

# Harmonizing Healing: Unveiling the Mechanisms and Potential of Music Therapy in Alzheimer's Disease

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Alzheimer's Disease (AD) is a neurodegenerative disease that affects millions of people worldwide, with no cure currently available. While pharmacological treatments offer some relief, non-pharmacological interventions like music therapy (MT) have gained attention for their safety, accessibility, and potential to improve the quality of life for AD patients. This paper explores the role and mechanisms of MT in mitigating the cognitive and emotional symptoms of AD, focusing on both Active Music Therapy and Passive Music Therapy. Through a review of clinical studies, we highlight how MT engages brain regions like the prefrontal cortex and caudal anterior cingulate gyrus, promoting neuroplasticity and enhancing memory recall, attention, and mood regulation. The release of neurotransmitters, such as dopamine, endorphins, and endocannabinoids, also plays a key role in these benefits by improving mood, reducing stress, and supporting cognitive function. Finally, we suggest further refinement of MT to enhance its efficacy in improving the quality of life for individuals with Alzheimer's disease.

## Introduction

Alzheimer's disease (AD) was first described by Dr. Alois Alzheimer in 1906, and since then has remained at the forefront of medical investigation. AD is recognized as the most common cause of dementia, affecting 6.7 million people worldwide as of 2023, a figure expected to double by 2060<sup>1</sup>. This high volume of patients imposes a burden on healthcare systems, patients, and their families. Although neither a cure nor a treatment halting the progression of the disease has been identified, it is important to acknowledge that pharmacological interventions for Alzheimer's have seen significant improvements. Monoclonal antibodies such as Aducanumab were first approved for AD treatment in 2021. While preclinical data for monoclonal therapies was encouraging, there has been little clinical efficacy<sup>2</sup>. Alongside the development of pharmacological therapies, researchers and clinicians have explored complementary, non-pharmacological interventions designed to manage symptoms and improve quality of life.

These non-pharmacological therapies have gained traction for their potential to help manage symptoms. Environmental adaptations such as reducing clutter, enhancing lighting, and sustaining thermal comfort help mitigate confusion and agitation<sup>3</sup>. Caregiver education is equally critical. New programs that teach caregivers effective strategies for managing AD symptoms have shown positive impacts on both caregiver well-being and patient outcomes<sup>3</sup>. Alongside these training programs, music therapy has been introduced as a potential adjuvant for current care practices<sup>4</sup>.

Music therapy (MT) is a therapeutic practice with ancient

roots and modern relevance. Music has long been used as a tool for improving mood and alleviating pain<sup>5</sup>. However, it wasn't until the mid-1940s that music therapy was formally recognized as a clinical discipline. As the field of music therapy expanded, researchers began to explore its potential benefits for a wide range of conditions, including neurodegenerative diseases like Alzheimer's.

The recognition of Alzheimer's as a growing global disease and music therapy as an evolving therapeutic practice has led to increasing interest in how music therapy can be used to improve the lives of individuals with AD. This paper explores the major mechanisms behind the positive effects of music therapy on Alzheimer's patients and examines how this practice can be further developed to enhance therapeutic outcomes.

## A Brief Review of Alzheimer's Disease

The signature symptom of Alzheimer's (AD), memory loss, is caused by a handful of factors. While neurons affected by the disease do not die initially, the buildup of amyloid plaques—abnormal clumps of protein fragments that accumulate between neurons—significantly disrupts synaptic connections, interfering with cell communication and eventually leading to neuronal damage. This disruption impairs neuronal function, resulting in problems with memory, cognition, and learning. Although the exact mechanisms behind amyloid-beta ( $A\beta$ ) buildup remain unclear, emerging research suggests that cholesterol synthesis plays a significant role in its regulation; cholesterol regulates  $A\beta$  production in neurons by directing amyloid precursor protein APP to lipid clusters, where it interacts with enzymes

