A Role for Music in Slowing Memory Decline in Alzheimer's Disease

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ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disease with cases rapidly rising, posing as a major global health concern. AD is characterized by progressive cognitive decline, with memory loss being a key symptom. Given that current pharmacological treatments are unable to halt or slow neurodegeneration in AD, interest has grown in nonpharmacological approaches. In particular, music-based interventions have been shown to improve cognitive function and emotional well-being in AD patients. This article reviews music's influence on neural mechanisms that underlie its enhancement of memory in AD, as well as evidence of memory improvement and musical-memory persistence in AD. Additionally, it proposes three mechanisms of how music may slow memory decline in AD: activation of the dopaminergic system, reduction of stress, and stimulation of neuroplasticity and neurogenesis. These findings support music as a promising intervention for countering memory decline and improving the quality of life for individuals with AD. Furthermore, music holds potential as an early intervention for preventing dementia.

KEYWORDS: Behavioral Neuroscience, Music, Alzheimer's Disease, Memory.

Introduction

Alzheimer's disease is a neurodegenerative disorder characterized by impairment of memory, language, and other thinking abilities, severe enough to disrupt everyday life. It is the most common form of dementia, affecting over 55 million people worldwide, with numbers projected to double by 2050.[1]

Pathological markers of AD include amyloid-β plaques and neurofibrillary tangles. Accumulation of these toxic proteins can lead to damaging effects such as oxidative stress, neuroinflammation, and mitochondrial dysfunction, damaging synapses and causing neuronal degeneration.[2] Amyloid-β plaques cause sustained activation of microglia, an immune cell found in the central nervous system, leading them to continuously release pro-inflammatory cytokines and neurotoxins that damage neurons.[3] Amyloid-β can also cause excitotoxicity, a potential process underlying neurodegeneration in AD. Excitotoxicity occurs when there is excessive activation of glutamate receptors,[4] leading to a high influx of calcium in neurons that triggers mitochondrial dysfunction, apoptotic pathways, and neuronal death.[5]

Among the most prominent symptoms of AD are the decline of short-term memory (STM) and long-term memory (LTM). On the cellular level, memory formation is linked to hippocampal long-term potentiation (LTP), the process by which synapses are strengthened through frequent activation.[6] Early-phase LTP correlates with short-term memory (STM) and involves strengthening pre-existing connections. Late-phase LTP underlies LTM storage and involves growing new synaptic connections, gene expression, and new protein synthesis.[7] In particular, autobiographical memory, which is a long-term memory of one's life history, is compromised. It includes both episodic memory, which involves recollection of personal events/experiences, and semantic memory, which encompasses facts about oneself.[8] The episodic component is the main feature in allowing life experiences to be recalled vividly. In AD, the decline of autobiographical memory diminishes self-knowledge, sense of identity, and quality of life.[9]

Since autobiographical memory loss affects cognitive and emotional well-being, finding effective interventions is important. While current pharmaceutical treatments, including cholinesterase inhibitors and memantine, for AD help reduce cognitive impairment,[10] they do not prevent the progression of the disease nor do they stop the underlying neurodegeneration.[11] Therefore, more interventions and non-pharmacological treatments are being considered. One such intervention is music therapy, which has been shown to improve mood, cognition, and behavior in AD patients.[12] In particular, many studies have demonstrated music's reduction of stress and positive influence on emotional state for those with AD.[13,14] Beyond emotional benefits, music is capable of evoking autobiographical memories in AD patients and may facilitate the formation and retrieval of long-term memories. Music might also be able to prevent or slow neurodegeneration, as found in a study where musicians had a 64% lower likelihood of developing dementia.[15]

Underlying the positive effects of music is the principle of neuroplasticity: the brain's ability to reorganize itself by forming new neural connections in response to experience or stimuli. Brain plasticity underlies learning and memory formation and occurs throughout a lifetime. Music's modulation of the brain is also demonstrated through the strong emotional responses it evokes, helping to form vivid memories. This paper will provide a review of music's ability to modulate the brain and enhance memory in AD. Furthermore, it will propose three mechanisms of how music may reduce cognitive decline and improve memory in AD: activation of the dopaminergic sys-

DOI: 10.36838/IJHSR87.168

tem, reduction of stress, and stimulation of neuroplasticity and neurogenesis.

