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Original article

Effect of Music Therapy on Alzheimer's Disease: How Music Combats Alzheimer's Disease?

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Abstract

Alzheimer's disease, the most prevalent form of dementia, is a fatal neurodegenerative disorder. The risk factors of Alzheimer's disease include age, genetics, lifestyle, and other external stressors. The Coronavirus disease 2019 (COVID-19) pandemic has brought along many changes and has exacerbated symptoms within persons with Alzheimer's disease such as depression, anxiety, and agitation, with this also accelerating cognitive decline and mental health of patients with Alzheimer's disease. COVID-19 has the capacity to increase risk of Alzheimer's disease within healthy people, as it also has capacities to target the central nervous system. Though Alzheimer's disease cases are continually rising dramatically, there is no cure. Current treatment options, such as drugs, are not easily accessible and have many limitations. As a result, non-pharmacological and easily accessible interventions, such as music therapy, have garnered interest. In this review, we summarized different music therapy techniques, outcomes of music therapy treatments, and the underlying mechanisms of music therapy. Though music therapy is a promising option for the treatment of Alzheimer's disease, due to limited results concerning long term benefits, the combination of music therapy with other non-pharmacological interventions such as physical exercise should also be considered.

Keywords: ***Alzheimer's disease, music therapy, mechanism, cognition, memory.***

Introduction

Alzheimer's disease (AD) is a progressive degenerative brain disease, and is the most common dementia among the elderly. AD affects at least 6.5 million people in the US and over 50 million people worldwide [1]. It is projected that the number of people living with AD could reach 12.7 million in the US and exceed 152 million globally by 2050 [1]. It is a highly disabling neurodegenerative disorder that involves progressive decline of cognitive and functional abilities. The brain becomes affected due to deposition of ß-amyloids and neurofibrillary tangles [2]. There are three broad phases during the course of AD: preclinical AD, mild cognitive impairment (MCI), and AD dementia. Table 1 summarized in details about the different phases in AD. Preclinical AD can last for 15-20 years, and subtle cognitive and behavioral changes occur, and brain structure changes such as β-amyloid and neurofibrillary tangles can be detected [3]. During MCI, symptoms of brain dysfunction are more evident, as memory deficits and inability to perform basic tasks are more prominent, and diagnosis often occurs at this stage as brain a3trophy and biomarkers can be verified more accurately [3]. Cognitive and memory abilities steadily decline during the dementia stage of AD [3]. Within the AD dementia phase, there are three subphases: mild, moderate and severe dementia. The first symptoms of AD tend to be memory, language and thinking problems since temporal, parietal, and frontal lobe structures involved in memory and speech, and the hippocampus and cerebellum are affected first [4]. As AD progresses, executive functions are significantly impaired as the cerebral cortex, and amygdala are impacted, and this is accompanied with neuropsychiatric, behavioral changes [4]. Eventually, the neuronal damage of AD becomes so extensive that it spreads to brain regions which control essential life functions, such as walking and swallowing, and ultimately, the damage causes fatality [4].

Table 1: Clinical stages of AD

Stage	Definition	Signs and symptoms
No Cognitive Decline	No evidence of cognitive deficits Stays mentally and physically active	None
Preclinical AD	No symptoms but possible biological changes in the brain	May have measurable brain changes that indicate Alzheimer's such as abnormal levels of beta-amyloid, changes in tau protein, and decreased metabolism of glucose

MCI due to AD	Mild symptoms such as misplacing objects or forgetting names, but does not interfere with everyday activities with no evidence of issues within work or social situations	Biomarkers of AD and subtle symptoms such as problems with memory, language, and thinking, but do not interfere with individuals' ability to carry out everyday activities
Mild AD	Symptoms become evident, and can interfere with some everyday activities	Mostly able to function independently but requires assistance with activities such as handling money Patient often seems less emotionally responsive
Moderate AD	Symptoms interfere with everyday activities, and patient requires assistance	Behavioral symptoms such as anger and suspiciousness Patients frequently cannot remember major events, many personal memories. Information of their life is also loosely held as patients may recall information on certain occasions but not others
Moderately Severe AD	Require assistance Emotional changes become most overt in this stage	Patients require assistance with even basic tasks such as dressing and hygiene, and subsequently become incontinent. Cognitive deficits become so severe that patients display little to no knowledge of their life circumstances Behavioral symptoms include frustration, verbal outbursts, and possibly violent behavior
Severe AD	Require continuous assistance with all activities	Speech becomes limited, with the patient eventually losing speech ability Physical rigidity manifests Vulnerable to infections; patients commonly die due to pneumonia, aspiration, and decubital ulcerations

Coronavirus disease 2019 (COVID-19) has greatly impacted the entire population. As COVID-19 has central nervous system (CNS) targeting and neuroinvasive capabilities, there has been cause for concern that COVID-19 infection could initiate or accelerate a long-lasting neurodegenerative process, and increase risk for AD [5]. AD patients frequently experience neuropsychiatric symptoms, such as psychosis, agitation, aggression, depression, apathy and anxiety; these symptoms are also significantly influenced by external stressors. Since the enforcement of COVID-19 prevention and control policies across the world, isolation measures such as lockdowns and confinement have proved to impact the mental health and damage the cognitive functions of people greatly, this impact particularly seen in the demographic of people with dementia [6]. Boutoleau-Bretonniere, et al. [6] carried out a study to assess the effects of isolation policies during the pandemic on neuropsychiatric symptoms in AD patients, and confirmed the correlation between the confinement and the neuropsychiatric deterioration: the longer the confinement, the worse the symptoms [6]. The effects of lockdown could even cause hallucinations in AD patients. Such neuropsychiatric degeneration can be attributed to the loneliness and lack of sensory stimulation experienced by AD patients living in the retirement housing, due to social isolation and separation from families, friends and community [7]. To date, the research of COVID-19 has only been around for three years; while the latency of AD can be as long as 20 years, there might be an increase of possible new cases in the next 10-15 years; however, the links between COVID-19 and AD can only suggest a correlation.