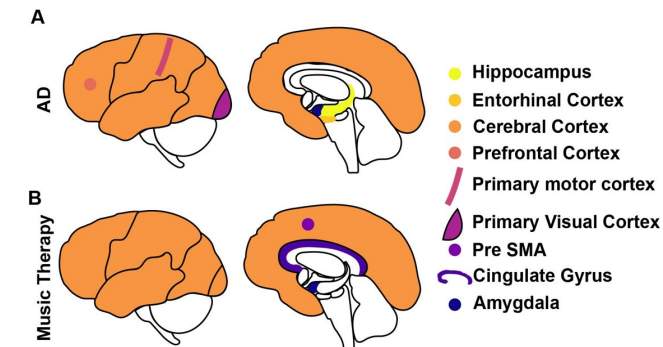
that produce  $A\beta$ , leading to plaque formation in Alzheimer's disease<sup>6</sup>. Furthermore, soluble oligomers—small, aggregated forms of proteins that consist of a few monomer units, but remain dissolved in solution—of  $A\beta$  cause neuronal hyperactivity, which is a key early event in AD. Hyperactivity induced by soluble  $A\beta$  oligomers contributes to synaptic failure and memory deficits<sup>7</sup>.

In addition to  $A\beta$ , tau, a protein responsible for stabilizing microtubules in neurons<sup>8</sup>, becomes abnormally phosphorylated, leading to the formation of intracellular neurofibrillary tangles. These tangles destabilize microtubules, which disrupts intracellular transport and synaptic transmission. This impairment ultimately leads to neuronal dysfunction and death<sup>9</sup>. Furthermore, the resident immune cells of the nervous system, called microglia, become activated in response to  $A\beta$  plaques and tau tangles. Activated microglia release inflammatory cytokines that can damage neurons, contributing to neurodegeneration<sup>10</sup>.

How these mechanisms function and the process by which they cause neurodegeneration are complex and still not fully understood. However, we do know that in early-stage AD, Amyloid plaques and tau tangles collect in and around the hippocampus, specifically the entorhinal cortex, the brain regions responsible for creating and storing memories (Figure 1A)<sup>11</sup>. So, as cells in the hippocampus degenerate, an early Alzheimer's patient will exhibit challenges retaining recently-learned information<sup>9</sup>. This first symptomatic stage of the disease is known as Mild Cognitive Impairment, or MCI. As the disease progresses, the buildup of amyloid plaques and tau tangles spreads to other brain regions, including the cerebral and prefrontal cortices<sup>9</sup>. At this point, patients begin exhibiting more intense cognitive impairments, such as struggles with thinking, reasoning, mood, and behavior<sup>12</sup>. This phase is considered severe Alzheimer's. To a degree, the primary sensory, motor, visual, and anterior cingulate cortices are spared from degeneration as the disease progresses<sup>13</sup>.

## Treatments

Although a healthy lifestyle can promote overall well-being and prevent disease later in life, there is no known regimen for the complete prevention of Alzheimer's Disease. Furthermore, there are few effective treatments to delay the progression of disease, and no known cures. Currently, existing Alzheimer's treatments can be categorized as either pharmacological or psychosocial. Pharmacological therapies include cholinesterase-inhibiting drugs such as donepezil, rivastigmine, and galantamine. These medications help patients quickly metabolize cholesterol, which can help slow the steep decline of memory-loss symptoms at any stage of the disease<sup>14</sup>. Pharmacological therapies also include memantine drugs, which act as non-competitive NMDA receptor antagonists and reduce excitotoxicity that can harm neurons. These drugs have been shown to



**Fig. 1** Brain regions discussed in music therapy and Alzheimer's disease. A) Relevant brain regions discussed in active or passive music therapy. B) Brain regions associated with Alzheimer's disease. Some regions illustrated are not often involved in degeneration and are highlighted to show relevance to key brain functions which may also be involved in music therapy.

improve cognitive function<sup>15</sup>. They do not, however, ultimately extend the lifespan of patients<sup>14</sup>.

Pharmacological therapies for AD are often not immediately recommended. Although there continues to be a strong focus on the development and refinement of therapeutics for AD, the clinical benefits of non-pharmacological and psychosocial interventions must also be considered. Psychosocial interventions are often employed before or alongside the use of pharmacological therapies. Additionally, since AD patients—even in later stages of the disease—retain the ability to interact with others, psychosocial interventions are particularly appealing as they can help maintain social skills, improve mood, reduce behavioral symptoms, and enhance overall quality of life<sup>16</sup>. These interventions include music therapy; art therapy, which uses art-making to help with cognitive and mental health issues; cognitive training, involving tools like pattern detection, list memorization, and touchscreen programs to lessen cognitive impairments; group or home-based exercise; reminiscence therapy, which involves recalling past pleasurable experiences to improve well-being; and many others<sup>17</sup>.