Discussion

Music Induces Neuroplasticity:

Musical engagement, whether active (direct participation) or passive (listening), can drive structural and functional neuroplasticity across the lifespan.[16] Musicians exhibit increased gray matter concentration, cortical thickness, and volume changes in their motor and auditory brain regions involved in musical performance.[17] Heschl's Gyrus, located in the temporal lobes and within the auditory cortex, has been found to have more gray matter concentration in musicians.[18,19] More cortical thickness in the auditory cortex can be linked to enhanced sound processing and perception.[20] Several studies have found increased gray matter in motor-related regions, including the premotor cortex, cerebellum, and supplementary motor area, which all play a role in the planning and execution of finger/body movements required for playing instruments.[21–23] Higher gray matter density is not only exhibited in motor areas, but also in places related to higher-order executive functions (mainly frontal gyri), associated with monitoring musical information and processing musical structures.[24,25] Research has also revealed higher gray matter density in the hippocampus among musicians, which is associated with context-dependent episodic memory.[23] Through these studies, it is clear that musical training correlates with structural modifications, indicating better processing and functioning in such regions.

Similar to gray matter differences, diffusion tensor imaging (DTI) studies have revealed greater white matter organization (via higher fractional anisotropy) for musicians in parts of the brain associated with motor control and sensory processing. Studies have revealed that musicians show more white matter integrity in the arcuate fasciculus, a white-matter fiber tract connecting supporting motor-auditory connectivity and auditory processing.[26] Additionally, musicians have greater fractional anisotropy in the corpus callosum, which links the two brain hemispheres for coordination and connects a variety of sensorimotor areas.[27] The cerebellum and striatum also exhibit more white matter integrity, as they are involved in learning repetitive, automated finger movements.[28] These findings indicate that musical experience increases myelination (via increased white matter), enhancing connectivity and processing speed in the brain.

Growing evidence has demonstrated that active music training can also modify functional activation in auditory, cognitive, and motor areas. One investigation found that skilled musicians exhibit a larger cortical representation of musical tones, suggesting they are more attuned to pitch/contour.[29] This shows that auditory cortex processing becomes more developed from musical exposure. Musicians also exhibit more activity in the dorsolateral and inferior frontal cortex (includes Broca's Area), superior temporal gyrus (contains Wernicke's Area), and motor areas.[30–32] Thus, musical practice induces cortical reorganization, shown through functional changes in activation and representation of music.

The above-mentioned studies include several limitations, which could be addressed in future studies. One limitation is not taking into account biological predispositions, making it difficult to attribute brain plasticity differences to musical training. Therefore, longitudinal studies are needed to prove a causal relationship between music experience and brain alterations. Existing longitudinal studies conducted on music-induced neuroplasticity yield structural and functional changes consistent with those summarized above. Studies employing music training on children found increased volume in primary motor regions and auditory regions, particularly the corpus callosum.[21,33,34] Furthermore, increased FA of white-matter tracts such as the corpus callosum, corticospinal tract, and superior longitudinal fasciculus have also been observed in longitudinal studies.[35] Notably, the magnitude of these differences correlated with practice time. Functionally, music training results in heightened activity in the premotor cortex, posterior parietal regions, and cerebellum.[36] These areas take part in auditory-motor mapping, and are shown to be activated similarly during passive music listening and active performance.[37] Based on existing findings, we can conclude that musical engagement induces neuroplasticity, stimulating new neuronal connections that may combat neurodegeneration.

While the above research has focused on comparisons between musicians and non-musicians, recent studies have examined music-induced neuroplasticity seen in AD patients. One study has shown that musical training and engagement drive functional and structural changes in the brain, particularly in the hippocampus, for individuals diagnosed with or at risk of developing AD. Findings suggest that musical perception skills (from musical training) can enhance connectivity in regions known to be affected in AD, particularly within the Papez circuit, including the right hippocampus and right posterior cingulate cortex[38]. Similarly, AD patients who underwent music intervention (listening to familiar music) exhibited greater fronto-temporal structural connectivity corresponding with enhanced memory.[39] Together, these findings demonstrate the potential of music to induce neuroplasticity in areas affected by AD, notably the hippocampus (which is implicated in memory), suggesting that music's influence may be a protective mechanism. However, in Fischer *et al.*, the experiment was run on individuals with early-stage cognitive decline, and music intervention was relatively short at 3-weeks. Additionally, in Matziorinis *et al.*, the study was mainly observational across three subgroups of those with musical engagement, music perception skills, and musical training. These limitations require us to further examine music's longitudinal effects for those with varying stages of cognitive decline.

