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CONCISE REVIEW

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The promise of music therapy for Alzheimer's disease: A review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with cognitive decline. Memory problems are typically among the first signs of cognitive impairment in AD, and they worsen considerably as the disease progresses. However, musical memory is partially spared in patients with AD, despite severe deficits in episodic (and partly semantic) memory. AD patients can learn new songs, encode novel verbal information, and react emotionally to music. These effects of music have encouraged the use and development of music therapy (MT) for AD management. MT is easy to implement and well-tolerated by most patients and their caregivers. Effects of MT in patients with AD include improved mood, reduced depressive scores and trait anxiety, enhanced autobiographical recall, verbal fluency, and cognition. Here, we review musical memory in AD, therapeutic effects of studies using MT on AD, and potential mechanisms underlying those therapeutic effects. We argue that, because AD begins decades before the presentation of clinical symptoms, music interventions might be a promising means to delay and decelerate the neurodegeneration in individuals at risk for AD, such as individuals with genetic risk or subjective cognitive decline.

KEYWORDS
Alzheimer's disease, music therapy, musical memory, neurodegenerative disease, nonpharmacological therapy

INTRODUCTION

Alzheimer's disease (AD) is currently the most widespread and fatal progressive neurodegenerative disorder among the elderly. AD comprises 60–80% of all dementia cases, with a current estimate of 55 million worldwide,[1] and projected to grow to 153 million by 2050.[2,3] AD is a progressive disease that begins decades before the presentation of clinical symptoms. AD is preceded by a preclinical phase, which can last for 15–20 years, that is followed by a prodromal period (referred to as mild cognitive impairment [MCI]) that may persist for 3–6 years prior to the onset of AD dementia.[4,5] The neuropathological features of AD involve the extracellular accumulation of amyloid-β peptide in amyloid plaques[6] and tau protein in intracellular neurofibrillary tangles. Pathological changes include mitochondrial impairment,[7] hypometabolism,[8] blood–brain barrier disruption,[9] oxidative stress,[10] and neuroinflammation.[11] In the early stages of AD, brain structural impairment develops along the Papez circuit (including, e.g., the hippocampal formation, anterior thalamic nuclei, posterior cingulate cortex, and entorhinal cortex).[12] As the disease progresses, additional atrophy occurs in a large array of brain areas, with posterior cingulate cortex, the precuneus, and the medial orbitofrontal being among the areas showing the most significant increase in neurodegeneration. Notably, areas that are largely spared include auditory areas, sensorimotor cortex, as well as pre- and supplementary motor areas.[13] Clinical symptoms of AD include progressive decline in cognition, memory, visuospatial ability, executive function, as well as language and speech production. AD patients report behavioral and psychological symptoms of dementia (BPSD), including depression, anxiety, apathy, agitation, problems with emotional control, sleep disorders, and problems living independently.[5]

MUSIC AND MEMORY IN ALZHEIMER'S DISEASE

Music is omnipresent across world cultures and has been regarded as an integral part of human nature.[14] Music has been used as a mnemonic device (i.e., using music as a memory- or learning-aid) to transfer stories and information across time through the use of song.[15] Many significant episodes of individuals' lives are accompanied by music. In such cases, the brain can store memories and emotions during an event with music.[16] Subsequently, retrieval of these memories and feelings can be triggered by the music associated with them.[17] This effect can be useful to help individuals with loss of autobiographical (episodic) memory. In AD patients, music can be used as an effective cue to recall autobiographical memories and elicit strong emotions, often offering a meaningful way to connect with themselves and their loved ones. While passively listening to music, patients can recall memories from their lives in greater detail,[18–20] even if the music is unrelated to the event.[21]

As we will show in greater detail below, controlled group studies have shown the benefits of music in AD patients on verbal encoding,[22,23] autobiographical recall,[18–20] performance on tests of cognitive and behavioral function,[24–26] enhancements in self-consciousness,[27] and improvements in trait anxiety and depressive symptoms.[28,29]

Music-evoked autobiographical memories and music-evoked emotions in AD

Autobiographical memory is the long-term memory for life experiences in which the "self is the object of knowledge;"[30] it is mostly episodic in nature. Episodic autobiographical memory relates to memories concerning spatial and temporal contexts.[31] Another component of autobiographical memory is emotion—emotional memories are easier to recall than memories without an emotional component.[32,33]

Interestingly, although AD patients have difficulties recalling autobiographically salient contents, they have a seemingly intact ability to recognize familiar melodies, and even in the advanced stage, several AD patients can sing along with music.[34] In addition, music-evoked autobiographical memories (MEAMs) have been suggested to be preserved in AD.[35] MEAMs are evoked using a musical cue and can relay spontaneous information about one's past. MEAMs can be quite vivid, highly detailed, and involuntarily remembered,[36,37] and they can spark immediate emotional reactions. For example, evaluating healthy participants, Janata *et al*.[36] found that brief musical clips of popular music were potent retrieval cues for autobiographical memory (both recent and remote memories).

