Investigation of the Interactions and Benefits of Music Therapy and TREM2 in the Reduction of Alzheimer's Disease by Sophie Nam

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, driven by complex interactions between genetic factors and environmental influences. Despite advancement in the understanding of AD, therapeutic approaches are limited. Among the potential therapeutic approaches, there are triggering receptor expressed on myeloid cells 2 (TREM2) and music therapy. TREM2 has been identified as a key genetic factor and potential therapeutic target for AD. TREM2, predominantly expressed in central nervous system (CNS) microglia, is involved in crucial microglial functions such as proliferation and phagocytosis. TREM2 also plays a role in regulating inflammatory responses and cell signaling pathways. Meanwhile music therapy has emerged as a promising non-pharmacological approach for managing AD symptoms, with evidence suggesting it can improve cognitive function, emotional well-being, and overall quality of life. This review evaluates both non-pharmacological and pharmacological treatments for AD, focusing on music therapy and the role of TREM2. We will discuss the current evidence supporting them and their potential mechanisms. Additionally, the review will explore a proposed connection between music therapy and TREM2, promoting further research into their combined effects. By providing a comprehensive overview, this review seeks to guide future studies and enhance therapeutic approaches for Alzheimer's disease.

Introduction

Alzheimer's disease (AD), the most common cause of dementia, is a neurodegenerative disease marked by progressive cognitive decline as well as behavioral and neuropsychiatric symptoms (Fang et al., 2017). Most patients diagnosed with AD initially exhibit memory impairment, which can then progress to executive dysfunction and difficulties with language and recognition. AD patients can also have trouble with daily life activities ranging from using technology to eating and dressing, increasing their reliance on family caregivers. AD affects an estimated 40 million people worldwide, mostly consisting of people over the age of 60, and with this number expected to double every 20 years, it has become a growing health concern worldwide (Scheltens et al., 2016).

Currently, there is a lack of effective treatment options for AD, and most treatments are focused on relieving the symptoms rather than a cure. This may be due to the fact that the exact cause of AD is still unknown. While the cause is unknown, extensive research has shown the accumulation of amyloid β-protein (Aβ) plaques and neurofibrillary tangles (NFTs) are the main pathological features of AD (Scheltens et al., 2016). Aβ plaques are formed from the extracellular accumulation of peptides, predominantly Aβ42, which are folded into beta-pleated sheet structures. These peptides are a result of amyloid precursor protein (APP) cleaved by the β- and γ-secretases.When there is abnormally increased processing of APP by the β- and γ-secretases or an imbalance in the production and clearance of these peptides, they accumulate (DeTure & Dickson, 2019). Aβ plaques have been shown to drive NFTs formation, neuronal cell death, and neuroinflammation, which subsequently causes cognitive decline (Y. Li et al., 2023). Injecting Aβ into the brains of transgenic mice with tau mutations led to an increase in NFTs, suggesting that Aβ enhances tau pathology (Bolmont et al., 2007). NFTs, thick bundles of hyperphosphorylated Tau near the cell surface of neurons, can also trigger neuronal cell

death and disintegration. The tau proteins that make up NFTs are hyperphosphorylated and abnormally folded in patients with AD leading to a loss of functioning, increased inability to stabilize neuronal microtubules to prevent tangling, and increasing aggregation. The volume and location of NFTs have been correlated with neuronal loss and disease severity (DeTure & Dickson, 2019).

Scientists have also discovered that inflammation in the brain plays a critical role in the pathogenesis of AD. Microglial cells are the macrophages of the central nervous system (CNS) that search for pathogens or deteriorating neurons as part of the first line of defense in the innate immune response (Cameron & Landreth, 2010). Normally, microglia help maintain synapses by pruning unnecessary synapses, modifying synaptic connections, and promoting new synapse formation (Cornell et al., 2021). However, the brains of patients with AD have shown increased levels of microglia, especially around Aβ plaques. When there is stress or damage, such as from the accumulation of Aβ plaques and NFTs found in AD, receptors on microglia bind to Aβ fibrils, activating an inflammatory response (DeTure & Dickson, 2019). Another immune cell abundant in the brain, astrocytes, plays a role in the additional inflammatory responses that occur in AD patients, causing neurotoxicity. However, this review paper will focus on microglia and its respective inflammatory response due to its particular importance to TREM2. TREM2 is a transmembrane receptor in the microglia of the CNS and mutations in the gene encoding it have been determined as one of the genetic factors in AD pathology.

While we are aware of the implications of TREM2 on the risk of AD, we have yet to determine the best therapeutic approach to utilizing these clear pathological pathways in the treatment of AD. This article will discuss the efficacy of both the nonpharmacological and pharmacological treatments of Alzheimer's disease, focusing on music therapy and TREM2. This will provide a reference for future studies into these two therapies. It will also propose a possible connection between the two therapies, promoting further research into this topic.