Since the COVID-19 pandemic, people across the world have to face challenges of increased external stressors, such as loneliness, anxiety, depression, and poor sleep quality. These stressors greatly impact both the physical and mental health of people. In order to cope, many people have started to engage with music. By using music as a proxy for social interaction, people experienced increased positive emotions, while people using music for solitary emotional regulation experienced increased negative emotions [8]. Utilizing music also empowers individuals and contributes to individual well-being through evoking sentiments of solidarity and kindness [9]. Music therapy (MT) has been looked into as a possible method of prevention and treatment for AD. Music is known to improve cognitive functions, and alleviate behavior such as agitation, anxiety, and depressions, these symptoms being greatly exacerbated by COVID-19 and commonly present as AD symptoms [5,10]. Music is also known to improve brain plasticity, and repair neural network damages [10] through activating a broad network in the brain, and changing brain structure [11]. In this review, we explore underlying mechanisms of MT, how MT could potentially provide an alternative method of AD treatment.

MT in AD treatment application

1. Music interacts with brain function

Music is believed to be therapeutic, as it interacts with the brain and benefits many brain functions, due to its social and engaging nature, and its personal and emotional involvement. The process of making music requires executive function, attention, auditory perception, memory, and motor control, these functions calling upon the activation of a wide range of brain neural circuits. Figure 1 shows how music interacts with the brain [12]. As a result of the interaction between music and the brain, making music requires the use of many brain regions and brain networks, leading to the enhancement of fine motor skills, symbolic system reading skills, memory skills, language skills, and other executive functions [12]. Music also affects neuronal learning, this effect lasting for a long period of time [12]. Many cortical and subcortical brain regions are involved in music related activities [13]. Also, many brain functions impacted by music are ones affected by AD. The cerebral cortex maintains the operation of a wide range of cognitive and executive functions such as awareness of sensory information, actuation of motor activity, and memory, attention, learning and decision making [14]. In addition, music activities are comprehensive tasks that involve signal integration from motor cortex, frontal, parietal, and temporo-occipital brain regions [14]. The frontal lobe is involved in executive functions, thinking, planning, organizing and problem solving, emotions and behavioural control, and personality [14]. The frontal lobe is also critical to obtain musical skills, and interpret and express emotion musically [14]. Multisensory regions in the parietal lobe and temporo-occipital areas integrate mechanoceptive and proprioceptive stimuli, process visual stimuli, and decode sensory input for retention of visual memory and language comprehension during the multisensory musical process [14]. The cerebellum, another important part of the brain, holds a key role in controlling motor coordination, which consists of comprehensive cognitive functions involving rhythm processing and music synchronization, seen especially when working with a metronome [14]. Lastly, the limbic system, the group of interconnected structures including the hypothalamus, hippocampus, amygdala and limbic cortex, is the key

for emotional and behavioural responses. These structures are responsible for the emotional perception of music, preserving and retrieving memories with music experience, and motivating engagement in music activities [14].

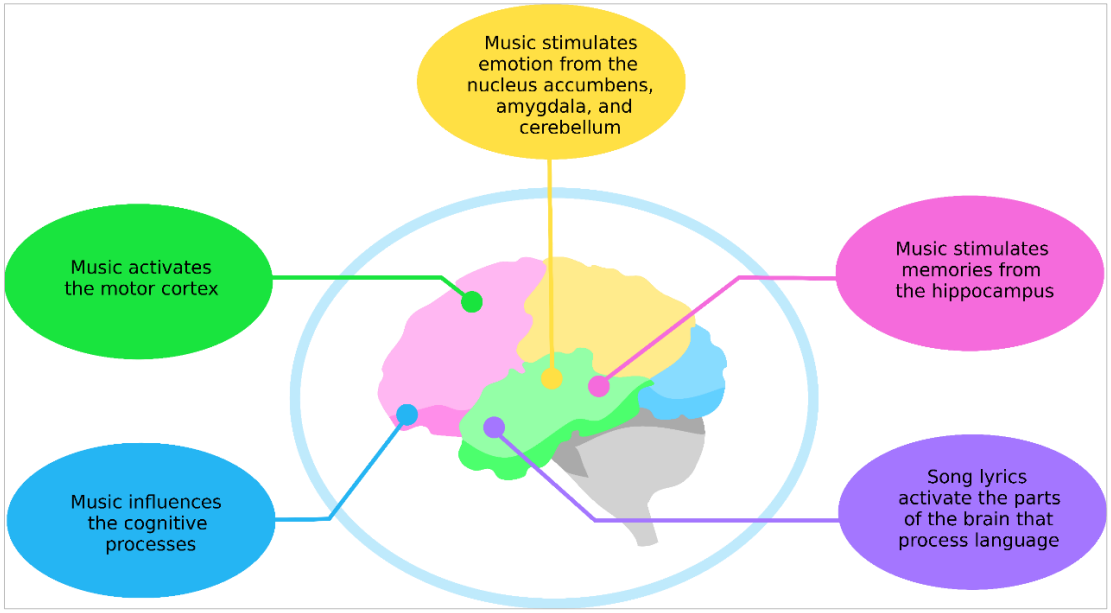

Figure 1: Music activates brain regions that are compromised by AD, Music activates the motor cortex, influences cognitive processes, stimulates sensory cortex, enhances memories and improves language skills.

2. MT application in AD

Since music demonstrates the potential to stimulate the brain regions degenerated in dementia related diseases, it provides a promising approach to improve cognitive dysfunction in the AD patients. It is found that music may improve age-related deterioration of cognitive function by the research on the relationship between music and pathological decline, such as risk of development of AD and the age of dementia onset [15]. Figure 2 shows a timeline of the history of MT in parallel with AD research development [16,17]. MT has long been recognized to improve cognition; subsequently, in recent years, the research of exploring MT as a non-pharmacological treatment for AD patients has grown rapidly with the main reasons listed below.