## Methods

A comprehensive search was conducted using the National Library Of Medicine's database, PubMed. Search terms included "Music Therapy" and "Alzheimer's Disease". Only clinical trials and randomized controlled trials from 1995 to 2023 were included in our analyses. The initial search yielded 67 studies. After a screening, 12 studies were selected for their relevance to Alzheimer's Disease and music therapy. The most common criteria for exclusion was studies which were not focused on music therapy for AD patients; they instead only referenced AD and MT.

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For each selected paper, we extracted eight key details. First, we noted the trial design (randomized controlled trial, crossover trial, etc.). Second, we determined the type of music therapy being used (active or passive). Third, we extracted a detailed description of the experiment. For studies with more than one group and one control, we recorded descriptions of all groups. Fourth and fifth, we recorded the frequency and duration of sessions. Sixth, we extracted patient demographics, including age, loss of cognitive function, race, and gender. Seventh, we described the control groups. Eighth, we noted the outcomes of each trial, including both positive and negative results. Results were compiled and examined to draw conclusions on (1) the efficacy of music therapy for AD with either active or passive implementation, (2) the benefits of each modality of MT, and (3) the key endpoints for measuring clinical benefit.

## Music Therapy

While music therapy (MT) practices often vary immensely by geography, background, and therapist<sup>18</sup>, the ultimate goal of music therapy is the same in all settings: to provide therapeutic benefit from music<sup>19</sup> by promoting wellness, managing stress, alleviating pain, expressing feelings, enhancing memory, and improving communication<sup>5</sup>. Music can have an effect on many of the diseases it is prescribed to combat; however, improving a patient's emotional well-being, social interactions, and overall quality of life can significantly enhance their ability to cope with their challenges. Several excellent reviews have recently examined the effects of MT. Although music therapy does not directly impact disease progression or lifespan, participants retain the ability to interact with and respond to music long after their memories and cognitive abilities degenerate. Additionally, MT can reduce agitation and stress, which are important factors in patient management<sup>20–22</sup>.

Although there is a wide variety in the practice of MT, most applications fall into two broad categories. First, active music therapy (AMT) involves the physical activity of playing and creating music. The second method, passive music therapy (PMT), is based on listening to live or pre-recorded music.

### *Active Music Therapy*

Active Music Therapy (AMT) is most accurately described as a session in which a patient plays and/or creates music alongside a therapist and sometimes a group of patients<sup>23</sup>. AMT sessions typically include the recreation, improvisation, or composition of music<sup>24</sup> using rhythmic training, musical instruments, and singing. An AMT session could begin with an activity where the therapist guides patients in simple rhythmic exercises using percussion instruments to establish a sense of rhythm and coordination. The session might then involve improvisational activities where patients improvise music, using instruments like drums,

pitched percussion instruments, or ukuleles. They are most often used to alleviate negative cognitive, emotional, social, and motor symptoms of neurological and psychological disorders<sup>25</sup>. Since AMT almost always requires in-person treatment, access may be limited amongst patients who can only communicate with a therapist virtually. However, for those who can access Active Music Therapy, the diversity of treatment is vast—improving technology and the wide range of AMT techniques means that almost any patient can experience the benefits<sup>18</sup>.

### *Passive Music Therapy*

In contrast to Active, Passive Music Therapy (PMT), sometimes referred to as Receptive Music Therapy, is the act of listening to music in a therapeutic scenario without creating or playing it<sup>23</sup>. This strategy can have benefits related to relaxation, emotional processing, and cognition<sup>23</sup>. A Passive Music Therapy session could include a patient sitting on a couch while a therapist chooses or plays songs with specific tempos, rhythms, or melodies to induce relaxation, reduce anxiety, or evoke positive memories. As the patient listens, they may be encouraged to relax and reflect. While the benefits may not be as overtly pronounced, Passive Music Therapy is still valuable and especially accessible as it can be easily administered virtually<sup>18</sup>. Both AMT and PMT have been examined in a variety of clinical trials, and have been demonstrated to improve both physical and mental outcomes (Table 1).

