcal{B}$ secretase to form C-terminal fragment $\mathcal{B}$ ($\mathcal{B}$ - CTF) and then cleaved once more by y-secretase to produce A$\mathcal{B}$ – the prime component of the A$\mathcal{B}$ plaques seen in Alzheimer's. In the non-amyloidogenic pathway or the way in which A$\mathcal{B}$ formation is considered less toxic than the amyloidogenic pathway, the a-secretase creates less-aggregated forms of A$\mathcal{B}$ that are less likely to form extracellular plaques. The major difference is where the cleavage occurs and which enzyme carries out the task that indicates whether the A$\mathcal{B}$ protein is toxic or non-toxic. In AD, toxic A$\mathcal{B}$ fibrils diffuse into the pre-synaptic clefts and interfere with the necessary cell signaling [M.19b]. As a result, the A$\mathcal{B}$ fibrils that cannot dissolve in water aggregate into the plaques that are present in AD. Furthermore, the polymerization of the A$\mathcal{B}$ protein into long strands of polypeptides leads to the activation of a group of enzymes named kinases, which hyperphosphorylate the microtubule-associated Tau protein. The gradual build-up of Tau eventually leads to the formation of intracellular NFTs that disrupt neural communication. The correlation between A$\mathcal{B}$ plaques and the aggregation of Tau has dominated AD research as the "Amyloid Cascade Hypothesis". This states that the abnormal build-up of A$\mathcal{B}$ is the primary event in AD, triggering Tau pathology and subsequently neuronal death [O.18].

Another consequence of the accumulation of A$\mathcal{B}$ plaques and the Tau associated NFTs is the increased production of reactive oxygen species (ROS). Since oxygen is an extremely electronegative element, it readily accepts free flowing electrons generated by mitochondrial oxidative metabolism, which produces

ROS. These species range from various types of anions to hydrogen peroxide, which both have unpaired valence electrons. Such ions and compounds will readily accept an electron to transition into a stable state with a full octet surrounding their outer shell. However, until they reach stability, ROS at high concentrations will react almost immediately with the four major macromolecules in the body: lipids, proteins, carbohydrates, and nucleic acids [KH12]. On one hand, ROS are crucial in physiological processes such as redox regulation and transcription of DNA. Nonetheless, they may also induce undesirable effects and even irreversible outcomes such as the aggregation of Alzheimer's.

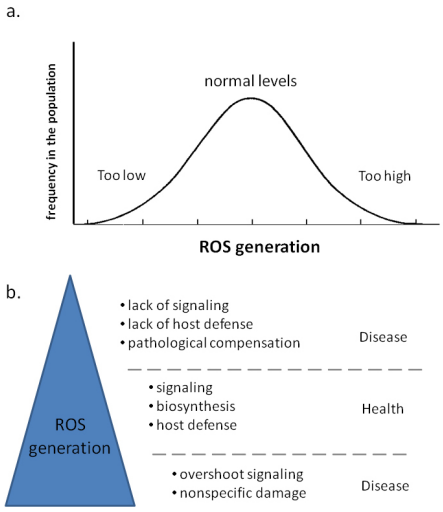

Figure 8: Levels of ROS and the Resulting Effect [KH12]

When ROS levels substantially decrease or increase past their optimal level of appearance, there can be dangerous consequences such as lack of signaling when they increase or overshoot signaling (signal is sent exceeding its target) when they decrease. In the context of AD, increased production of ROS by the interrelation between A$\mathcal{B}$ plaques and NFTs raises the risk of oxidative stress: a condition caused by the imbalance of ROS in cells and tissues, impairing the body's ability to detoxify these reactive substances [A.17]. Elevated levels of ROS leading to oxidative stress can exacerbate age and disease-dependent mitochondrial dysfunction, reduce antioxidant defences around synaptic activity, and disrupt neuronal cell signaling, ultimately leading to cognitive dysfunction [E.17]. Even in the absence of ROS, A$\mathcal{B}$ plaques and high levels of Tau can independently worsen mitochondrial dysfunction and interrupt cell communication, which inevitably contributes to a perilous cycle in the body with disruptive homeostatic control.

The intricate pathology of AD, in summary, is marked by hallmark features of neuronal and synaptic loss, A$\mathcal{B}$ plaques, NFTs, ROS, and oxidative stress.