First, music is shown to stimulate neural networks, enhance brain plasticity, and reduce the risk of sensory deprivation [18]. Music activates a broad network in the brain, as it increases activity in frontal, temporal, parietal, and subcortical regions. Playing musical instruments can activate connections between distant brain regions, therefore strengthening not only motor- and auditory-related functions, but also general cognitive functions [11].

The second reason lies in the benefits of neuropsychiatric behaviour improvement that music is shown to bring to AD patients [19]. Music has been demonstrated to induce positive emotional and physiological responses, and stimulate the parasympathetic or sympathetic nervous system. Hence, some of the neuropsychological symptoms that occur frequently in AD patients, such as pain, anxiety, agitation, depression, aggression, delusion and sleep deprivation, can be suppressed [20].

Lastly, given the increasing rates of dementia, there is increasing demand from healthcare to develop low-cost, easily accessible, and non-invasive approaches. MT has gained an increasing amount of interest because it is a safe treatment with many benefits that meet the need of both AD patients and caregivers. Studies have shown that MT can alleviate both the physical impact and the mental impact that AD brings to the patients, their caregivers, their families [21]. As a safe alternative intervention, caregivers found MT can be a great relief for them. Comparing to other non-pharmacological interventions for AD, MT showed lower drop-out rate and better adherence from behavioural studies [19].

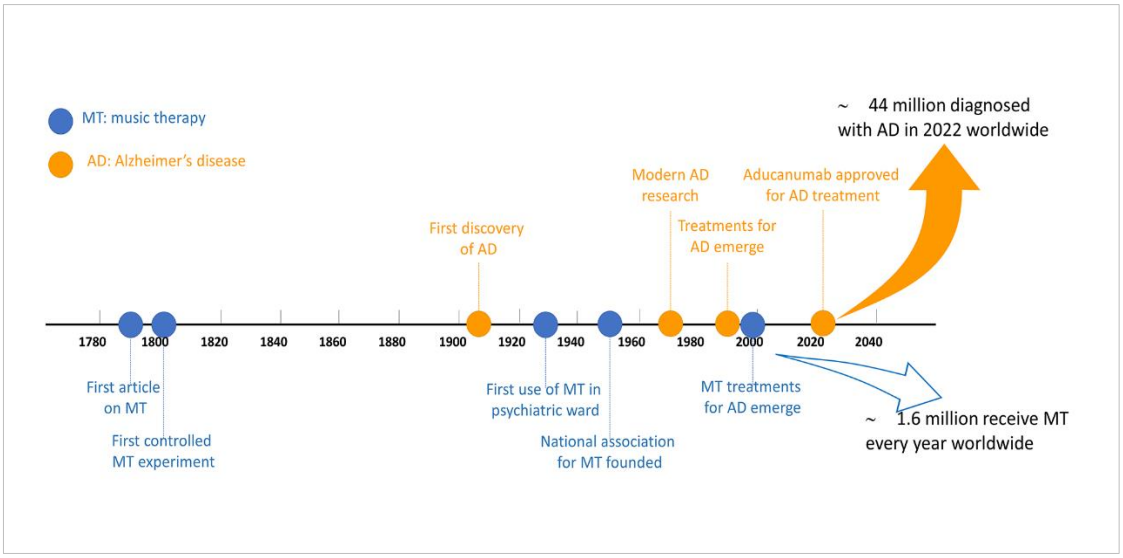

Figure 2: Milestones of AD history and MT history. MT (blue dot) has been used couple centuries back from today, and has been used for psychiatric treatment not long after AD (orange dot) has been identified. Then, with the AD disease greatly increased in numbers, MT has been used more in AD treatments as an alternate treatment method.

3. MT techniques

Music has a long history of being used in the field of dementia and has proved to be an effective method. There are different techniques of MT, roughly can be grouped into two categories: passive music intervention (PMI), which means inactive listening of music and active music intervention (AMI), which involves interactive music with patients playing and/or creating musical sounds and rhythms.

3.1 PMI

PMI, used by many researchers, is usually based on music listening, and involves the patient to respond verbally. The aim of receptive techniques is generally to arouse an emotional response or memories, subdue negative moods, promote relaxation and reduce anxiety [22]. The major design of the intervention includes the type of music, the duration of intervention, the frequency of the intervention and the types of outcome measures.

As early as 1990, Prickett et al. [23] carried out a study with a group of 69 - 87 year old (n = 10) AD patients residing in an intermediate care facility. Two types of materials were presented, both lifelong familiar materials and brand-new materials, either in the form of song or words, to the participants. The format of the sessions follows lifelong familiar materials alternating with brand-new materials and assessment of the memorization of the songs and words of the participants. The results show that compared with spoken words, patients recalled the words of songs significantly better. For both the newly introduced songs and long-familiar songs, most patients attempted to engage with the therapist with greater accuracy, suggesting that with PMI, patients can be stimulated to active participation upon the use of long-familiar songs and can retain skills to comprehend and react to new music with consistent practice.

Studies of the efficacy of MT in AD patients have focused on the alleviation of neuropsychiatric behaviours: aggression, depression, anxiety and social isolation [24,25]. Fukui et al. [24] investigated the secretion of 17β-estradiol and testosterone during PMI treatment of AD. Those hormones are supposed to have preventive effects on AD. The study population consisted of patients diagnosed with AD residing in a special nursing home (n=6). During the sessions, the therapist played music and songs to the patients. Before and after each session, the change of salivary hormone levels demonstrated that the music stimulation significantly increased testosterone level, and problematic behaviour could be reduced by PMI.