## Results

In several studies, AMT showed significant benefits. For instance, AMT interventions like rhythmic clapping, singing, and dancing in Gómez-Gallego et al. resulted in improved cognition, behavior, and functional states in AD patients, whereas PMT in the same study only stabilized behavior with no cognitive improvements. Similar effects were observed in Prinz et al., where a music-based exercise program led to improved physical function and enhanced cognitive abilities like verbal fluency and attention. Five out of six AMT trials reviewed showed similar results. Passive Music Therapy (PMT) demonstrated efficacy in stress and mood management. Innes et al. found that listening to music improved cognitive function, mood, and sleep quality. Sakomoto et al. showed short-term reductions in stress and long-term improvements in behavioral symptoms when AD patients listened to music. Simmons-Stern et al. showed that AD patients had better recognition of sung lyrics compared to spoken words, suggesting that music enhances memory retention in these individuals. However, some PMT studies, like Petrovsky et al., noted more limited effects. Although tailored music interventions improved sleep latency, the overall results did not meet initial expectations. Out of the four studies involving personalized interventions or caregiver involvement, three

**Table 1** Alzheimer’s Studies Related to Active and Passive MT

Study	Trial Design	Active/ Passive	Practice	Duration of Therapy	Frequency of Sessions	Patient Demographics	Control Groups	Outcomes
Gómez-Gallego et al. <sup>26</sup>	Quasi-experimental, cluster randomized	Both	AMT: Rhythmic clapping to songs, dancing, music quizzes, group singing. PMT: Listening to pre-recorded music with verbal reflection after listening.	45 min	Twice a week for 3 months.	90 AD patients. AMT: 28 participants (71.5% women), PMT: 21 participants (61.9% women). Control: 41 participants (54.5% women) with mild-to-moderate AD diagnosis.	Watching nature documentaries with ambient sounds, no music.	AMT improved cognition (MMSE), behavior, functional state. PMT stabilized behavior but no cognitive improvements. Control group showed worsening behavior.
Innes et al. <sup>27</sup>	Randomized Controlled Trial	PMT	Kirtan Kriya meditation or relaxing instrumental music from classical composers like Bach and Mozart.	12 min	Daily for 12 weeks.	60 adults, aged 50-84, mostly female (87%) and non-Hispanic white (94%), all with cognitive decline.	None	Both groups improved in cognition, mood, sleep, QOL (Memory Function Questionnaire). KK had greater stress reduction, mood, and QOL improvement.
Reschke-Hernández et al. <sup>28</sup>	Randomized Crossover Trial	AMT	Small group live singing of participant-preferred songs with guitar.	25 min	Three times per week for 2 weeks.	32 residents (6 men, 26 women), aged 65-97 years, with mild to severe dementia.	Verbal discussion on same topics as music therapy.	Improved positive emotions and social engagement (Observed Emotion Rating Scale, Menorah Park Engagement Scale, Dementia Mood Picture Test).
Sakamoto et al. <sup>29</sup>	Randomized Controlled Trial	Both	Listening to selected music (passive) or music-related activities (active) like clapping, singing.	30 min	Every other day, for 6 weeks.	39 participants (26 women, 13 men), aged 65+ years, severe Alzheimer’s disease.	None	Short-term stress reduction, improved emotional state (Faces Scale, autonomic nerve index), reduced dementia symptoms (BEHAVE-AD Rating Scale).
Simmons-Stern et al. <sup>30</sup>	Randomized Controlled Trial	PMT	Lyrics of unfamiliar children’s songs displayed, sung or spoken with instrumental accompaniment.	30 min	Once weekly for 10 weeks.	AD group: 13 patients (9 males, 3 females) Healthy group: 14 older adults (4 males, 8 females).	Healthy adults	AD patients: Better recognition for sung vs. spoken lyrics (recognition memory test). Healthy controls: No significant difference.
Petrovsky et al. <sup>31</sup>	Randomized Controlled Trial	PMT	Tailored music based on preferences to improve sleep quality.	30 min	Daily for 28 days.	33 older adults with dementia, 72.7% female, 81.8% Black/African American.	No intervention	Music improved sleep latency (actigraphy), though results were less beneficial than anticipated.
Prinz et al. <sup>32</sup>	Randomized Controlled Trial	AMT	Music-based exercise program (strength, balance, coordination) to music rhythm.	1 hr	Twice per week for 24 weeks.	69 participants (58 female, 11 male), ages 70+, with mild to moderate dementia.	Usual care	Improved leg strength, grip, balance, gait, reaction time, cognition, verbal fluency, attention, and quality of life (Qualidem).
Garrido et al. <sup>33</sup>	Factorial Experiment	PMT	Personalized playlists (8-9 min) with breaks.	30 min	One session	99 participants, 67 females, 32 males, aged 63-99 years, mild to severe cognitive impairment.	Within-subject factors (depression, anxiety, apathy, cognitive decline).	Highest pleasure (Observed Emotion Rating Scale) for those with low depression and high apathy. Lower pleasure in severe cognitive impairment cases.
Pac Soo et al. <sup>34</sup>	Randomized Controlled Trial	AMT	Caregivers trained to engage persons with dementia using music (singing, listening, movement, instruments).	30 min	5 sessions per week for 12 weeks.	Dementia patients at home with caregivers.	Reading intervention and standard care.	Improved QOL (QoL-AD), cognition (MMSE), caregiver distress (NPI-Q), resilience (RS-14), competence (SSCQ), caregiver-patient relationship (QCPR).
Ceccato et al. <sup>35</sup>	Randomized Controlled Trial	AMT	STAM-Dem protocol (cognitive rehab, music and sound-based exercises for attention, memory).	45 min	Twice per week for 12 weeks.	Elderly dementia patients, 65+, mild to moderate cognitive impairment in residential facilities.	Standard care, no music therapy.	Improved cognitive abilities in attention, memory (MMSE, MPI, MDP).
Innes et al. <sup>36</sup>	Randomized Controlled Trial	PMT	Relaxing instrumental music and Kirtan Kriya Meditation.	12 min	Daily for 12 weeks.	Adults 50-84 with subjective cognitive decline and weekly memory issues for 6+ months.	Kirtan Kriya meditation group	Improvements in memory (MFQ), cognitive performance (TMT-A/B, DSST).
Innes et al. <sup>37</sup>	Randomized Controlled Trial	PMT	Kirtan Kriya Meditation or classical music.	12 min	Daily for 12 weeks.	60 adults, average age 60.6, majority female (85%), non-Hispanic white (93%).	Each group served as control of the other	Improvements in well-being (PWBS), sleep quality (PSQI), mood (POMS), QOL (SF-36).