The interconnectedness between these factors wholly contributes to the cognitive and behavioral decline associated with AD. Ongoing research continues to shed light on novel aspects of AD pathology, which holds a degree of promise for lessening the impact of this neurological disorder.

2.3 Neuropsychiatric and Cognitive Symptoms of AD

As Alzheimer's progresses, the burden of both neuropsychiatric and cognitive symptoms can pose significant challenges for both AD patients and caregivers. Neuropsychiatric symptoms (NPS) are non-cognitive disturbances that pertain to mental health defects and psychiatric disorders. NPS are interconnected to both neurological (brain-related) and psychiatric (mental-health related) aspects. On the other hand, cognitive symptoms refer to anything harmed in the brain processes involving thinking, learning, problem-solving, understanding, and decision-making. Memory, attention, language, executive functions, perception, and reasoning are just a few concepts that fall under the umbrella of cognitive processes. The most common forms of NPS in AD are apathy, depression, aggression/agitation, and sleep disorders.

To begin, apathy is the most persistent and frequent NPS recorded in all the AD stages [S.11]. This symptom is characterized by a lack of motivation for goal-directed actions and cognitive activity [G.06]. In AD, the primary psychiatric correlate of apathy is depression, but depression is neither necessary nor sufficient to produce apathy; 94% of AD patients with some form of depression had no apathy [G.06]. When accounting for other NPS, apathy is difficult to isolate from the various symptoms of dementia, but there are a few neuroimaging techniques that could generate some answers. Many studies hint towards the involvement of prefrontal dysfunction and deficits within frontostriatal circuits [M.18]. Areas within these circuits such as the anterior cingulate cortex (ACC), prefrontal cortex (PFC), and sections of the basal ganglia play a pivotal role in the progression of apathy in AD [M.18].

Depression trails behind apathy as the second most commonly encountered NPS in AD patients. Depression can be identified as an affective disorder containing bits and pieces of despair, apathy, insomnia, unwillingness, anxiety, incompetence, fear, gloominess, and sadness [C.19]. The additional stress implemented by depression in the AD population can detrimentally decrease a patient's quality of life. As a matter of fact, depression occurs in an astonishingly substantial percentage of almost 20-30% of AD patients. Women are expected to experience a much higher depression rate (almost two times more than men) when contracting AD, indicating that gender plays a role in the depressive state of a patient [C.19]. It is important to note that cognitive dysfunction may seem like depression because the two are quite commonly confused with each other. Even though it is difficult to capture a definitive diagnosis for depression in AD, both disorders influence each other through several, overlapping pathological features. For instance, aberrations in the cholinergic transmission are present in both AD and depression, which fuses together a pathophysiological intersection [C.19]. As previously discussed, the cholinergic hypothesis of AD proposes

that the deterioration of cholinergic neurons – that release the AcH neurotransmitter – is primarily responsible for memory loss and learning deficits. In addition, the ability of the cholinergic system in triggering depression has also been suggested in clinical studies nearly 50 years ago [S.19a]. With respect to changes in the cholinergic system, the hippocampal region is the crossroad where cognitive deficits meet with depressive manners [E.22a].

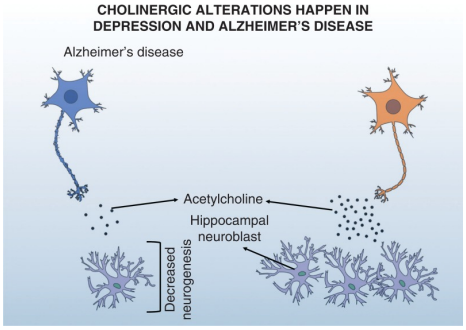

Figure 9: Cholinergic Alterations in Depression and AD [C.19].

Decreases in the cholinergic innervations of the brain reduce hippocampal neurogenesis and function, which can result in depression. The chances of this occurring are much higher for an AD patient compared to the general population though.