Music-evoked Emotions Enhance Memory:

Music is known to evoke strong emotional responses, which make musical memories especially vivid, and allow music to facilitate memory formation and retrieval.[40,41] Emotional arousal has been reported to modulate memory through activation of β-adrenoreceptors (activated by norepinephrine) in the basolateral amygdala, which consequently promotes synaptic plasticity in the hippocampus.[42] Thus, music-evoked emotions can trigger similar noradrenergic activity to enhance long-term memory formation and facilitate synaptic plasticity. By acting as an emotional tag, music strengthens the encoding and retrieval of memories, making them enduring and better remembered.

A variety of functional neuroimaging studies have shown that music modulates activity in brain regions associated with emotion. The researchers found that activity in the medial prefrontal cortex (mPFC) is positively correlated with autobiographical salience (personal meaningfulness) and positive feelings evoked by the music. Such a result indicates that the medial prefrontal cortex is a hub that integrates music, autobiographical memories, and emotion.[43] Music activates neural structures involved in emotion, namely the amygdala, hippocampus, and auditory cortex. Music also stimulates reward network structures such as the striatum, anterior cingulate cortex, orbitofrontal cortex, and nucleus accumbens.[44,45] These findings show that music-evoked emotions activate a broad brain network integrating emotional, memory, and reward systems. This overlapping activation of memory and emotion in many brain regions may be why music is such a strong enhancer for episodic memory, making it beneficial in dementia in stimulating personal memories.

Music Enhances Memory in AD:

Although memory loss is a prominent feature in those with AD, musical memory (memory of music) is often remarkably preserved in those with AD, allowing music to serve as a trigger for autobiographical memories and a connection to their past. In one case study of an 84-year-old woman with severe AD, researchers found that despite her cognitive impairment, she could recognize familiar melodies, sing along with them, and distinguish familiar from unfamiliar melodies.[46] Additionally, a separate study involving patients with mild to moderate AD found that they retained high familiarity for well-known music and maintained good pitch error detection.[47] These findings show that musical memory is uniquely preserved in AD, as individuals still remember familiar songs. Corroborating the sparing of musical memory structurally, it has been shown that the pre-supplementary motor area (pre-SMA) and the anterior cingulate cortex (ACC), both of which are involved in long-term music encoding, had minimal atrophy and hypometabolism (biomarkers of AD).[48] Therefore, since the brain circuits underlying musical memory are less affected in AD and relatively spared, using music as a stimulus may help bolster memory networks, preserving them to prevent memory loss in AD.

To support our understanding of the resilience of musical memory in individuals with AD, we can look at music-evoked autobiographical memories (MEAMs), which exhibit music's power to bring back episodic memories, serving as a cue to relay information of the past.[40,47,49–51] In a study involving patients with AD, individuals were asked to remember autobiographical events after being exposed to familiar music (self-picked) or silence.[49] Results showed that in contrast to memories evoked in silence, memories evoked after music exposure were more specific, retrieved faster, and contained more emotional significance. This suggests that music is able to promote faster recall of a more vivid and emotional memory. In a similar investigation, participants with mild AD listened to Vivaldi's "Spring" in one session and were exposed to silence during another.[50] Autobiographical Memory Interviews conducted after each condition revealed that participants recalled significantly more events from their three life periods (childhood, early adulthood, and recent) following the music condition. The improvement in autobiographical memory recall scores indicates that music enhances recollection of one's lifespan. A different investigation on elderly individuals with mild to moderate dementia found an improvement in recall when answering autobiographical questions while exposed to familiar music.[51] MEAMs are special due to their persistence, often remaining intact despite cognitive decline. This resilience is evident in the previously mentioned study by Cuddy *et al.*, who discovered that the proportion of familiar song melodies that triggered MEAMs in AD patients was not significantly different from that of healthy older adults.[47] These results demonstrate music's resilience and enhancement of autobiographical memory recall in AD patients.

The power of music-evoked autobiographical memories might be rooted in music's ability to bring about emotions.[52] The study on AD above revealed that the pre-SMA and ACC are involved in long-term music memory, and are among the variety of regions activated by music-evoked emotions.[52] The overlapping of emotion and memory-related processing in these areas, and the fact that they are among the last to degenerate in AD,[53] show the role of emotion in helping to preserve musical memory in individuals with AD.