To better predict and diagnose cognitive decline and dementia, extensive studies developed several blood biomarkers, these considered to be promising tools for AD treatment. Innes et al. [26] conducted a 12-week randomized clinical trial to assess the effects of music listening on change in biomarkers of cellular aging: telomere length (TL), telomerase activity (TA), and plasma amyloid-β (Aβ) levels in older adults (n = 53) with cognitive decline. Plasma Aβ and peripheral blood mononuclear cell TL and TA were measured after 3 months and compared with the baseline values. Other assessments include stress, cognition, mood, sleep, and quality of life at 3-month intervals. Among the biomarkers that were recorded, both TL and TA levels were found to increase significantly, suggesting a correlation of TL and TA increase with improvements in certain cognitive and psychosocial measures.

In recent years, more and more studies have utilized personalized music and playlists to alleviate the psychological and behavioural symptoms in people with dementia [25,27]. Garrido et al. [27] carried out an experiment to investigate the influence of music listening on neuropsychiatric symptoms including depression, anxiety, apathy, and cognitive decline in AD patients. Based on personal preferences, three music playlists were played to patients (n = 99) with dementia. The assessment includes activation of facial action units and behavioural responses. The patients with low depression but high levels of apathy showed high level of pleasure during music listening. Interestingly, patients with high levels of depression exhibited high levels of sadness during music listening. The effects of personalized music were evaluated in another study of nursing home residents (n=20) with dementia [25]. During the four-week study period, nursing staff played individualized music playlists for 30 minutes every other day and assessed participants' behavioural and psychological symptoms pre-and post-intervention. The results show that significant improvement in sleep quality, social participation and agitation can be achieved by implementing music intervention in the institutionalized care setting. These studies suggest that MT for people with dementia need to take multiple factors, such as personal preference, mental health history and symptoms into account.

3.2 AMI

Studies have found that patients with dementia have trouble in reacting to environmental stimuli, suggesting that the interaction of environmental stimuli plays an important role in dementia treatment [28,29]. For elderly patients with severe dementia, research has been focused on AMI, rather than PMI [30,31]. AMI consists of a high degree of personal involvement, as patients are motivated to express their emotions by creating musical sounds and rhythms. Such interventions require a feed loop between the patient and the therapist, therefore cultivating an engaging environment during the intervention. AMI is a method that helps developed strong relationships between the patient and the therapist, and in turn reduce isolation, and enhance socialization during the therapeutic intervention process.

AMI is effective in reducing agitation in patients. Studies [29,32] of patients with severe AD residing in nursing facilities showed that AMI method was effective to agitation. The intervention included generalized music (pre-determined playlist) and receptive music listening, individualized music (playlist designed specifically for individual participants related to their positive memory) and interactive music (clapping, singing, and dancing). There was a much stronger positive effect on participants receiving individualized music intervention and interactive music intervention. Both short-term and long-term effects of music and cooking interventions on agitation of AD patients were compared by Narme et al. [32]. The results of both pleasant interventions with the duration of 4 weeks showed improvement of agitation in the participants. The intervention group (n = 18) received two 1-hour sessions a week of AMI, and the control group (n = 19) received a cooking intervention. The improvement of agitated behaviours was significant for the AMI group. However, the effects quickly diminished at the follow-up evaluations, indicating weak adherence of the intervention influence. Another behavioural problem in people with dementia is psychomotor agitation. Ridder et al. [29] conducted the study to assess the effect of individual AMI on agitation in persons with moderate/severe dementia. The trial was design to have a group of participants with dementia (n = 42) receive treatment of six weeks of individual AMI and six weeks of standard care. The sequence of the treatment was randomized. Outcome measures include agitation and quality of life. To promote engagement and initiative, AMI given on a biweekly basis during the six weeks intervention included different types of activities: vocal or instrumental improvising, singing, dancing/moving, and listening. The results showed that agitation increased during standard care but decreased during AMI.

The similar finding was confirmed by a study on the effects of AMI in moderate and severe dementia of AD. The participants (n = 38) were randomized into two groups, a therapy group and a control group [33]. The treatment in the therapy group included both PMI and AMI sessions and lasted six weeks. During the session, three or four patients participated the AMI with the music therapist while the rest of the therapy group underwent PMI as they passively listening to the music. The study showed that the therapy group exhibited a significant reduction in activity disturbances, aggressiveness and anxiety. However, there was no long-lasting

benefits, positive effects from the MT diminished 4 weeks after the treatment.

Brotons and Koger [34] evaluated speech content and fluency and found that MT vastly improved speech content and fluency rather than oral sessions with a specialized therapist. Other studies have also recognized the effects of AMI on speech improvements, as Giovagnoli et al. [35] studied the effect of combining drug and AMI in patients with moderate AD and found that combining AMI and memantine can improve communication as well as the psycho-behavioural profile. Sakamoto et al. [31] conducted a study with patients (n = 39) with severe AD divided randomly to PMI and AMI groups and a no-music control group. Individualized music was used in both PMI and AMI groups. The results show greatest improvement in emotional state and long-term reduction in behavioural and psychological symptoms of dementia for the AMI group compared with PMI group and the control group. Another study found that AMI was more effective for enhancing verbal fluency, alleviating psychiatric symptoms and improving memory [20]. These effects, however, were not long term, as they diminished 3 months after completion of the study.

As a result of AMI, cognition in AD patients also improves. Gomez-Gallego et al. [36] carried out a study to compare the efficacy of AMI and PMI in AD patients. AD patients (n = 90) were divided randomly into three groups to receive either AMI, PMI, or the usual care. The assessment includes cognition, behaviour, daily living activities, and motor function. Compared with PMI group and control group, the percentage of patients showing improvement in cognitive decline, behavioural disturbance, daily living activities and motor function was higher in the AMI group, suggesting a more effective intervention approach. Dorris et al. [37] examined the effects of active music-making interventions for older adults with MCI. The analysis includes 21 studies with 1472 participants and concludes that active music-making has a small but statistically significant effect on cognitive functioning.