Aggression/agitation in AD often stems from communication difficulties, which can be properly addressed with appropriate intercessions. To begin, aggression exists in a wide range of forms such as defensive (fear-induced), predatory, dominance, inter-male, maternal, isolation-induced, irritability-associated, etc. [EI.17]. In order to alleviate these types of symptoms in an ethical manner, medication use and physical restraint are advised by doctors and various healthcare providers. However, antipsychotic medications are associated with adverse side effects such as an increased stroke risk, and physically constricting an AD patient induces negative psychological and physical effects [S.19b]. Even though the molecular mechanisms in functional and pathological agitation in AD remain incompletely understood, promising scientific initiatives are frequently conducted. One past example includes the definitive explanation of the comprehensive spectrum of brain abundant neurotransmitters that appear to have both triggering and preventing impacts on aggressiveness [EI.17].

Lastly, sleep disorders are typical symptoms of AD that appear early on in the disease, which is quite distinct from other symptoms such as depression and apathy that appear later on. There is a wealth of evidence available to support the claim that sleep quality and duration are crucial to consolidate memory for future retrieval and to remove the build-up of A$\mathcal{B}$ and hyperphosphorylated Tau in AD patients' brains [A.20]. Individuals with AD that struggle with a normal sleep schedule exhibited a major alteration in the sleep/wake cycle, with a growth in the number of nighttime awakenings and an increase in disturbances

of nocturnal sleep [A.20]. Sleep disorders such as sleep breathing disorders and restless leg syndrome negatively alter circadian fluctuations of A$\mathcal{B}$ in the interstitial brain fluid and cerebrovascular fluid (CVF) related to the production of A$\mathcal{B}$ plaques [G.18]. Such sleep abnormalities evoke the increased production of the pathological Tau protein and A$\mathcal{B}$ plaques. In order to aid AD patients in adopting healthy sleep patterns, the development of specific procedures to improve sleep structure and quality are being expanded on constantly. There are a plethora of NPS associated with AD, and there is extensive, favorable research being done on alleviating these symptoms.

Conversely, the major cognitive symptom in Alzheimer's is memory loss. If asked to name a disease that affects memory, most doctors would probably choose Alzheimer's. The six major memory systems include episodic, semantic, simple classical, procedural, working, and priming memory. Of these major categorizations, the deterioration of episodic memory is the most clinically abundant cognitive symptom in AD [E.08]. Episodic memory is utilized when consciously recalling a particular episode in one's life, such as watching a movie with a family member. Dangers arise from a loss in episodic memory when AD patients forget if certain medications have been taken or even if the stove is turned off or not [E.08]. Working memory and long-term, explicit memory are impacted early in the course of this disease [H.13]. The first brain lesions unique to AD appear in the poorly myelinated limbic neurons in areas affecting memory, such as the hippocampus. For instance, hippocampal volume reduces from 2.5 mL to almost 1.6 mL in the brain of an AD patient, especially as the disease progresses [H.13]. Even with the inclusion of various AD criteria and hippocampal biomarkers, there remain several barriers in neurological testing for memory loss in AD.

Other cognitive symptoms of AD are impaired problem solving and language levels. Something as simple as following a recipe or even paying the bills can occur as AD worsens. Language impairments are caused by a decrease of sociolinguistic aspects such as the meaning of words, difficulties with fitting a word and phrase into a situation, and word comprehension [K.15]. These two prevalent cognitive symptoms appear early on in AD, so they are used occasionally to help diagnose a patient with AD.

3 Music and the Brain

The exploration of non-pharmacological interventions for AD has garnered significant attention in recent times; however, promising avenues have been underemphasized or overlooked. Cognitive decline, NPS, and memory impairment present a pressing necessity for a quick and efficient way to mitigate AD's symptoms and risks. Amidst this scholarly discussion, the interplay between music and AD has emerged as a potential candidate to enhance the quality of life of an Alzheimer's patient. This section solely focuses on the relationship between music and the brain.

3.1 Observed Effects of Music on the Brain

The ability for humans to perceive and enjoy music is a universal trait that originated centuries ago and is still carried with us. Music is one of the most powerful and diverse sensory, cognitive, and emotional experiences [T.17]. Our brains light up when interpreting and perceiving music, and our bodies respond in several ways, reflecting the powerful connection between music and our well-being. Not only does music reduce feelings of separation and loneliness, it also evokes cherished memories and maintains self-esteem, competence, and independence [T.17]. From a cognitive standpoint, music boosts communicative abilities, memory, self and environmental presence, and verbal and non-verbal expressions [M.21b]. The improved projection of all these skills originates from the organ responsible for formulating the very essence of what a human being is: the brain. On top of encoding music, various parts of the brain are also engaged based on the type of music traveling from the auditory cortex to the brain's nerve signals. This concept is demonstrated below in Figure 10.