Music Therapy

What is Music Therapy?

Music therapy (MT) is the use of music with a certified therapist to improve certain therapeutic areas, such as communication, expression, and movement, and address physical, emotional, mental, social, and/or cognitive needs. For many years, it has been used as a nonpharmacological treatment for patients with dementia, including AD patients, in nursing homes and hospitals (Satoh et al., 2015). Since MT has a variety of approaches and techniques, it provides dementia patients with diverse possibilities for treatment. With an increasing amount of research demonstrating the benefits of MT, music can play an important role in improving the neuropsychological, cognitive, and behavioral symptoms of AD.

Music has been found to influence various aspects of the human body; however, this article will concentrate specifically on its effects related to AD. Music can be especially useful for increasing attention and improving mood by distracting AD patients from negative stimuli such as depression, pain, and anxiety. Music also affects all major limbic and paralimbic structures of the brain, which are responsible for generating and regulating emotions (Koelsch, 2009). Since emotions are known to affect the endocrine and immune system, MT may influence the hormone levels and inflammation in AD patients. Several studies have shown that music both stimulates cognitive activation and reduces neuropsychiatric symptoms, leading to

improvements in mental wellbeing and cognitive processes such as memory, executive function, and speech in AD patients (Lyu et al., 2018).

Different Applications of MT for AD

Music and its elements such as rhythm and melody have been utilized in diverse ways to provide a treatment for patients with dementia. This section will summarize the different applications of MT for patients with dementia, especially AD, including active music therapy, MT involving caregivers, listening to music, and background music.

Active music therapy (AMT) involves the making of music with AD patients individually or in a small group within a therapeutic setting, and requires the use of a qualified music therapist. In AMT, sound elements and music are used for musical activities, involving musical improvisation and/or music exercises. These can range from singing songs to playing instruments and rhythmic movement (Raglio et al., 2014). Satoh M et al. had 10 AD patients sing their favorite songs for 6 months using karaoke to observe if the neuropsychiatric symptoms of AD such as psychomotor speed and memory improved. The Sound Training for Attention and Memory (STAM) protocol for dementia utilized structured exercises with musical elements such as clapping to a drum to improve cognitive function in dementia patients. With this protocol in a randomized and controlled trial, they found an increase in scores for the Immediate Prose Memory Test (MPI), Deferred Prose Memory Test (MPD), and Attentional Matrices, indicating significant improvements in attention and memory (Ceccato et al., 2012). These studies indicate that AMT can be used to improve multiple cognitive deficits associated with dementia. In addition, psychologically, AMT has been shown to improve communicational and relational skills. A randomized and controlled study involving singing activities found that AMT significantly improved speech content and fluency in dementia patients, as measured by the Western Aphasia Battery (Brotons & Koger, 2000). Therefore, there is strong evidence supporting AMT with numerous successful scientific studies that include randomized and controlled clinical trials.

Music therapy can also involve family caregivers, including AMT with caregivers or caregiver singing. AMT with caregivers consists of musical activities for both the patient and the caregivers where the music therapist facilitates the relationship between the two. Caregiver singing is when the family caregiver performs songs and/or vocalizations, melodies without lyrics, in a personal setting such as the patient's home. Both therapies strive to improve communication and relationship between the patient and the caregivers . Nursing and care can frequently induce stress and exhaustion in caregivers, and the dementia patients may react aggressively and defensively. This approach causes dementia patients to focus more on the caregiver, potentially creating a positive relationship and reducing the patients' resistance to different nursing activities such as assisting in dressing and escorting (Raglio et al., 2014). Lena M Hammar et al. studied the impact of caregiver singing on decreasing resistiveness and increasing positive emotions. They found that resistant behavior such as pulling away was significantly reduced, and positive emotions such as pleasure increased in 10 dementia patients during caregiver singing intervention. Other studies also showed caregiver singing increasing mutuality in the interactions between caregivers and dementia patients as well as enhancing calmness and sincerity in dementia patients (Götell et al., 2009). These studies, however, did not include samples of a big size and used qualitative data analysis, making it difficult to confidently conclude the benefits.

Listening to music has been used by many researchers as a receptive musical intervention. It aims to reduce behavioral and psychological symptoms of dementia as well as improve

cognitive functions. After listening to a Mozart piano sonata, spatial-temporal reasoning, the ability to mentally transform 3-D objects in space, improved in AD patients (Johnson et al., 1998). In another study where the AD patients listened to Mozart's Sonata and Pachelbel's Canon, the experimental patients showed less decline in the Cognitive Abilities Screening Instrument (CASI) and CASI-estimated mini-mental state examination scores compared to the control group, though these differences were not statistically significant. Further analysis of the cognitive domains within CASI revealed a significant improvement in abstraction, the ability to deal with ideas and concepts, in MT intervention than in the control. However, regarding other cognitive domains, there was no difference between the control and the MT group (C.-H. Li et al., 2015). Listening to preferred or familiar music, in particular, significantly improved symptoms of dementia. Eva M. Arroyo-Anlló et al. found that listening to familiar Spanish songs either stabilized or improved self-consciousness (SC) in patients with mild to moderate AD. The group listening to familiar songs also had better scores than the group listening to unfamiliar songs in both the Mini-Mental State Evaluation (MMSE) and Frontal Assessment Short (FAS) tests.