reported improvements in QoL, and two reported improvements in cognitive function. Pac Soo et al., which trained caregivers to use AMT with patients, had significant improvements in QoL, cognition, and depression. Tailored approaches, such as the personalized playlists in Garrido et al. and the sessions incorporating participant-preferred songs in Reschke-Hernández et al., were particularly effective in enhancing emotional engagement and social interaction. Taken together, the results across the reviewed studies affirm the potential of music therapy, particularly AMT, in improving cognitive, emotional, and physical outcomes in AD patients. Personalization of therapy, active engagement with music, and integrating caregiver involvement emerge as key factors in enhancing the efficacy of music therapy interventions.

## Discussion

### *Musical Memory Recall in Alzheimer’s Disease*

Despite the early degeneration of the temporal lobes, Alzheimer’s patients retain the ability to recall old songs and memories associated with music<sup>13</sup>. Even patients without Alzheimer’s who have severe temporal lobe damage often retain this ability<sup>38</sup>. This suggests that, while the temporal lobes may be involved in encoding musical memories, they may not be the sole region involved in recall. Instead, musical memory retrieval is a mechanism powered by a broad network in the brain. While this network does include the temporal lobes, much of the network lies outside the temporal lobes and is therefore spared until further degeneration<sup>21</sup>. Additionally, the functions of regions that face severe degeneration early on may be partially compensated by other brain areas. It is known that after region-specific

brain damage, compensation will occur through processes including circuit reorganization, neurogenesis, axonal growth, and dendritic plasticity<sup>39</sup>. It is through these processes that a brain, including that of an Alzheimer's patient, adjusts after a loss of function. A recent study found that among these compensatory regions are the ventral pre-SMA and caudal anterior cingulate gyrus (Figure 1B)<sup>39</sup>. These regions not only remain largely untouched by AD for much of the disease but are highly involved in the encoding and retrieval of musical memories<sup>13</sup>. These results are consistent with other work<sup>40</sup> which determined that engagement with music activates the brain's salience network (including the caudal anterior cingulate gyrus), leading to improvements in brain network synchronization<sup>39</sup>. It can then be inferred that in AD, musical memories can be recalled because the pre-SMA and caudal anterior cingulate gyrus, which are already involved in this process, are able to compensate for the loss of function caused by AD in the temporal lobes.