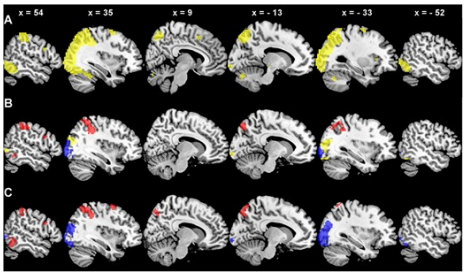

Figure 10: Brain Areas Engaged Based on Emotion Category of Music [P.19].

Different brain areas are engaged according to the emotion category of music in different colors – joyous music (red), tense music (yellow), and sad music (blue). Based on conclusive results and statistically significant data, the type of musical input is allocated to different parts of the brain connected by a bilateral fronto-parietal network [P.19]. From a structural, cross-section view of the cerebral cortex, it is clear that music in the brain can alter our perception and emotional response based on the area it activates. For example, music with a fast tempo and a major mode tend to evoke a positive/happy response, but a slow tempo induces a negative/sad mood. The functional standpoint of listening to music over time is an increase in the brain's alpha waves that are associated with relaxation and a calm state of mind [V.18]. The brain's alpha waves are also robustly responsible for human cognition and emotions, which generates distinct physiological and psychological effects on the body [V.18].

Additionally, music causes the release of certain neurotransmitters, which evokes important emotions, memories, and feelings. For instance, dopamine is released in the mesolimbic reward system while listening to music, which increases the body's natural reward sensation. Serotonin, a neurotransmitter involved in mood regulation and learning, also increases in the presence of audi-

tory stimuli. Higher concentrations of dopamine and serotonin in the caudate-putamen and nucleus accumbens (areas linked to reward and motor control) signify that music has a direct impact on the synaptic activity of these brain areas and the amount of neurotransmitters released in a healthy manner.

3.2 Musical Activation of Various Brain Areas

Many structures are engaged in the process of musical activation, which is the stimulation of the brain's cerebral cortex into a state of alertness/attention.

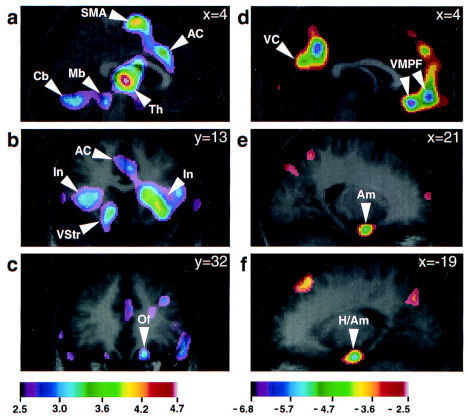

Figure 11: Regression Analysis Correlation (rCBF) of Neuroanatomical Regions Scanned After Exposure to Music [J.01].

Through the help of Magnetic Resonance Imaging (MRI) scans, Figure 11 depicts various brain parts engaged due to musical activation. These include the left dorsomedial midbrain (Mb), bilateral cerebellum (Cb), right thalamus (Th), left ventral striatum (VStr), and the hippocampus/amygdala (H/Am). The amygdala, especially, plays an important role in the body's perception of music. As a part of the brain's limbic system, the processing for emotions, fear, and aggression originate from the amygdala – a small, almond-shaped structure. The amygdala's gray matter volume (GMV) is directly correlated with an individual's melodic interval perception, which is the time taken to differentiate two successive events [J.14]. In music, interval perception refers to how we perceive the pitch gap between two notes played successively. This suggests that the optimal GMV of the amygdala is an integral part of both perceiving and processing the emotions generated by music. To further support this claim, people with a decreased amygdala GVM portrayed impaired emotional responses to music such as not recognizing sad or fearful music and not demonstrating a sense of pleasure when listening to pleasant music [J.14].

Another structure of the limbic system is the hippocampus, which is also activated by the presentation of music. This structure is fundamental in the consolidation of both short-term and long-term memory and is involved in state

regulation, motivation, defensive behavior, and anxiety in response to specific stimuli [D.06]. Typically, the hippocampus is associated with the processing of unpleasant (permanently dissonant) music compared to pleasant (consonant) music [D.06]. Just how some brain structures can perceive components like rhythm and pitch, the hippocampus recognizes harmonious sounds and separates them from unstable and tense sounds.