Though uncommon, some studies use background music as a therapy for patients with dementia. Background music involves playing music in a certain environment, not intended for specific patients. Having music in the background serves a role in relaxation and increases well being. Playing Swedish songs and pop music as background music during dinner reduced irritability and depression in dementia patients, which resulted in the patients eating more (Ragneskog et al., 1996). Vivaldi's 'Spring' movement from 'The Four Seasons' was also used as background music during recall tests in AD patients. The test results revealed that background music improves autobiographical memory, memories from one's life (Irish et al., 2006).

When the results of these different applications of MT were compared, some were more effective than others. In a study where AD patients were randomly split up into active, receptive, and control interventions, active music therapy improved cognition, behavior, and function while listening to preferred music only served to stabilize neuropsychiatric symptoms (Gómez-Gallego et al., 2021). Additionally, Mayumi Sakamoto et al. compared a group of AD patients passively listening to music, a group participating in interactive activities such as singing and dancing, and a control group with no music. They discovered that the interactive group had a greater long-term reduction in behavioral and psychological symptoms of dementia based on the Behavior Pathology in Alzheimer's Disease (BEHAVE-AD) Rating Scale compared to both passive music intervention and the control. These studies suggest that the applications of MT that require the dementia patients to actively participate are the most beneficial in many aspects of improving symptoms of dementia.

Beneficial Effects of MT

Music therapy has been proven to be beneficial to many different symptoms of dementia. With the ability to reduce levels of anxiety, depression, and aggressiveness in addition to improving cognitive function, music therapy has the potential to improve not only the lives of AD patients but also the caregivers that they rely heavily on.

In addition to the beneficial effects of each type of MT explained above, MT has an important connection to hormone levels. Sarah Cheour et al. measured the levels of salivary testosterone and cortisol in mild AD patients before and after MT. Music therapy was shown to increase the production of salivary testosterone while improving Mini-Mental State Examination (MMSE) scores. Another study observed the changes in 17β-estradiol levels after MT. There was a

significant increase in 17β-estradiol levels in AD patients with low hormone levels, indicating MT's ability to restore normal hormone levels (Fukui et al., 2012).

Changes in hormone levels have been shown to be extremely important in AD pathology. As people age, the brain levels of testosterone in men and estradiol in women, particularly during menopause, decrease. This age-related reduction in sex hormones has been associated with greater risk of developing AD (Akwa, 2020). Studies found brain testosterone levels to be lower in men with AD than control subjects, and inversely related to soluble Aβ levels. Similarly in women, AD patients showed significantly lower estradiol (E2) levels in their brain than women of the same age without dementia (Rosario et al., 2011). Estrogen plays a protective role on nerves and regulates cell proliferation. Additionally, estrogen reduces the β amyloid peptide content in neurons, a common pathological feature in Alzheimer's disease, and protects against β peptide neurotoxicity (Nilsen et al., 2006). Neurosteroid levels were also observed to be significantly lower in AD patients than healthy old adults (Akwa, 2020). Neurosteroids such as progesterone and allopregnanolone are steroids synthesized in the brain that influence brain development, have neuroprotective effects, and regulate neuroinflammatory responses (M. Wang et al., 2024). There were decreased concentrations of both dehydroepiandrosterone (DHEA), a hormone used to make androgens and estrogens, and progesterone (PROG), a hormone that plays an important role in the menstrual cycle and pregnancy, in certain regions of the brain, including the frontal cortex, striatum, and hippocampus in AD patients (Akwa, 2020). Therefore, MT's natural ability to increase hormone levels can potentially be beneficial in treating AD.

Music therapy also provides benefits without the negative side effects of pharmaceutical treatments of AD. The current pharmaceutical treatments for AD have many adverse side effects and are hard to account for in patients with comorbidities. The most common pharmaceutical treatment for AD is acetylcholinesterase inhibitors (AChEIs), such as donepezil, galantamine, and rivastigmine. AChEIs have various side effects, such as anorexia, vomiting, and muscle cramps. They also can lead to more severe side effects, such as long-term liver damage (Massoud & Léger, 2011). Another pharmaceutical treatment for AD is a class of drugs called glutamate regulators, such as memantine. This class of drugs regulates the activity of glutaminergic neurons, facilitating synaptic plasticity and neuronal development, and therefore, improving the cognitive symptoms of AD (Chen et al., 2017). This drug is more tolerated by patients, however, it still has side effects, which include dizziness and headaches (Massoud & Léger, 2011). MT, on the other hand, has not shown any significant side effects and has the ability to improve many different symptoms of dementia at once, suggesting a greater importance of MT as a treatment for AD.