4. Underlying mechanism

The pathophysiologies related to AD have been studied at three scales: molecular, cellular and neural scales [38]. At the molecular scale, AD is associated with β-amyloid plaques and neurofibrillary tangles. At the cellular level, AD is characterized by neuronal degeneration and synaptic loss. At the neural-systems scale, AD is associated with atypical neural activity across multiple frequency bands. Such multi-scale pathologies eventually lead to memory and cognition impairment, neuropsychiatric and behavioural changes. Despite extensive and productive research investigating the mechanisms of MT, there exists a considerable gap in the understanding of underlying mechanisms of music for AD on cellular and molecular level. Here we discuss possible mechanisms.

4.1 Music and physiological arousal

The interest in the potential benefits of music listening grew rapidly after the study by Rauscher et al. [39] on the phenomenon known as "Mozart effect" was published. In the study, they found that the participants who listened to a recording of music composed by Mozart performed much better on spatial tasks compared to that of those in the control group who were presented no sound. However, many subsequent studies have attempted to replicate the results but with mixed success. Thompson et al. [40] found that the participants exhibited better spatial abilities when presented with up-tempo happy music (Mozart sonata), compared to being presented slow, sad sounding music (Albinoni's Adagio) or no sound. However, after adjusting the level of mood, the improvements from listening to Mozart's sonata disappeared, suggesting "Mozart effect" is artificial. They then formulated the arousal-and-mood hypothesis: performance on a variety of cognitive tasks is influenced by the listener's arousal level and mood.

Music may modulate autonomic nervous system, and trigger intense emotional feelings and responses. As a consequence, some physiological changes are induced such as respiration, heart rate and blood pressure [41]. Different types of music have different effects, as high-arousal music e.g. faster tempo, exciting pieces, can stimulate sympathetic response of the autonomic nervous system, while low-arousal music e.g. slower tempo, relaxing pieces can trigger parasympathetic response of the autonomic nervous system [41].

4.2 Music and neuroplasticity, neurogenesis

In professional musicians, repetitive activation of the brain regions induces neuroplasticity observable with modern neuroimaging techniques, e.g., magnetic resonance imaging. Gray matter was shown to be highest in professional musicians while it was significantly lower in nonmusicians in a number of brain regions that support the complex behaviour of playing music [11]. The right cerebral hemisphere is known to regulate functions related to artistic performances. Researchers have discovered that due to injuries in the left hemisphere, people with neurocognitive disorders and aphasia retain functional musical capacities [14]. Such finding initiated the development of MT as a tool for oral rehabilitation and respiratory control [42].

The brain's ability to adapt is defined as brain plasticity, a process which includes both functional and structural changes to the brain. Brain imaging has become a powerful tool to gain information of how the human brain adapts to complex demands. Using brain imaging, the structures of nervous tissue and the gross anatomical structures of the brain can be monitored during study [43]. Using MRI, the brain anatomy of skilled musicians was compared with that of nonmusicians, with the results confirming that long-time instrumental practice leads to significant structural changes in the motor cortex area [44]. In addition, Gaser and Schlaug [11] studied the brain anatomy of professional musicians, amateur musicians and nonmusicians, and identified enlargement of gray matter volume in auditory, motor and visual regions in professional musician group, indicating a substantial structural adaptation caused by long-term music training. Studies found that long-time music playing not only induces the adaptation of gray matter structures, but also promotes the adaptive changes of white matter structures. Halwani et al. [45] reported differences in the arcuate fasciculus for singers, instrumentalists and nonmusicians. The arcuate fasciculus is a bundle of axons connecting the temporal and frontal brain regions. Their finding gives evidence that long-term music training leads to tract volume increase and structural complexity of the white matter.

It is known that learning to sing or to play a musical instrument can generate happiness, which is related with the transmitter substance dopamine. Dopamine plays critical roles in motor control, motivation, executive function, reinforcement learning and reward. Dopamine is released through the mesolimbic pathway, also known as the reward pathway to modulate reinforcement learning and facilitate reward learning. Using PET scanning, Salimpoor et al. [46] examined both dopamine-release and psychophysiological measures of autonomic nervous system activity of the participants when they listened to pleasant music. They employed an innovative approach by using functional MRI to monitor the dopamine release process, and found that enormous dopamine release occurred at the peak of emotional arousal, suggesting the correlation between the intense pleasure during music listening and the activation of dopamine release. Studies have reported that dopamine plays an important role in regulating hippocampus plasticity and modulating cognitive process. The release of dopamine activates the rewarding memory formation and therefore promoting strong emotional responses [47]. Furthermore, dopaminergic systems are largely involved in both motor and cognitive control processes. Studies identified the strong correlation between age-related dopamine losses and cognitive decline in AD patients [48]. This further supports the hypothesis that MT could be a potential approach to improve cognitive deficit by stimulating dopamine release.

Fukui and Toyoshima [49] proposed that listening to music facilitates the regeneration and repair of cerebral nerves by adjusting the secretion of steroid hormones. Music can regulate levels of steroids including cortisol, testosterone and estrogen. The study suggests that music promotes steroid production following the route along the auditory system, which is mainly controlled by the cerebral limbic system. It has been reported in several studies there is a strong correlation between elevated cortisol levels and some essential AD symptoms [50]. Corticosteroids are hormones, known as stress mediators, and play an important role in the human brain. The increase in secretion of corticosteroids regulates the emotion and cognition, causing behavioural and physiological changes. Chu et al. [51] reported the study on the cortisol level in the saliva of elderly people with dementia in a MT program. Elderly participants (n=104) with dementia were randomly divided into an intervention group and a control group to receive a six-week long treatment with either group music sessions for the intervention group or the usual care for the control group. The results show that improvements in depression, suggesting that elevated cortisol levels in conjunction to MT also alleviates AD symptoms such as depression by improving patients' mood.