El Haj *et al*. investigated MEAMs in healthy adults and patients with probable AD comparing a self-selected music condition to a silent condition.[20] They found that memories evoked during the music condition were retrieved faster, were more specific, emotionally laden, and had a greater impact on mood. Self-selected music has also been linked to an increased frequency of the use of emotional words during recall.[38] Cuddy *et al*.[35] used familiar musical excerpts to stimulate MEAMs in healthy young, older adults, and patients with mild-to-moderate AD. Familiar instrumental music evoked episodic memories in all participants, including AD patients. Older patients also reported positive feelings toward memories versus younger participants, signaling a "positivity effect"[39] toward the information recalled. These findings also reflect how MEAMs can bolster self-knowledge and be used as a resource to enhance social and communication functioning in AD, and to demonstrate how music can be used as a means for cognitive stimulation.

Notably, even exposure to unfamiliar music can enhance episodic memory recall in AD patients. For example, patients with mild AD were asked about significant life events on two different occasions, with and without Vivaldi's "Spring" from *The Four Seasons* playing in the background.[19] In the music condition, AD patients showed significant enhancements in recall of autobiographical memory (as assessed with the Autobiographical Memory Interview), as well as significant reductions in trait anxiety (as measured on the State–Trait Anxiety Inventory). Similar results have been reported by other groups, reporting that effects are stronger when background music is self-selected by the patient.[18,40] Such findings are important because by enhancing the recall of autobiographical memories, music may help to restore a sense of identity in patients with dementia.

The ability for music, especially familiar music,[41] to evoke memories is combined by its ability to evoke emotions. A meta-analysis of functional neuroimaging studies on music and emotion indicated activity changes in the anterior hippocampal formation (among numerous other structures).[42] Thus, the anterior hippocampus is involved in music-evoked emotions, in addition to its well-established role in autobiographical memory. This colocalization of music-evoked emotions and memory functions might be one reason why episodic memory recall can be facilitated with music. However, further neuroscientific research is required to investigate such links in more detail, and as we will discuss in the next section, the hippocampus is not the only brain structure where music-evoked emotions and memory functions are colocalized.

Preservation of memory for music in AD

Musical memory (i.e., memory for music), has been thought to be partly independent from other memory systems. Case studies have revealed that AD patients have partial preservation of musical memory,[43] even while experiencing rapid cognitive decline.[44] Individualized music programs are increasingly used for patients with AD dementia: the use of personalized or favorite music has resulted in improvements in depression, anxiety, agitation, and BPSDs, yet the brain mechanisms for these benefits are not well understood.

Jacobsen *et al*.[45] reported that the neural encoding of long-known music (compared to recently known or unknown music) involves the caudal anterior cingulate cortex (ACC) and the ventral pre-supplementary motor area (pre-SMA) in healthy adults. Notably, both regions have also been shown to be among the last brain regions to degenerate in AD, showing little to no significant cortical atrophy or hypometabolism.[46–48] In addition, both pre-SMA and caudal ACC also play a role in music-evoked emotions.[49,50] These findings suggest that musical memory and music-evoked emotions are also colocalized in the pre-SMA and caudal ACC, and these regions being last to degenerate in AD might explain why musical memory is surprisingly well preserved in AD patients.

King *et al*. investigated the use of personalized musical training, including patients' favorite songs lasting over the course of 3 weeks.[51] The authors used functional magnetic resonance imaging (fMRI) following the training period and measured functional connectivity during a musical task involving forward and reverse musical stimuli. Forward playing music elicited activation in the SMA. This result is consistent with reports of the SMA as a region associated with activation to familiar music.[52,53]

THERAPEUTIC EFFECTS OF MUSIC THERAPY FOR AD PATIENTS

The accessible and versatile nature of music makes it ideal to use in patient populations. Music therapy (MT) is typically implemented by a trained music therapist who also follows a protocol based on professional standards in MT.[54] MT can involve active (e.g., playing an instrument, singing, clapping, and dancing) or receptive (e.g., music listening) methods.