Limitations to MT

Despite the beneficial results from these clinical trials, there is still a lack of scientific evidence to declare MT as an effective treatment for AD. This may be due to the fact that most of the studies involving MT did not have a truly representative clinical trial. In most of the studies, many patients withdraw from the study, resulting in not enough subjects for an accurate conclusion. Some studies had a dropout rate as high as 61.5%. The main reasons for these patients dropping out were due to the lack of variety in music and the impatience to complete MT (C.-H. Li et al., 2015). Additionally, though active music therapy was the most effective when compared with other types of MT, patients with severe dementia had trouble participating in these musical

activities and expressing emotions (Sakamoto et al., 2013). This indicates that active music therapy may be limited to patients in early or mild stages of AD.

The long-term effects of MT have yet to be studied in depth. Most studies only observed the short-term effects of MT, measuring the improvements in behavior, mood, and cognition during intervention. Even the studies that observed the long-term effects of MT have shown inconsistent durations for which improvements in dementia symptoms lasted. Some studies mentioned that the effects of MT disappeared after four weeks (Svansdottir & Snaedal, 2006). Others stated that the effects did not last more than three months after MT was used for three months (Lyu et al., 2018). This indicates that MT most likely requires consistent intervention, however, the high dropout rate suggests a difficulty in the willingness of AD patients to consistently participate in MT.

It is also important to note that most studies involving music therapy did not stop anti-dementia medication. In other words, MT was used as an addition to the ongoing treatment rather than as the main treatment for dementia. This makes it difficult to evaluate the potential for MT to be an effective stand-alone treatment for AD.

TREM2

What is TREM2?

Triggering receptor expressed on myeloid cells 2 (TREM2), a transmembrane receptor in the immunoglobulin superfamily, is predominantly expressed in microglia of the CNS and has been linked to Alzheimer's disease (AD). TREM2 contains an extracellular domain composed of a single V-type immunoglobulin domain, an ectodomain, a single transmembrane helix, and a cytosolic tail (Deczkowska et al., 2020). The extracellular domain of TREM2 has the ability to bind to Aβ, lipopolysaccharide (LPS), and various apolipoproteins such as ApoE, which function as ligands that can activate TREM2 signaling. The extracellular domain of TREM2 can be cleaved by α-secretase enzymes (including ADAM10 and ADAM17) to release soluble TREM2 (sTREM2), which has been associated with increased clearance of Aβ and reduced AD (Y. Li et al., 2023). Importantly, due to the absence of a signal transduction or trafficking motif in its tail, TREM2 must be associated with the intracellular adapter protein DNAX-activation protein 12 (DAP12) and DAP10. When TREM2 interacts with ligands, DAP 12 and DAP10 are phosphorylated, initiating intracellular signal transduction and therefore, allowing the microglia to execute their essential roles as the brain’s macrophages (Deczkowska et al., 2020). Though TREM2 was first discovered to contribute to Nasu-Hakola disease (NHD), it plays a specific role in the development of AD as well. It is involved in microglial activation around amyloid plaques to prevent accumulation of Aβ (Konishi & Kiyama, 2018). It has been shown, with overexpression, to improve the pathological symptoms of AD, including plaque load and cognitive impairment (Lee et al., 2018).

Mutations in TREM2’s encoding gene have been identified as risk factors for AD. A hypomorphic missense mutation, R47H, significantly raises the risk of Alzheimer's disease (AD) (S. Wang et al., 2020). This mutation results in the loss of ligand-binding ability, causing the phagocytosis of the ligands that interact with TREM2 such as Aβ and ApoE (Deczkowska et al., 2020). This phagocytosis results in an inability to bind to Aβ, resulting in a reduction in the clearance of Aβ. Other TREM2 variants like R62H also contribute to increased risk, though to a lesser extent (S. Wang et al., 2020).

TREM2's Role on Inflammation and Microglia

TREM2 and its various functions have been extensively studied in the context of Alzheimer's disease (AD) and microglial activity. This section will summarize the different roles of TREM2 in AD, including its impact on microglia-mediated inflammatory responses and its influence on microglial phagocytic function and survival. While the literature around this topic is extensive, this review will focus on the main signaling pathways that can be tied to a therapeutic approach that combines the noninvasive treatment of MT and manipulation of the appropriate TREM2 pathway.