4.3 Music and neuroinflammation

At the onset and during the progression of AD, inflammation has appeared to play an important role. Kinney et al. [52] suggested neuroinflammation as the underlying mechanism for AD and provided an overview of the connection between signals related with neuroinflammation and the development of AD. They presented evidence of the correlation between inflammatory signals and advancement of AD degeneration to postulate the underlying mechanism of neuroinflammation. The review also suggests an interplay between the sustained inflammation in the brain and the deterioration of β-amyloid plaques and neurofibrillary tangles, the two main factors controlling the neurodegeneration of AD. This indicates that inflammatory mechanisms can also be viable targets for therapeutic development as well. Research found that music caused physiological changes through activation of the autonomic nervous system, and in turn, reduced stress [53]. Moreover, music could regulate immune system activity and affect the neuroendocrine stress response [54]. Such positive effects of music on immune system activity further prove that MT can be an effective treatment for AD.

5. Limitation

The long-term benefits of MT remain ambiguous. Evidence for short-term improvement in mood and reduction in behavioural disturbance was consistent, but there were no high-quality longitudinal studies that demonstrated long-term benefits of MT. However, most studies in the literature demonstrate only good efficacy of MT for early and mid-stages of AD; the results of the studies of the efficacy of MT for late-stage of AD are still inconsistent.

Limited sample size and high variability in the studies present difficulty in designing study methods with effective duration and frequency of music intervention to achieve consistent, high-quality results. High variability in participant conditions (age, disease severity, cognitive level), outcome measures, and duration of intervention may lead to inconsistent results. In addition, high variability lies in the diversity of intervention scopes, whether in improving specific symptoms or improving quality of life. All of the above mentioned are some factors but not the only factors that present difficulty in determining the effectiveness of MT.

Although researchers have demonstrated that music intervention can protect cognition of AD, especially autobiographical and episodic memories, psychomotor speed, executive function, and global cognition, it is still considered an adjunct method for interventions of AD. MT in itself is not sufficient or as effective as being combined with other treatment methods.

As there is no standard method for carrying out MT, many physicians are not aware of non-pharmacological interventions such as MT, and many physicians poorly implement MT within treatment of AD patients. Studies have shown low familiarity of non-pharmacological intervention for physicians, indicating a practical barrier between the AD patients and the access to non-pharmacological intervention [55]. Despite the proven beneficial effects, non-pharmacological interventions have been found rarely or poorly implemented in aged care facilities [56,57].

Conclusion

Given the rapidly rising rate of AD cases, especially after the outbreak of COVID-19, there has been growing concern of an increase and worsening of AD cases due to both neurological and social damage caused by COVID-19. As a result, there is a growing demand to find safe and low-cost measures to take care of AD patients. MT is a promising treatment that is considered to be well-tolerated and a low-cost non-pharmacological alternative. The outcomes of different MT treatments suggest that MT is effective in alleviating neuropsychiatric symptoms and reducing cognitive decline, especially when AD patients were treated using AMI technique. However, there are limited longitudinal studies to investigate the long-term efficacy of MT. A main objective of future research should be focused on the investigation of longitudinal effects of music on AD patients. Although studies were conducted to propose the underlying mechanisms of how MT can effectively treat AD at different levels, there is a gap in understanding the brain changes due to MT. More studies on brain imaging and biomarkers in AD patients treated with MT will provide stronger evidence-based conclusions and quantifiable measures.

In addition to pharmacotherapy for dementia, the combination of several different cognitive stimulations, multisensory stimulation, to treat AD as an alternative can be studied more extensively. Technology can be implemented to track AD patients' progress with current treatment, to personalize patients' treatment plans, and to help alleviate AD symptoms. As technology increasingly improves and becomes more integrated within medicine, AD patient treatment plans can be monitored and created using technology such as artificial intelligence (AI). By incorporating AI within a patient's treatment, the progression of AD within a patient can be better observed, and a personalized effectual treatment plan and methods can be assigned to a patient.

Ethics approval and consent to participate

Not applicable.

List of abbreviations

Aβ: amyloid-β
AD: Alzheimer's disease
AI: artificial intelligence
AMI: active music intervention
CNS: central nervous system
COVID-19: coronavirus disease 2019
MCI: mild cognitive impairment
MT: music therapy
PMI: passive music intervention
TL: telomere length
TA: telomerase activity

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

GM and XF initiated and wrote the manuscript. GM, JF and BM conducted literature search. GM and JF designed and illustrated figures. All authors read and approved the final manuscript.

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References

[1] C. Patterson, "World Alzheimer report 2018," 2018, [Online]. Available: https://apo.org.au/node/260056

[2] J. A. Hardy and G. A. Higgins, "Alzheimer's disease: the amyloid cascade hypothesis," Science, vol. 256, no. 5054, pp. 184–185, 1992.

[3] "2023 Alzheimer's disease facts and figures," Alzheimers Dement, vol. 19, no. 4, pp. 1598–1695, 2023.

[4] M. A. DeTure and D. W. Dickson, "The neuropathological diagnosis of Alzheimer's disease," Mol Neurodegener, vol. 14, no. 1, Article ID 32, 2019.

[5] L. Wang, P. B. Davis, N. D. Volkow, N. A. Berger, D. C. Kaelber, and R. Xu, "Association of COVID-19 with New-Onset Alzheimer's Disease," J Alzheimers Dis, vol. 89, no. 2, pp. 411–414, 2022.

[6] C. Boutoleau-Bretonnière et al., "The Effects of Confinement on Neuropsychiatric Symptoms in Alzheimer's Disease During the COVID-19 Crisis," J Alzheimers Dis, vol. 76, no. 1, pp. 41–47, 2020.

[7] M. El Haj, F. Larøi, and K. Gallouj, "Hallucinations and Covid-19: Increased Occurrence of Hallucinations in Patients with Alzheimer's Disease During Lockdown," Psychiatr Q, vol. 92, no. 4, pp. 1531–1539, 2021.