One example of a study that used MT for AD patients is a randomized controlled trial conducted in 298 mild, moderate, and severe AD patients using singing versus usual care.[55] They assessed the effects of MT on cognitive function and well-being, and participants were randomized into three groups (singing, lyric reading, and control) receiving different interventions over the course of 3 months. Patients were tested at baseline, after 3 months, and after 6 months. Active MT was found to be more effective for improving verbal fluency and alleviating psychiatric symptoms, as well as caregiver distress, in comparison to the lyric reading group. They found that active MT (singing) was effective for enhancing memory, specifically on immediate and delayed recall on the auditory verbal learning test, and language abilities in mild AD patients. These effects, however, were not sustained 3 months after completion of the study. The authors also reported reductions in psychiatric symptoms (measured with the neuropsychiatric inventory) and caregiver distress in patients with moderate or severe AD. Findings suggest that MT can be useful for speech and language training in patients, and is able to be effective for controlling psychiatric and behavioral symptoms in patients with severe AD. The authors also suggest that group music interventions may help to improve social interaction between people with dementia, promoting relaxation and decreasing overall agitation. The authors conclude that the continuous use of MT can be beneficial for AD patients either in a short-term or long-term capacity.

Although this study demonstrated the promising effects of MT, there are relatively few studies that have investigated AD patients exclusively,[19,24,27,28,55–61] and to the best of our knowledge, no meta-analyses on the effects of MT in AD are available. A meta-analysis on effects of MT in dementia patients in general, including dementias other than AD, reported a small effect of active MT on global cognition (but this effect was not present when both active and receptive studies were combined).[62] Similarly, a meta-analysis on dementia patients in general reported that MT possibly reduces depressive symptoms.[63] However, both meta-analyses also noted that overall scientific quality of studies was low, that there was large variability between studies, and a need for high-quality randomized controlled trials with sufficiently large sample sizes. It should be noted, however, that a few studies on effects of AD specifically (not dementia in general) support the conclusion that MT has beneficial effects on cognitive function, behavioral symptoms of dementia, and mood in patients with AD.[19,24,28,55,57–61]

POTENTIAL BRAIN MECHANISMS UNDERLYING POSSIBLE EFFECTS IN AD

In the following, we suggest three possible neural mechanisms underlying positive effects of music interventions on cognition and mood in AD patients.

The first mechanism is stimulation of neurogenesis (i.e., generation of new neurons) and neuroplasticity (e.g., structural changes in the brain, including formation of new synapses, axonal sprouting, and myelinization of nerve fibers). Neurogenesis and neuroplasticity occur throughout the lifespan;[64] notably, the dentate gyrus of the hippocampal formation generates neurons that migrate mainly into the hippocampus.[65] A meta-analysis showed that music-evoked emotions can activate the anterior hippocampal formation, and it is tempting to speculate that such activation might also stimulate neurogenesis.[42] In AD patients, such music-evoked neurogenesis may lead to a deceleration of atrophy in anterior hippocampal formation and, perhaps, to a reversal of loss of hippocampal volume. The support of hippocampal integrity (by music stimulating neurogenesis) would have beneficial effects on both memory functions and mood. Notably, as reported above, we assume that the anterior hippocampus plays a particular role for social bonding and attachment-related emotions.[66,67] Music is particularly powerful in the engagement of social functions, such as communication, coordination of movements, cooperation, and social cohesion.[68] This function of music has been suggested to be evolutionarily adaptive.[69] Thus, shared musical experiences, which are typical for active MT, may be effective in activating anterior hippocampal formation.

A second possible mechanism underlying beneficial effects of music in AD patients is the stimulation of dopamine release. Beyond activation of the hippocampus, music has been shown to have a strong capacity to activate the brain's reward network.[42,70] Among other structures, this network encompasses the mesolimbic dopaminergic reward pathway, that is, dopaminergic neurons in the mesencephalon projecting into the ventral striatum, including the nucleus accumbens. Specifically, music-evoked pleasure has been shown to increase dopamine availability in the ventral striatum,[71] and administration of risperidone (a dopamine antagonist) leads to decreased hedonic

TABLE 1 List of outcome measurements used in the ALMUTH study

Domain	Tests used
BrainAGE	Brain Age Gap Estimation using structural T1-weighted MRI scans
Depressive symptoms	Geriatric Depression Scale (GDS)
Cognitive status	The Mini-Mental State Examination (MMSE)
Episodic memory	The Free and Cued Selective Reminding Test (FCSRT)
Verbal memory	The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory Test
Self-perceived decline	The Subjective Cognitive Decline Questionnaire (SCD-Q)
Executive functions	The Delis–Kaplan Executive Function System's (D-KEFS) Color Word Interference Test (CWIT)
Independence	Instrumental Activities of Daily Living (I-ADL)Personal Activities of Daily Living (P-ADL)
Music perception	The Mini-version of the Profile of Perception of Music Skills (Mini-PROMS)
Physical ability	Six-minute walk test Grip strength test The Short Physical Performance Battery (SPPB) The International Physical Activity Questionnaire (IPAQ) short version
Sensorimotor function	Finger Tapping Test (FTT)
Integrity of fiber tracts	Diffusion Tensor Imaging (DTI)
Default mode network	Resting State Functional MRI (fMRI)
Caregivers' quality of life	Beck's Depression Inventory (BDI-II) The Burden Scale for Family Caregivers (BSFC)