TREM2 plays an important role in the microglia-mediated inflammatory response. Specifically, TREM2 overexpression decreases the microglia-mediated inflammatory response. TREM2 also reduces inflammation and improves cognitive function via the PI3K/AKT/FoxO3a signaling pathway (Y. Li et al., 2023). When TREM2 is activated, it interacts with an adapter protein called DNAX-activating protein of 12kDa (DAP12), which subsequently activates the phosphatidylinositol 3-kinase (PI3K) enzyme. PI3K then phosphorylates and activates AKT (also known as Protein Kinase B), which is a key regulator of cell survival and metabolism, and promotes cell survival by inhibiting pro-apoptotic pathways and factors. AKT phosphorylates the transcription factor FoxO3a, leading to its inactivation. In its phosphorylated state, FoxO3a is unable to activate genes involved in pro-inflammatory responses and oxidative stress, reducing inflammation in the brain (Y. Wang et al., 2020). Additionally, TREM2 can enhance the phagocytic function of microglia as well as regulating the proliferation, or rapid growth, and survival of microglial. Recent studies have demonstrated that microglia bind to Aβ through TREM2, consequently limiting the spread of pathological phosphorylated Tau (Y. Li et al., 2023). TREM2 knockdown has been shown to increase the microglia-mediated inflammatory response (Y. Li et al., 2023). In microglia, the absence of TREM2 leads to increased transcription of pro-inflammatory factors such as tumor necrosis factor alpha (TNFα) and nitric oxide synthase-2 (NOS2), contributing to the formation of Aβ plaques and neurodegeneration (Takahashi et al., 2005). TREM2 functional deficiency also leads to a weakened response of microglia to Aβ plaques, aggravating neuronal damage. Studies have shown that TREM2 knockdown lessens microglia phagocytosis and reduces Aβ plaque formation (Y. Li et al., 2023).

TREM2 as Potential Treatment for AD

TREM's role in microglia function and inflammation, described above, highlights its significance in Alzheimer's disease (AD). TREM2 helps microglia support neuron recovery and enhances their neuroprotective effects by regulating inflammatory responses and increasing microglial survival. The essential role of TREM2 in AD suggests its potential as a biomarker or therapeutic target for future AD diagnosis or treatment. Though there have rarely been any human clinical trials involving TREM2, research with AD mouse models have provided valuable information on the use of TREM2 for potential treatments of AD. This section will summarize the TREM2 therapies that have been researched, including the use of soluble TREM2 (sTREM2), monoclonal antibodies, and lentivirus transfection.

Recent studies have researched the development of a TREM2 agonist that when tested on mouse models showed improvements in AD symptoms, indicating the possibilities for activating TREM2 as a treatment for AD. TREM2 agonist, AL002c, treatment in an AD mouse model increased microglia proliferation, enhanced the phagocytic activity of microglia, improved risk-taking and anxiety behavior, and reduced the microglial-mediated inflammatory response. In the first-in-human phase I clinical trial for AL002c, it caused no serious side effects and

increased microglia activation, indicating the safety and tolerability of this antibody (S. Wang et al., 2020). Another monoclonal antibody, Ab-T1, that binds to the extracellular domain of TREM2 was shown to activate microglia and reduce neuroinflammation as well as improve cognitive function. This antibody demonstrated high affinity for both human and mouse TREM2, suggesting its effectiveness in recognizing and binding to TREM2 (Fassler et al., 2021). With successful results, both antibodies are promising candidates for further investigation in the treatment of AD. Using these antibodies or developing better equivalents, proves there is potential for targeting TREM2, allowing significant advancements in managing and treating AD.

Research into soluble TREM2 (sTREM2) has also shown potential in addressing AD. Increased levels of sTREM2 have commonly been associated with AD. sTREM2 levels are found to be elevated in the cerebrospinal fluid (CSF) of patients with sporadic AD, which is why sTREM2 has been considered a biomarker for AD (Y. Li et al., 2023). However, sTREM2 has been found to play a much more complex role. Though sTREM2 is elevated during the early symptomatic stages of AD, sTREM2 could also have protective effects. Through a direct stereotaxic injection of a recombinant sTREM2 protein into the hippocampus of AD mouse models, a study observed the reduction of the accumulation of Aβ plaques, enhancement of microglial proliferation, and improvements in spatial memory. The study also used Adeno-Associated Virus (AAV) to deliver the gene encoding sTREM2 into the brains of AD mouse models and study the long-term effects of sTREM2. sTREM2 was found to significantly decrease overall plaque accumulation in both the hippocampus and the cortex (Zhong et al., 2019).

Many studies have demonstrated that overexpressing TREM2 can significantly improve symptoms of Alzheimer's disease (AD). Various methods, such as using transgenic mice or in vitro models, have provided valuable insights into TREM2's potential benefits. One study using a lentiviral vector to overexpress TREM2 in the brains of AD mice, showed significant reductions in amyloid-beta deposition, neuroinflammation, and cognitive deficits (Jiang et al., 2014). These findings suggest that TREM2 can potentially be targeted to treat AD by utilizing monoclonal antibodies, sTREM2, and AAV and lentiviral vectors.