[8] L. K. Fink, L. A. Warrenburg, C. Howlin, W. M. Randall, N. Chr. Hansen, and M. Wald-Fuhrmann, "Viral tunes: changes in musical behaviours and interest in coronamusic predict socio-emotional coping during COVID-19 lockdown," Humanities and Social Sciences Communications, vol. 8, no. 1, Article ID 180, 2021.

[9] P. Alvarez-Cueva, "Music to Face the Lockdown: An Analysis of Covid-19 Music Narratives on Individual and Social Well-Being," Social Inclusion, vol. 10, no. 2, pp. 6–18, 2022.

[10] M. Habib and M. Besson, "What do Music Training and Musical Experience Teach Us About Brain Plasticity?," Music Perception - MUSIC PERCEPT, vol. 26, pp. 279–285, 2009.

[11] C. Gaser and G. Schlaug, "Brain Structures Differ between Musicians and Non-Musicians," J. Neurosci., vol. 23, no. 27, Article ID 9240, 2003.

[12] A. Abbott, "Music, maestro, please!," Nature, vol. 416, no. 6876, pp. 12–14, 2002.

[13] E. Altenmüller and G. Schlaug, "Apollo's gift: new aspects of neurologic music therapy," Prog Brain Res, vol. 217, pp. 237–252, 2015.

[14] O. Brancatisano, A. Baird, and W. F. Thompson, "Why is music therapeutic for neurological disorders? The Therapeutic Music Capacities Model," Neurosci Biobehav Rev, vol. 112, pp. 600–615, 2020.

[15] S. Benz, R. Sellaro, B. Hommel, and L. S. Colzato, "Music makes the world go round: The impact of musical training on non-musical cognitive functions—A review," Frontiers in Psychology, vol. 6, Article ID 2023, 2016.

[16] "History of music therapy," https://www.timetoast.com/timelines/history-of-music-therapy.

[17] "Music therapy fun facts," https://metromusictherapyga.com/music-therapy-fun-facts/.

[18] G. E. Lancioni, N. N. Singh, M. F. O'Reilly, J. Sigafoos, and L. Desideri, "Music Stimulation for People with Disorders of Consciousness: A Scoping Review," Brain Sci, vol. 11, no. 7, Article ID 858, 2021.

[19] M. Gómez Gallego and J. Gómez García, "Music therapy and Alzheimer's disease: Cognitive, psychological, and behavioural effects," Neurologia, vol. 32, no. 5, pp. 300–308, 2017.

[20] J. Lyu et al., "The Effects of Music Therapy on Cognition, Psychiatric Symptoms, and Activities of Daily Living in Patients with Alzheimer's Disease," J Alzheimers Dis, vol. 64, no. 4, pp. 1347–1358, 2018.

[21] L.-C. Popa, M. C. Manea, D. Velcea, I. Şalapa, M. Manea, and A. M. Ciobanu, "Impact of Alzheimer's Dementia on Caregivers and Quality Improvement through Art and Music Therapy," Healthcare (Basel), vol. 9, no. 6, Article ID 698, 2021.

[22] H. Abeles, "Responses to music," in Handbook of music psychology, 2nd ed.

[23] C. A. Prickett and R. S. Moore, "The Use of Music to Aid Memory of Alzheimer's Patients," Journal of Music Therapy, vol. 28, no. 2, pp. 101–110, 1991.

[24] H. Fukui, A. Arai, and K. Toyoshima, "Efficacy of music therapy in treatment for the patients with Alzheimer's disease," Int J Alzheimers Dis, vol. 2012, Article ID 531646, 2012.

[25] L. Weise, N. F. Töpfer, J. Deux, and G. Wilz, "Feasibility and effects of individualized recorded music for people with dementia: A pilot RCT study," Nordic Journal of Music Therapy, vol. 29, no. 1, pp. 39–56, 2020.

[26] K. E. Innes et al., "Effects of Meditation and Music-Listening on Blood Biomarkers of Cellular Aging and Alzheimer's Disease in Adults with Subjective Cognitive Decline: An Exploratory Randomized Clinical Trial," J Alzheimers Dis, vol. 66, no. 3, pp. 947–970, 2018.

[27] S. Garrido, C. J. Stevens, E. Chang, L. Dunne, and J. Perz, "Music and Dementia: Individual Differences in Response to Personalized Playlists," J Alzheimers Dis, vol. 64, no. 3, pp. 933–941, 2018.

[28] M. Sakamoto, H. Ando, and A. Tsutou, "Comparing the effects of different individualized music interventions for elderly individuals with severe dementia," Int Psychogeriatr, vol. 25, no. 5, pp. 775–784, 2013.

[29] H. M. O. Ridder, B. Stige, L. G. Qvale, and C. Gold, "Individual music therapy for agitation in dementia: an exploratory randomized controlled trial," Aging Ment Health, vol. 17, no. 6, pp. 667–678, 2013.

[30] C. Holmes, A. Knights, C. Dean, S. Hodkinson, and V. Hopkins, "Keep music live: music and the alleviation of apathy in dementia subjects," International Psychogeriatrics, vol. 18, no. 4, pp. 623–630, 2006.

[31] M. van der Vleuten, A. Visser, and L. Meeuwesen, "The contribution of intimate live music performances to the quality of life for persons with dementia," Patient Education and Counseling, vol. 89, no. 3, pp. 484–488, 2012.