In addition to the compensatory mechanisms present amongst AD patients, emotionality in music also improves recall. A musical stimulus, especially an emotional one, can cause a brief increase in attention and a decrease in stress<sup>41</sup>, which can improve recall for anyone, not just AD patients<sup>42,43</sup>. Additionally, emotional music can evoke specific autobiographical memories<sup>42</sup>. When hearing a song from one's childhood, it is a common experience to relive emotions and events associated with that song. This phenomenon occurs for several reasons. Primarily, long-term potentiation (LTP), or the process by which synaptic connections between neurons become stronger in forming memories, is strongest when a memory is emotional<sup>44</sup>. Since music is emotional, memories associated with music are oftentimes emotional, meaning the connections between neurons responsible for "holding" these memories are stronger<sup>42</sup>. With stronger LTP, the mechanisms behind AD are less able to debilitate and kill neurons involved in musical memory<sup>45,46</sup>. This is also a factor in improved recall.

Passive Music Therapy, specifically listening to nostalgic songs, can be an effective non-pharmacological treatment for Alzheimer's disease. This is due to its ability to enhance memory recall by engaging the pre-SMA and caudal anterior cingulate gyrus, along with its unique role in promoting Long Term Potentiation.

### ***Cognitive benefits of MT for AD***

In addition to enhancing memory recall, MT offers a range of cognitive benefits for individuals with Alzheimer's disease AD that extend beyond memory. These benefits include improvements in attention, executive function, mood regulation, and social cognition, all of which can help a patient maintain a higher quality of life as the neurodegeneration progresses<sup>47</sup>. The underlying mechanisms behind these cognitive benefits are thought to involve the engagement of multiple brain regions

during music therapy.

Rhythm-based AMT activities, such as drumming or tapping along to a beat, engage the prefrontal cortex (PFC), which plays a significant role in motor functions, beat prediction, and cognitive processing. The PFC is central to the execution of complex motor actions, which are used to play and predict in rhythmic activities like drumming<sup>48</sup>. In this process of anticipating and executing, the PFC can also engage other brain regions, such as the premotor and striatal areas<sup>49</sup>, which are additionally involved with motor control and learning. The engagement of the PFC for a sustained period of time (including a music therapy session) not only enhances attentional control and working memory but also promotes neuroplasticity, which can lead to improved cognition in individuals with Alzheimer's disease<sup>50</sup>. One of the mechanisms behind this is spike-timing-dependent plasticity (STDP), where the timing of action potentials influences whether synapses strengthen or weaken. In rhythmic activities, the precise timing of beats can entrain neural circuits, potentially promoting beneficial plasticity in regions like the hippocampus and PFC<sup>45,51</sup>.

Furthermore, AMT is especially efficacious in promoting the secretion of neurotransmitters that are known to have cognitive benefits. Upon listening to music, endorphins<sup>52</sup> may be secreted in the pituitary gland and hypothalamus. They can alleviate pain, lower stress, and improve mood<sup>53</sup>. Endocannabinoids are also released in response to music<sup>52</sup> in the synapse to balance bodily functions such as eating, anxiety, learning and memory, reproduction, and metabolism<sup>54</sup>. Music can also induce dopamine release<sup>52</sup> in the substantia nigra, ventral tegmental area, and hypothalamus<sup>55</sup>, playing a role in memory, movement, motivation, mood, and attention<sup>15</sup>. These responses to music, along with the activation of key brain regions, can create an environment that fosters cognitive resilience against AD.

## **Conclusion**

Herein we have explored the benefits of both Active Music Therapy (AMT) and Passive Music Therapy (PMT) in mitigating Alzheimer's Disease symptoms. Analysis of published trial data highlights how music therapy enhances memory recall, improves attention and executive function, reduces anxiety, and elevates mood in AD patients. These effects occur through the activation of specific brain regions such as the pre-SMA, caudal anterior cingulate gyrus, and prefrontal cortex, alongside the release of neurotransmitters including endorphins, endocannabinoids, and dopamine. The ability of AD patients to engage with and respond to music underscores the current value and potential of music therapy as a non-pharmacological intervention. Although promising outcomes are presented, music therapy continues to evolve and offers room for improvement. One key area for advancement is the personalization of therapy sessions, as highlighted by many of the extracted studies.

Recognizing that emotional and nostalgic songs can enhance recall, therapists could integrate songs with historical, cultural, or emotional significance into PMT sessions. Incorporating such music in both PMT and AMT could further promote the secretion of neurotransmitters that deliver additional cognitive benefits. Embracing personalization holds the potential to enhance the efficacy of music therapy and improve the quality of life for Alzheimer's Disease patients.

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