Limitations to TREM2 Targeted Treatments

While there are promising therapies involving TREM2 that have been studied, targeting TREM2 still has its limitations. One major limitation is the risk associated with all invasive therapies, which is that it could lead to unintended complications, especially considering the delicate nature of the brain. Most of the proposed therapies have only used mouse models to test their efficacy. Humans could react differently to the therapy or have severe side effects. Additionally, TREM2 plays specific functional roles at different stages in AD, making it difficult to develop a single treatment targeting TREM2 that accounts for all stages of AD. A study comparing the role of TREM2 in AD mouse models at early and late stages of the disease found that TREM2 deficiency reduced amyloid plaque number and area in the early stages of AD, while in later stages, there was an increase in plaque size and accumulation (Jay et al., 2017). Having complete opposite effects when at different stages of AD, TREM2 therapies may require specificity and consideration of disease progression, making it difficult to create effective treatments.

Similar to music therapy, there are unknowns with the long-term effects of TREM2 therapies. The progression of neurodegenerative diseases is often slow and variable, making it difficult to predict the long-term effects of TREM2 therapies. Additionally, since TREM2 affects

the inflammatory response in the brain, the immune system could adapt to TREM2-targeted therapies over time, reducing their efficacy or leading to resistance.

Connection Between MT and TREM2

Through this review multiple studies were discussed showing the potential benefits of music therapy and TREM2 on reducing the progression and symptoms of AD, and potentially improving patient outcomes. Independently, both approaches are promising and provide therapeutic hope to the population suffering from AD; however, is there a world where these two therapies can interact? Though music therapy and TREM2 seem completely irrelevant to each other, there is a possible connection between the mechanisms of both therapies with regard to AD.

As explained previously, music therapy has been observed to increase levels of estrogen and other sex hormones in AD patients. Estrogen has been found to activate the P13K/AKT pathway. Estrogen, specifically 17β-estradiol, binds to estrogen receptors (ERs) such as ERα (Estrogen Receptor alpha), located on the cell membrane or inside the cell. The activated ERα can interact with and activate Phosphoinositide 3-Kinase (PI3K). This activation leads to the inhibition of the apoptosis signal-regulating kinase 1 (Ask1) pathway, which would otherwise promote apoptosis in response to amyloid-β (Aβ) toxicity (Mateos et al., 2012). Since TREM2 has also been associated with the P13K/AKT pathway, this suggests that MT and TREM2 have a connection through a single pathway. This gives insight into the mechanisms of MT and TREM2, and how they could affect each other. Given its role in promoting cell survival and inhibiting apoptosis, the PI3K/AKT pathway is a promising therapeutic target for AD. This pathway is where multiple neuroprotective signals converge, including those mediated by TREM2 and estrogen. In the TREM2 study, PI3K/AKT activation leads to the downstream activation of FoxO3a, contributing to anti-inflammatory effects and preventing apoptosis. In the estrogen study, PI3K/Akt activation is essential for protecting neurons from Aβ toxicity, further highlighting the pathway's central role in promoting cell survival and preventing apoptosis.

Currently, the direct use of estrogen in the treatment of AD is controversial. Hormone replacement therapy (HRT) has had inconsistent results, showing both a negative correlation between HRT on the risk of dementia and a positive correlation between HRT and the risk for dementia. A short-term hormone therapy using estradiol found improvement in visual and semantic memory, indicating the favorable effects of HRT on dementia (Wharton et al., 2011). On the other hand, a menopausal hormone therapy with oestrogen and progestin was shown to be strongly associated with the risk of developing dementia, including AD (Pourhadi et al., 2023). Another type of hormone therapy involving estrogen and progestin was also shown to increase the risk of dementia in postmenopausal women aged 65 years or older and was not able to prevent cognitive decline (Shumaker et al., 2003). Additional studies have indicated that the positive effects of hormone therapy may be due to providing the therapy at a specific time, also known as the critical window theory. One study found that hormone therapy may reduce the risk of AD only when initiated near menopause and instead increase risk when started later in life (Whitmer et al., 2011). Hormone replacement therapy can also cause side effects such as increasing the risk of breast cancer, blood clots, heart disease, and stroke (Cho et al., 2023). Therefore, the direct use of it as a therapeutic target is limited. However, naturally increasing estrogen levels through a noninvasive method such as MT, can firstly, provide the beneficial effects of HRT without the risk, and secondly, provide a novel approach to enhancing TREM2 activation without directly treating a patient with estrogen. This approach combined with the

development of a therapeutic TREM2 treatment can significantly increase TREM2 activation, increase Aβ clearance, and reduce inflammation, resulting in improving AD outcome. Furthermore, the use of MT with a TREM2 treatment could have other beneficial effects on inflammation. As mentioned, MT has been shown to reduce stress, anxiety, and depression. These negative emotions are, when prolonged, associated with increased inflammation (Kim et al., 2022); therefore, by combining MT with TREM2 treatment, there is the utilization of a noninvasive therapy that can improve inflammation through a reduction of chronic distress, and a more invasive therapy that can reduce inflammation through microglia activity.