The studies above have primarily focused on music's facilitation of autobiographical memory, but music has also been shown to engage with other forms of memory. Interestingly, musical procedural memory, the ability to play an instrument, is relatively spared in AD pathology until the late stages, unlike explicit memory forms, which are impaired.[54] While early AD primarily affects the temporal lobes and frontal brain regions (implicating explicit or short-term memories), procedural memory involves the cortico-striatal and cortico-cerebellar systems, resulting in their possible preservation.[55,56] Case studies on a pianist with AD who could still play previously-learned pieces and an amateur trombonist with AD who continued to play in a band, evidence the endurance of this motor-based musical memory.[57,58] Thus, music engages multiple memory types, highlighting its wide reach.

A growing body of research has been investigating the music interventions on memory in AD patients, revealing improved memory and executive function.[59–61] To address the need for longitudinal data, one 12-month randomized controlled trial assigned participants with mild AD, mild cognitive impairments, or memory complaints into one of three groups: music intervention (singing lessons), active control group (physical activity), or the passive control group. Researchers aim to examine music's effect on cognitive decline, brain structure (grey/white matter), brain function, and depressive symptoms.[62] Since the results in 2022 were not deemed feasible due

DOI: 10.36838/IJHSR87.168

to participants having difficulty adhering to the protocol, they have extended recruitment to include pre-AD patients, and findings may shed light on how music-induced plasticity correlates with memory.

Mechanisms Underlying Music's Benefit on Memory & Cognition:

Below are several proposed mechanisms synthesized from studies discussing how music may help improve memory and reduce cognitive decline in individuals with dementia.

The first mechanism concerns music's influence on the dopaminergic system. Dopamine, a neuromodulator, is known to play a critical role in reward-based learning, motivation, and memory consolidation.[63] Music influences our emotional state and can evoke feelings of pleasure, a component of reward.[64] Imaging studies have revealed activity changes in structures related to reward-processing and emotion when listening to music, such as the nucleus accumbens (NAc), ventral tegmental area (VTA), anterior cingulate cortex (ACC), and orbitofrontal cortex, underscoring that listening to music is a pleasurable experience.[52,65] Music's engagement with the reward circuitry is linked to its activation of dopaminergic pathways, specifically the mesolimbic. In the mesolimbic system, dopaminergic cells originate in the VTA (midbrain) and project to structures such as the nucleus accumbens, amygdala, and hippocampus.[66] Music-evoked pleasure is associated with an increase in dopamine availability at synapses. One study using [^{11}C]raclopride, which acts as a D2 antagonist, found a decrease in raclopride binding potential (which reflects extracellular dopamine concentration) in the NAc during peak moments of emotional pleasure. [67] The increase of dopamine availability might reflect an increased release of dopamine in the NAc, providing evidence of music's activation of the mesolimbic reward system. Furthermore, in another investigation, researchers found that levodopa (a drug that increases dopamine in the brain) heightened music's pleasurable experience and arousal in participants while risperidone (a dopamine receptor antagonist) reduced both.[68] These findings show that music, when inducing pleasure, can activate dopaminergic pathways in the reward system, stimulating dopamine release.

According to the neo-Hebbian framework for episodic memory formation, dopamine release in the mesolimbic system is required in converting early LTP (related to STM) into late-LTP (related to LTM) in the hippocampus. Dopamine strengthens synaptic connections (LTP) in the hippocampus through protein synthesis, supporting memory consolidation.[69] Therefore, increasing dopamine transmission promotes memory consolidation, making memories stronger and more persistent.

It is shown that music can activate dopaminergic pathways, and dopamine can support memory consolidation. Therefore, even though there is no direct evidence showing how music-evoked dopamine bolsters memory, it can be hypothesized that music-evoked dopamine release might act as a neuromodulatory signal that enhances memory formation (summarized in paragraph above), especially during rewarding and pleasurable musical experiences.[67–69]