To add, more neuroimaging studies indicate that an overlap in musical activation occurs in the superior temporal gyrus (STG), middle temporal gyrus, middle frontal gyrus, parietal lobe, supplementary motor area, and premotor cortex [X.19]. During music listening, both the left and right brain hemispheres are activated, and the right temporal cortex is even involved in the perception of pitch patterns [X.19]. Clearly, the underlying workings of music is a neurologically ubiquitous process with differing structures involved in an attentive brain.

3.3 The Difference Between Classical and Non-classical Music

There has been a widespread interest in music's effect on the brain, and there exists a plethora of beneficial reasons why music is nature's own "medicinal treatment". Nevertheless, is this due to music as a whole or – more exactly – a type of music? This section will analyze the differences among classical music and non-classical music and determine which one reaps the most advantages for the brain and the body.

One concept that delves into classical music's influence on the brain is the Mozart effect. This phenomenon is observed as an improvement in certain brain functions and abilities from repeatedly listening to classical pieces composed by the popular 19th century musician, Wolfgang Amadeus Mozart. In a study where subjects listened to Mozart's Sonata for 2 Pianos, it was concluded that participants demonstrated significantly greater spatial-reasoning skills compared to periods of listening to relaxation instructions attempting to decrease blood pressure [S.01]. Spatial reasoning is simply the ability to comprehend and effectively draw conclusions. Sonata for 2 Pianos is also proven to drastically increase relative alpha band power, which increases the brain's alpha wave patterns [R.18]. Once again, an increase in alpha wave patterns is associated with an alert and relaxed state of mind.

Nevertheless, Mozart's music is not the only form of classical music that demonstrates these improvements in brain functions. In one study, after listening to either Gustav Mahler's Adagietto Symphony 5, white noise, or no music, participants' semantic memory recollection increased when listening to the classical piece compared to the white noise and no music [E.14]. Semantic memory is a type of long-term memory involved in remembering words, concepts, and permanent knowledge such as languages. The mean values for the cognitive task associated with semantic memory was 39.90 for the Mahler group but 36.39 and 38.34 for the white noise and no music groups, respectively [E.14]. The higher value for the Mahler group indicates that classical music has its own

set of benefits that cannot be derived from other types of music. Furthermore, music with a long-term periodicity, whether of Mozart or other classical composers, resonates within the brain to enhance spatial-temporal performance and even decrease seizure activity [S.01]. For instance, Greek-American musician Yanni's compositions – similar to those of Mozart's Sonatas in tempo, melody, harmony, and structure – were also effective and reproduced the exact results that improved cognitive abilities like reasoning and memory [S.01]. However, the effects of music may not be dependent on a specific piece. Even though robust evidence demonstrates classical music's ability to improve cognitive skills such as memory and learning, music that is personally liked by subjects turns out to enhance alpha wave and beta wave frequencies in the temporal brain regions as well [R.18]. Therefore, non-classical music such as rock, pop, hiphop, rhythm and blues, and even jazz could potentially generate the same results; this would greatly depend on the preferences of the individual though.

3.4 The Purpose of Music Therapy

Music Therapy (MT) is an art-based intervention which utilizes music experiences within a therapeutic manner to address patients' physical, cognitive, emotional, and social needs [M.19a]. Both participants and music therapists interact within a structured framework, which concludes in conversations about the patient's emotions and/or experiences [C.17]. MT is known to alleviate a patient's symptoms and improve their quality of life especially in fields of health care such as neonatology, neurodegeneration, and pediatric oncology [C.17]. Regarding the brain, the influence of MT results in mood improvement, enhanced cognitive functions in memory, and provides a sense of connection for patients who may feel alone [L.23]. Moreover, MT is a gradual process as results are not observed in just a few days. After a few weeks of prolonged exposure, though, a significant increase in the brain's alpha waves indicates that a novel form of art-based therapy is something that participants habituate and adapt to [V.18]. As weeks go by, music-listening groups undergoing MT even experience more joyous and relaxed emotions [V.18].