While these two therapeutic approaches are seemingly extremely different, there are connections that, if studied, can improve outcomes in AD. Combining agents that activate TREM2, such as the TREM2 therapies discussed above and MT should be further explored as a potential therapeutic strategy for AD and other neurodegenerative diseases.

Conclusion

Music therapy (MT) and TREM2 can both be considered as potential treatments of Alzheimer's Disease (AD), alleviating behavioral and cognitive symptoms and having neuroprotective effects. However, they are currently not perfect solutions, as limitations still exist. Further research should be conducted to verify their effectiveness, clarify their mechanisms, and identify any potential risks. Despite these challenges, MT and TREM2 show promise as valuable components in the evolving field of AD treatments.

Works Cited

Akwa, Y. (2020). Steroids and Alzheimer's Disease: Changes Associated with Pathology and Therapeutic Potential. International Journal of Molecular Sciences, 21(13), Article 13. https://doi.org/10.3390/ijms21134812

Bolmont, T., Clavaguera, F., Meyer-Luehmann, M., Herzig, M. C., Radde, R., Staufenbiel, M., Lewis, J., Hutton, M., Tolnay, M., & Jucker, M. (2007). Induction of Tau Pathology by Intracerebral Infusion of Amyloid-β-Containing Brain Extract and by Amyloid-β Deposition in APP × Tau Transgenic Mice. The American Journal of Pathology, 171(6), 2012–2020. https://doi.org/10.2353/ajpath.2007.070403

Brotons, M., & Koger, S. M. (2000). The impact of music therapy on language functioning in dementia. Journal of Music Therapy, 37(3), 183–195. https://doi.org/10.1093/jmt/37.3.183

Cameron, B., & Landreth, G. E. (2010). Inflammation, microglia, and alzheimer's disease. Neurobiology of Disease, 37(3), 503–509. https://doi.org/10.1016/j.nbd.2009.10.006

Ceccato, E., Vigato, G., Bonetto, C., Bevilacqua, A., Pizziolo, P., Crociani, S., Zanfretta, E., Pollini, L., Caneva, P. A., Baldin, L., Frongillo, C., Signorini, A., Demoro, S., & Barchi, E. (2012). STAM Protocol in Dementia. American Journal of Alzheimer's Disease and Other Dementias, 27(5), 301–310. https://doi.org/10.1177/1533317512452038

Chen, R., Chan, P.-T., Chu, H., Lin, Y.-C., Chang, P.-C., Chen, C.-Y., & Chou, K.-R. (2017). Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: A meta-analysis. PLoS ONE, 12(8), e0183586. https://doi.org/10.1371/journal.pone.0183586

Cho, L., Kaunitz, A. M., Faubion, S. S., Hayes, S. N., Lau, E. S., Pristera, N., Scott, N., Shifren, J. L., Shufelt, C. L., Stuenkel, C. A., & Lindley, K. J. (2023). Rethinking Menopausal Hormone Therapy: For Whom, What, When and How long? Circulation, 147(7), 597–610. https://doi.org/10.1161/CIRCULATIONAHA.122.061559

Cornell, J., Salinas, S., Huang, H.-Y., & Zhou, M. (2021). Microglia regulation of synaptic plasticity and learning and memory. Neural Regeneration Research, 17(4), 705–716. https://doi.org/10.4103/1673-5374.322423

Deczkowska, A., Weiner, A., & Amit, I. (2020). The Physiology, Pathology, and Potential Therapeutic Applications of the TREM2 Signaling Pathway. Cell, 181(6), 1207–1217. https://doi.org/10.1016/j.cell.2020.05.003

DeTure, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. Molecular Neurodegeneration, 14(1), 32. https://doi.org/10.1186/s13024-019-0333-5

Fang, R., Ye, S., Huangfu, J., & Calimag, D. P. (2017). Music therapy is a potential intervention for cognition of Alzheimer's Disease: A mini-review. Translational Neurodegeneration, 6, 2. https://doi.org/10.1186/s40035-017-0073-9

Fassler, M., Rappaport, M. S., Cuño, C. B., & George, J. (2021). Engagement of TREM2 by a novel monoclonal antibody induces activation of microglia and improves cognitive function in Alzheimer's disease models. Journal of Neuroinflammation, 18(1), 19. https://doi.org/10.1186/s12974-020-01980-5