experience of music. In addition, dopaminergic systems beyond the reward system are involved in the regulation of motor functions. Importantly, age-related dopamine losses are associated with age-related cognitive deficits, and dopamine is depleted in persons with AD.[72] Thus, another interesting hypothesis is that the stimulation of the release of dopamine with music-making may prevent age-related cognitive decline. Corroborating this hypothesis, is a study estimating the age of the brains of participants, finding that the estimated brain ages of professional, and especially of amateur musicians, were younger than their chronological age.[73] These rejuvenating effects on the brain might have been, in part, due to the release of dopamine during music making. This notion is consistent with the finding that lifelong musical practice has been associated with reduced risk of dementia and MCI.[74]

A third possible mechanism is associated with inflammatory processes. Music-evoked emotions can reduce stress and give rise to physiological changes through activation of the autonomic nervous system.[75,76] In addition, music can influence the neuroendocrine stress response and modulate immune system activity (e.g., modulate the release of cytokines).[77] This is relevant because the presence of a sustained immune response in the brain has emerged as a core pathology in AD.[78] Thus, positive effects of music on immune system activity might also mitigate neurodegeneration in AD.

ALZHEIMER'S AND MUSIC THERAPY STUDY

Our group is currently carrying out a study investigating therapeutic effects of music in patients with, or at risk for, AD. The Alzheimer's and Music Therapy Study (ALMUTH, NCT03444181) tries to address the limitations above by including two well-tolerated and positively integrated non-pharmacological therapies, namely, physical activity (PA) and MT, specifically singing lessons with music therapists, in addition with a passive control group (no intervention). The study includes patients with mild-to-moderate AD and excludes participants with other forms of dementia (e.g., frontotemporal, Lewy body, vascular, and mixed dementia). The study is an open-label parallel three-arm randomized controlled trial conducted over the duration of 12 months. Weekly therapy sessions, totaling to 40 sessions per year, are offered. The music intervention consists of weekly singing lessons, a twice-monthly choir group session, as well as daily practicing. The PA intervention includes weekly PA sessions that are performed in a group setting with daily practicing. Sessions are personalized based on the activity level of the participant. The study includes neuropsychological testing and magnetic resonance imaging (MRI) acquisitions with repeated assessments at baseline, and after 12 months. MRI scanning involves the acquisition of T1-weighted imaging, diffusion tensor imaging (DTI), and fMRI (one with, and one without music listening, counterbalanced across participants). Neuropsychological assessments (Table 1) are undertaken investigating fine motor skills, executive functioning, processing speed, inhibition, memory and attention, depression, activities of daily living, physical performance, previous musical background, and perceptual abilities as measured by the profile of music perception skills.[79,80] Brain aging scores are determined using brain age gap estimation (BrainAGE),[81] a machine learning algorithm, which determines the rates of acceleration or deceleration of brain aging. The aim of the study is to determine if active therapy can decelerate brain aging by reducing the gap between biological (chronological) and estimated brain aging over the course of a year and if improvements in depressive symptoms can be achieved.

Initially, the ALMUTH study was conducted exclusively in mild-to-moderate AD patients; however, a feasibility assessment and randomized pilot trial of the ALMUTH study found that the strict inclusion of AD patients was not feasible.[82] Therefore, milder forms of memory impairment have been included, namely, individuals with MCI, subjective cognitive decline (SCD), and subthreshold SCD.[83] The updated ALMUTH protocol taps into the longer preclinical AD phase by offering training across varying stages of memory impairment and seeks to uncover if enhancements in mood, activities of daily living, cognition, and brain plasticity as measured by neuroimaging methods (e.g., fiber tractography, voxel-based morphometry, resting-state functional connectivity, DTI structural connectivity, and BrainAGE) can reflect changes in the brain due to a musical or physical intervention.

CONCLUDING REMARKS

Despite severe memory problems, patients with AD can remember music, and music can facilitate recall of episodic memories, even if the music is not related to the recalled events. This can help AD patients to preserve their sense of personal identity. In addition, music has been used as a therapeutic means to stimulate social bonding in persons with AD. Consequently, MT has been suggested to improve mood, reduce depression and anxiety, enhance autobiographical recall and verbal fluency, enhance cognitive function, and manage BPSDs in patients with AD, but there is still a paucity of high-quality empirical evidence. However, MT is a safe and promising adjunctive therapy to alleviate BPSD. Potential beneficial effects of music interventions on brain degeneration are currently being investigated.

AUTHOR CONTRIBUTIONS

The authors contributed equally to this review.

COMPETING INTERESTS

The authors declare no competing interests.

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