Even though there aren't effective treatments developed for different neurodegenerative diseases such as AD, MT and other music-related non-pharmacological therapies have garnered more attention as a method to boost cognitive and behavioral functions. For one, MT induces plastic changes in a few brain networks; this is a process known as neuroplasticity [L.23]. Neuroplasticity is a unique process that involves adaptive structural and functional alterations to the brain. This concept is of extreme importance since it allows the brain to reorganize itself and change its activity in response to distinct stimuli after injuries such as a stroke.

To summarize, the impact of music, especially classical music, on the brain is remarkably pervasive. It engages numerous brain areas, triggers the release of a greater quantity of neurotransmitters, and has the potential to reshape the brain itself. Given music's proven effectiveness in improving cognitive functions like spatial reasoning and memory, it is imperative to explore and research whether

classical music, as a non-pharmacological intervention for AD patients, could ameliorate the neuropsychiatric and cognitive symptoms of AD.

4 Alzheimer's Disease and the Influence of Classical Music

AD is a formidable and deeply puzzling neurological disease that proceeds to challenge medical research and potential therapeutic interventions. As healthcare professionals and scientists strive to unravel the complexities of this disorder, unconventional and non-pharmacological avenues for exploration have emanated. In the midst of these, classical music intervention in AD has captivated the interest of many. Not only does this convergence prompt questions regarding curative advantages, but it also delves into the extreme effect classical music may have on NPS, cognitive symptoms, and the overall quality of life for AD patients. In this section, the multifaceted interrelation between AD and classical music will be discussed, seeking answers to uncover the ways in which art may offer hope to AD patients.

4.1 Classical Music's Effect on Neuropsychiatric Mechanisms of Alzheimer's

To reiterate, NPS are defined as non-cognitive disturbances pertaining to mental health defects and psychiatric disorders. Some of the NPS that were detailed in this paper include apathy, depression, aggression/agitation, and sleep disorders. In this section, classical music's effect – especially Mozart's effect – on the neuropsychiatric mechanisms of AD will be discussed.

To begin, it is well-known that glimpses of aggression, confusion, and agitation in elderly individuals with AD are significant problems for both the patients and their caregivers. The soothing melodies and captivating rhythms have demonstrated promise in lessening aggressive outbursts of anger and frustration. In patients with Alzheimer's Disease and other related dementias (ADRD), cognitive impairment plays a significant role in triggering aggression.

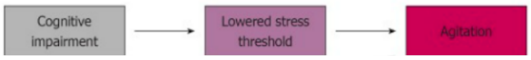

Figure 12: Gerdner's Mid-Range Theory of Music Intervention for Agitation [L.05].

Figure 12 illustrates the concepts underlying Gerdner's Mid-Range Theory, which asserts that cognitive decline is key to elevating agitation. The precursor to aggression results in the impaired and decreased ability to perceive and process sensory information, resulting in a lowered stress threshold and an elevated anxiety potential [L.05]. Simply, this indicates that, as AD progresses, fewer stressors are necessary to meet the stress threshold, resulting in agitation. When testing this popular theory, one research group evaluated the agitation levels of AD patients after they listened and actively paid attention to classical "relaxation" music for almost six weeks. The overall change in agitative measures, words, and actions was recorded using the Modified Cohen-Mansfield Agitation Inventory. The results of the study concluded that classical music intervention supports Gerdner's music theory since a significant reduction in agitation occurred, which was far less with other music types [L.05].

Another significant NPS of AD is depression, characterized by a deterioration in emotional, behavioral, and social functions. When applying an arts-based intercession such as concert classical music, a wide range of previously deserted feelings are induced in AD patients who are now capable of battling the hopelessness and sadness present in depressive states. For instance, classical compositions such as Chopin's Nocturnes are linked to improved mood, thereby reducing depressive symptoms. With just five sessions of classical-music therapy, depression and behavioral problems greatly lessened in people with ADRD [dRLSBGCGA22].

As previously addressed, the lack of interest/motivation or apathy is another challenging condition frequently recorded in AD. Classical music possesses the ability to stimulate emotional responses by releasing certain neurotransmitters such as dopamine and serotonin, which naturally rekindles attention, engagement, and a general interest in daily activities. After a 12 week classical music therapy intervention on apathy, AD patients demonstrated a tremendous improvement in not just interest levels but also depression, orientation, anxiety, and aggression [dRLSBGCGA22].