In addition to music-evoked dopamine's modulation of memory, it could combat excitotoxicity in AD, which would consequently lead to less memory loss. Several studies on music promoting dopamine release have found that the effect is mediated through D2 receptors and mainly observed in the nucleus accumbens and lateral neostriatum.[67,70] Due to the widespread projections of dopamine in various circuits, it is plausible that music causes dopamine levels to rise in connected regions, especially the midbrain and hippocampus. Building upon this, dopamine might play a role in protecting the brain from excitotoxic damage. A study using neurons from the hippocampus, cortex, and midbrain treated cells with high concentrations of glutamate and, additionally, with varying doses of dopamine.[71] Results revealed that dopamine helped prevent neuronal death in all brain regions by preventing the onset of delayed calcium deregulation (DCD), a feature of excitotoxicity. The neuroprotective effect was eliminated in the presence of a D2 antagonist. Thus, it may be hypothesized that music stimulates dopamine release across multiple brain regions, with dopamine binding to D2 receptors to modulate calcium signaling. This counteracts glutamate-induced excitotoxicity, ultimately resulting in less neurodegeneration in individuals with progressing AD.

The second mechanism by which music can counter the deficits of AD is associated with music's regulation of neuroinflammation through its effects on stress, which modulates the brain's immune system. The stress response is regulated by the HPA axis, a neuroendocrine system. When the body experiences stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which travels to the pituitary gland, prompting it to release adrenocorticotropic hormone (ACTH). ACTH subsequently activates the adrenal glands, resulting in the release of glucocorticoids (GC) such as cortisol.[72]

While this response is essential for survival, prolonged stress leads to chronic or sustained activation of the HPA axis, promoting neurodegeneration.[73] Additionally, abundant studies on animal models have also revealed how stress contributes to AD pathogenesis through increasing Aβ levels, total tau accumulation or phosphorylation, and cognitive impairment.[74,75] GCs, induced by stress, can cross the blood-brain barrier (BBB), allowing them to travel from the bloodstream into the brain, where they can play a role in brain immunity. Since microglial cells contain GC receptors, GCs can directly influence microglial activity.[76] Research has shown that GCs can exacerbate neuroinflammation by priming microglia, increasing their sensitivity, and causing them to produce stronger pro-inflammatory responses to immune challenges and stressors.[77] Supporting this, an experiment exposing rats to psychological stress found heightened microglia reactivity (more microglia activation and more sensitive immune response), suggesting that stress contributes to a sustained immune response (causing neuroinflammation). Accordingly, other studies have found that high GC levels increased microglia and pro-inflammatory cytokines, highlighting the link between stress and inflammation.[78,79] Thus, these findings show that stress, through GCs, dysregulates microglia, upregulating pro-inflammatory pathways and worsening neuroinflammation.

Music interventions, however, have been shown to reduce stress and activation of the HPA-axis as evidenced by lower levels of cortisol,[80–82] and decreased plasma levels of pro-inflammatory cytokines.[83,84]

Therefore, music's ability to downregulate the HPA-axis and reduce stress may slow neuroinflammation, reducing cognitive decline.

The third mechanism of music's neuroprotective effects on memory revolves around music's ability to stimulate neuroplasticity and possibly neurogenesis. As reviewed above, music can enhance connectivity between brain regions, modulate activity, and increase the volume of structures. Plastic changes in the CNS caused by music show that learning music creates new neuronal connections and increases synapse formation, combating neurodegeneration.[85] Brain atrophy, caused by neurodegeneration, is a prominent marker of AD, pronounced particularly in the hippocampus, but also occurring in other structures such as the amygdala, neocortex, and entorhinal cortex.[86,87] Accordingly, since learning and listening to music helps create new neuronal connections and cause plastic changes in many regions of the brain, music may decelerate brain atrophy (especially in the hippocampus), increasing memory function and cognition.

Supporting this idea, music plasticity-based training has been shown to potentially preserve brain functions in the elderly and prevent the onset of dementia. A study demonstrated that elderly musicians have better auditory processing, working memory, and visuospatial ability than elderly nonmusicians.[88] Similarly, older adults who underwent music training had improved executive functioning and working memory.[89] Studies have also shown that older adults who are musicians have less risk of developing dementia, exhibiting music's protective effect on age-related decline.[15,90] Thus, music interventions can be cognitively stimulating, helping to prevent cognitive decline in those with AD.

It is also known that the hippocampus may be a region where neurogenesis can occur.[91] As music can modulate activity in the hippocampus, it is speculated that music might be able to facilitate neurogenesis by modulating the secretion of steroid hormones, which have been shown to increase cerebral plasticity and play a role in brain cell restoration.[92] Thus, through inducing neuroplasticity and neurogenesis, music might be able to slow or prevent neurodegeneration in patients with AD.