[32] P. Narme et al., "Efficacy of musical interventions in dementia: evidence from a randomized controlled trial," J Alzheimers Dis, vol. 38, no. 2, pp. 359–369, 2014.
[33] H. B. Svansdottir and J. Snaedal, "Music therapy in moderate and severe dementia of Alzheimer's type: a case-control study," Int Psychogeriatr, vol. 18, no. 4, pp. 613–621, 2006.
[34] M. Brotons and S. M. Koger, "The impact of music therapy on language functioning in dementia," J Music Ther, vol. 37, no. 3, pp. 183–195, 2000.
[35] A. R. Giovagnoli, V. Manfredi, L. Schifano, C. Paterlini, A. Parente, and F. Tagliavini, "Combining drug and music therapy in patients with moderate Alzheimer's disease: a randomized study," Neurol Sci, vol. 39, no. 6, pp. 1021–1028, 2018.
[36] M. Gómez-Gallego, J. C. Gómez-Gallego, M. Gallego-Mellado, and J. García-García, "Comparative Efficacy of Active Group Music Intervention versus Group Music Listening in Alzheimer's Disease," Int J Environ Res Public Health, vol. 18, no. 15, Article ID 8067, 2021.
[37] J. L. Dorris, S. Neely, L. Terhorst, H. M. VonVille, and J. Rodakowski, "Effects of music participation for mild cognitive impairment and dementia: A systematic review and meta-analysis," J Am Geriatr Soc, vol. 69, no. 9, pp. 2659–2667, 2021.
[38] P. Tichko, J. C. Kim, E. Large, and P. Loui, "Integrating music-based interventions with Gamma-frequency stimulation: Implications for healthy ageing," Eur J Neurosci, vol. 55, no. 11–12, pp. 3303–3323, 2022.
[39] F. H. Rauscher, G. L. Shaw, and C. N. Ky, "Music and spatial task performance," Nature, vol. 365, no. 6447, pp. 611–611, 1993.
[40] W. F. Thompson, E. G. Schellenberg, and G. Husain, "Arousal, mood, and the Mozart effect," Psychol Sci, vol. 12, no. 3, pp. 248–251, 2001.
[41] G. Kreutz, C. Quiroga Murcia, and S. Bongard, "Psychoneuroendocrine research on music and health: An overview," in Music, health, and wellbeing., New York, NY, US: Oxford University Press, 2012, pp. 457–476.
[42] V. Demarin, M. R. Bedeković, M. B. Puretić, and M. B. Pašić, "Arts, Brain and Cognition," Psychiatr Danub, vol. 28, no. 4, pp. 343–348, 2016.
[43] M. Bangert and G. Schlaug, "Specialization of the specialized in features of external human brain morphology," Eur J Neurosci, vol. 24, no. 6, pp. 1832–1834, 2006.
[44] K. Amunts et al., "Motor cortex and hand motor skills: structural compliance in the human brain," Hum Brain Mapp, vol. 5, no. 3, pp. 206–215, 1997.
[45] G. F. Halwani, P. Loui, T. Rüber, and G. Schlaug, "Effects of practice and experience on the arcuate fasciculus: comparing singers, instrumentalists, and non-musicians," Front Psychol, vol. 2, Article ID 156, 2011.
[46] V. N. Salimpoor, M. Benovoy, K. Larcher, A. Dagher, and R. J. Zatorre, "Anatomically distinct dopamine release during anticipation and experience of peak emotion to music," Nature Neuroscience, vol. 14, no. 2, pp. 257–262, 2011.
[47] L. Speranza, U. di Porzio, D. Viggiano, A. de Donato, and F. Volpicelli, "Dopamine: The Neuromodulator of Long-Term Synaptic Plasticity, Reward and Movement Control," Cells, vol. 10, no. 4, Article ID 735, 2021.
[48] L. Bäckman, L. Nyberg, U. Lindenberger, S.-C. Li, and L. Farde, "The correlative triad among aging, dopamine, and cognition: current status and future prospects," Neurosci Biobehav Rev, vol. 30, no. 6, pp. 791–807, 2006.
[49] H. Fukui and K. Toyoshima, "Music facilitate the neurogenesis, regeneration and repair of neurons," Med Hypotheses, vol. 71, no. 5, pp. 765–769, 2008.
[50] S. Ouanes and J. Popp, "High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature," Front Aging Neurosci, vol. 11, Article ID 43, 2019.
[51] H. Chu et al., "The impact of group music therapy on depression and cognition in elderly persons with dementia: a randomized controlled study," Biol Res Nurs, vol. 16, no. 2, pp. 209–217, 2014.
[52] J. W. Kinney, S. M. Bemiller, A. S. Murtishaw, A. M. Leisgang, A. M. Salazar, and B. T. Lamb, "Inflammation as a central mechanism in Alzheimer's disease," Alzheimers Dement (N Y), vol. 4, pp. 575–590, 2018.
[53] S. Khalfa, P. Isabelle, B. Jean-Pierre, and R. Manon, "Event-related skin conductance responses to musical emotions in humans," Neurosci Lett, vol. 328, no. 2, pp. 145–149, 2002.
[54] S. Koelsch, A. Boehlig, M. Hohenadel, I. Nitsche, K. Bauer, and U. Sack, "The impact of acute stress on hormones and cytokines and how their recovery is affected by music-evoked positive mood," Scientific Reports, vol. 6, no. 1, Article ID 23008, 2016.
[55] J. Cohen-Mansfield, A. Juravel-Jaffe, A. Cohen, I. Rasooly, and H. Golander, "Physicians' practice and familiarity with treatment for agitation associated with dementia in Israeli nursing homes," Int Psychogeriatr, vol. 25, no. 2, pp. 236–244, 2013.
[56] E. S. van der Ploeg, T. Mbakile, S. Genovesi, and D. W. O'Connor, "The potential of volunteers to implement non-pharmacological interventions to reduce agitation associated with dementia in nursing home residents," Int Psychogeriatr, vol. 24, no. 11, pp. 1790–1797, 2012.
[57] K. S. Kverno, B. S. Black, M. T. Nolan, and P. V. Rabins, "Research on treating neuropsychiatric symptoms of advanced dementia with non-pharmacological strategies, 1998-2008: a systematic literature review," Int Psychogeriatr, vol. 21, no. 5, pp. 825–843, 2009.