Finally, sleep disruption is also a common problem among older adults, especially individuals with AD. Quality sleep and a controlled circadian rhythm serve important restorative functions and indirectly influence our core body temperature and even the body's melatonin and cortisol levels [A.21]. Calming, tailored classical music improves sleep quality in the elderly population with ADRD because of reduced stress levels and modulated arousal levels [A.21].

Classical music's therapeutic effects are robustly attributed to a plethora of neurological mechanisms in AD. Music can actively engage many brain regions such as the amygdala and the hippocampus of the limbic system even in the more

advanced stages of this deadly disease. From alleviating depression, apathy, and agitation to improving sleep patterns, classical music therapy should be encouraged and conducted by trained professionals in AD senior homes in order to offer fragments of comfort in the midst of uncertainty.

4.2 The Cognitive Benefits of Classical Music in Alzheimer's

AD presents a series of challenges to both neuropsychiatric and cognitive function, gradually stripping away an individual's memories and reasoning abilities. Cognitive functions refer to anything related to the processes of thinking, learning, problem-solving, etc. While no treatment for AD exists, ongoing research sheds light into the therapeutic influence of classical music on the cognitive symptoms of AD, especially through the Mozart effect.

When we recognize a familiar tune or common melody in public, we are quick to connect a moment from our past to that song due to memories. In cases of AD, musical memory is usually the last to erode away compared to semantic and episodic memory. For instance, a 92-year-old woman with dementia was able to recall the three movements of Beethoven's Moonlight Sonata ranging from 14-16 minutes in length. This begs to address the discovery that brain regions associated with musical memory are the last to be disrupted in Alzheimer's. There exists a functional neuroanatomical foundation for the vulnerability of all memories in AD including musical memory. Therefore, musical memory serves as an informative concept of the neural networks harmed in AD. Patients with AD perform better on tasks involved in recognition memory and semantic memory when classical music is accompanied by a spoken recording [A.10]. As previously mentioned, music processing involves a matrix of neural networks, recruiting from many brain areas such as the basal ganglia, hypothalamus, and amygdala [A.10]. By stimulating memory circuits in the brain, classical music underscores the importance of music therapy for AD patients.

Finally, the deterioration of reasoning skills such as spatial-reasoning is another major cognitive symptom of AD. Spatial reasoning is defined as the ability to understand and manipulate visual information and stimuli, and it plays a significant role in problem solving and other daily tasks. Even though AD presents hurdles for an AD patient's reasoning ability, the science behind classical music's intricate mechanisms can engage various brain areas involved in reasoning and comprehension. Just after listening to Mozart's Sonata for Two Pianos for 10 minutes, AD patients demonstrated significantly better spatial reasoning, which is a common outcome of the Mozart effect [S.01]. Furthermore, several physiological pathways are activated in response to classical music stimuli, which modulates body responses like improved reasoning [M.14]. These results, however, are not demonstrated through the Mozart effect alone. The Schubert effect is another widespread classical music topic similar to Mozart's effect, which also results in a better performance to spatial tasks after a period of time [M.14].

In the realm of AD, where cognitive decline lowers a patient's quality of life, classical music emerges as an inspiration to enhance memory and reasoning skills. Even though this intervention is not pharmacological in nature, the

symphonies of classical music are proven to provide solace and relief for both the neuropsychiatric and cognitive mechanisms of AD.

5 Conclusion

Alzheimer's is one of the extreme medical mysteries in the healthcare field with unanswered questions regarding its etiology, pathology, and diagnosis. Nonetheless, it is clear that various genetic and environmental risk factors such as age, PSEN mutations, gender, obesity, T2D, and CVD are somewhat responsible for the progression and development of AD. In terms of AD's pathology, several distinctive signs such as A$\mathcal{B}$ plaques, NFTs, elevated ROS levels, and oxidative stress are extremely prominent.

After a thorough examination of the effects of classical music on the progression of Alzheimer's, the implementation of classical music therapy in senior homes and assisted living care centers is of utmost importance. The researched, observed effects of classical music intervention result in enhanced memory, reduced NPS, and redeveloped cognitive abilities. Classical music therapy's ability to alleviate NPS such as depression and agitation as well as cognitive symptoms, including learning defects and reduced spatial reasoning, underscores the value of music as a non-pharmacological intervention that effectively improves an AD patient's quality of life alongside existing treatments.

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