In conclusion, music can slow memory decline through these potential pathways. Figure 1 reviews all of the mechanisms that have been discussed.

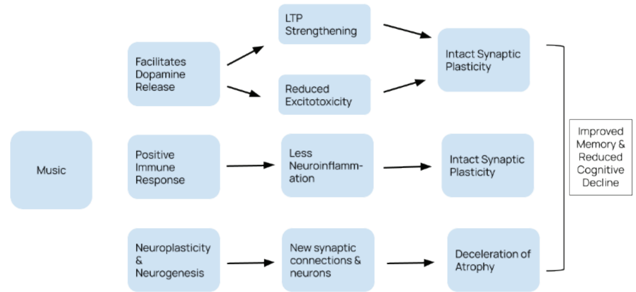

Figure 1: Model of the mechanisms underlying music's role in slowing memory decline. It involves the stimulation of dopamine release, reduction of stress (decreases HPA-axis activation), and induction of neuroplasticity and neurogenesis. This figure was adapted from the following studies.[12,93,94]

Conclusion

This article reviewed several ways in which music enhances our memory and highlights its potential as an intervention to improve memory and slow cognitive decline in individuals with AD. Music is an effective and nonpharmaceutical treatment. Importantly, literature shows that even through progressive memory decline, AD patients can retain memories of music.[46,47] Specifically, patients exhibit better recall of autobiographical experiences associated with music.[40,47,49–51] Additionally, music listening and musical training also improve AD patients' cognitive function and memory.[59–61] Thus, due to the persistence of musical memory and music's cognitive boost, this art medium can serve as a beneficial therapy for neurodegenerative diseases and early intervention for preventing dementia.

There are several mechanisms underlying music's benefit on memory decline. Music induces neuroplasticity, promoting structural and functional changes primarily in cognitive, motor, and auditory regions. Thus, musical training or listening to music facilitates new neuron connections and might even create new neurons, underscoring its potential in combating the progression of neurodegeneration.[85,92] Music also elicits emotion, which helps strengthen memory formation and retrieval primarily through activation of the dopaminergic system.[40,41,45,52] Furthermore, music's benefit on the immune system (reduction of stress and inflammation) might mitigate neuroinflammation and consequently cognitive decline and memory loss.[80–84]

Despite these conclusions, there are limitations. The cellular mechanisms by which music may enhance memory have limited studies, especially in humans, and therefore have limited empirical evidence. Studies on the direct effect of music on dopamine and memory, examining processes on the neuronal level, or music on neuroinflammation and microglia would be useful. In addition, musical memory retention in AD might vary according to the stage of AD or cultural differences between individuals. Since there is limited research on how musical memory is well-preserved in AD, more research is needed to verify and expand its depth.

Further longitudinal studies with large sample sizes should be done on AD patients to determine if music can alter the course of neurodegeneration or improve memory in the long run. It would also be important to investigate whether music's

DOI: 10.36838/IJHSR87.168

beneficial effects require continuous exposure, suggesting that these effects are short-lived after the experiment, or if a certain duration, type, or frequency of exposure is sufficient to produce long-lasting effects. One way to investigate this is through follow-ups on patients after intervention. Such studies could also experiment across different stages of dementia, with different genres of music, personalized or generalized music, and active or passive music interventions to see if there is clear evidence for music's benefit in memory decline. Utilizing artificial intelligence may serve as a way forward in developing personalized music therapy or music-related apps for patients with AD. It could help adapt interventions to music preference, emotional status, and cognitive levels. While this review paper focuses on music's impact on memory for AD patients, a lot of researchers have explored music therapy on non-memory issues associated with dementia. Findings have revealed music interventions to reduce anxiety, depression, and aggressiveness in individuals with AD.[14,95,96] The impact of music on various cognitive and behavioral issues is an important and promising area of study that could be explored further in the future.

In conclusion, this review has demonstrated that music is an underappreciated but potentially effective strategy to combat AD memory decline. Further work is needed to understand the mechanisms and the precise efficacy, but this area of research shows major potential for developing effective alternative therapies in patients afflicted with memory dysfunction in neurodegenerative disorders.

■ Acknowledgments

I would like to thank Dr. Jorge Avila, Assistant Director at the Undergraduate Research Center for Sciences at UCLA, for his guidance and support in this research paper. I'm also grateful to my parents for their encouragement throughout this process.

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DOI: 10.36838/IJHSR87.168