Fukui, H., Arai, A., & Toyoshima, K. (2012). Efficacy of Music Therapy in Treatment for the Patients with Alzheimer's Disease. International Journal of Alzheimer's Disease, 2012, 531646. https://doi.org/10.1155/2012/531646

Gómez-Gallego, M., Gómez-Gallego, J. C., Gallego-Mellado, M., & García-García, J. (2021). Comparative Efficacy of Active Group Music Intervention versus Group Music Listening in

Alzheimer's Disease. International Journal of Environmental Research and Public Health, 18(15), 8067. https://doi.org/10.3390/ijerph18158067
Götell, E., Brown, S., & Ekman, S.-L. (2009). The influence of caregiver singing and background music on vocally expressed emotions and moods in dementia care. International Journal of Nursing Studies, 46(4), 422–430. https://doi.org/10.1016/j.ijnurstu.2007.11.001
Irish, M., Cunningham, C. J., Walsh, J. B., Coakley, D., Lawlor, B. A., Robertson, I. H., & Coen, R. F. (2006). Investigating the Enhancing Effect of Music on Autobiographical Memory in Mild Alzheimer's Disease. Dementia and Geriatric Cognitive Disorders, 22(1), 108–120. https://doi.org/10.1159/000093487
Jay, T. R., Hirsch, A. M., Broihier, M. L., Miller, C. M., Neilson, L. E., Ransohoff, R. M., Lamb, B. T., & Landreth, G. E. (2017). Disease Progression-Dependent Effects of TREM2 Deficiency in a Mouse Model of Alzheimer's Disease. The Journal of Neuroscience, 37(3), 637–647. https://doi.org/10.1523/JNEUROSCI.2110-16.2016
Jiang, T., Tan, L., Zhu, X.-C., Zhang, Q.-Q., Cao, L., Tan, M.-S., Gu, L.-Z., Wang, H.-F., Ding, Z.-Z., Zhang, Y.-D., & Yu, J.-T. (2014). Upregulation of TREM2 Ameliorates Neuropathology and Rescues Spatial Cognitive Impairment in a Transgenic Mouse Model of Alzheimer's Disease. Neuropsychopharmacology, 39(13), 2949–2962. https://doi.org/10.1038/npp.2014.164
Johnson, J. K., Cotman, C. W., Tasaki, C. S., & Shaw, G. L. (1998). Enhancement of spatial-temporal reasoning after a Mozart listening condition in Alzheimer's disease: A case study. Neurological Research, 20(8), 666–672. https://doi.org/10.1080/01616412.1998.11740582
Kim, I.-B., Lee, J.-H., & Park, S.-C. (2022). The Relationship between Stress, Inflammation, and Depression. Biomedicines, 10(8), 1929. https://doi.org/10.3390/biomedicines10081929
Koelsch, S. (2009). A Neuroscientific Perspective on Music Therapy. Annals of the New York Academy of Sciences, 1169(1), 374–384. https://doi.org/10.1111/j.1749-6632.2009.04592.x
Konishi, H., & Kiyama, H. (2018). Microglial TREM2/DAP12 Signaling: A Double-Edged Sword in Neural Diseases. Frontiers in Cellular Neuroscience, 12. https://doi.org/10.3389/fncel.2018.00206
Lee, C. Y. D., Daggett, A., Gu, X., Jiang, L.-L., Langfelder, P., Li, X., Wang, N., Zhao, Y., Park, C. S., Cooper, Y., Ferando, I., Mody, I., Coppola, G., Xu, H., & Yang, X. W. (2018). Elevated TREM2 Gene Dosage Reprograms Microglia Responsivity and Ameliorates Pathological Phenotypes in Alzheimer's Disease Models. Neuron, 97(5), 1032-1048.e5. https://doi.org/10.1016/j.neuron.2018.02.002
Li, C.-H., Liu, C.-K., Yang, Y.-H., Chou, M.-C., Chen, C.-H., & Lai, C.-L. (2015). Adjunct effect of music therapy on cognition in Alzheimer's disease in Taiwan: A pilot study. Neuropsychiatric Disease and Treatment, 11, 291–296. https://doi.org/10.2147/NDT.S73928
Li, Y., Xu, H., Wang, H., Yang, K., Luan, J., & Wang, S. (2023). TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomedicine & Pharmacotherapy, 165, 115218. https://doi.org/10.1016/j.biopha.2023.115218
Lyu, J., Zhang, J., Mu, H., Li, W., Champ, M., Xiong, Q., Gao, T., Xie, L., Jin, W., Yang, W., Cui, M., Gao, M., & Li, M. (2018). The Effects of Music Therapy on Cognition, Psychiatric Symptoms, and Activities of Daily Living in Patients with Alzheimer's Disease. Journal of Alzheimer's Disease, 64(4), 1347–1358. https://doi.org/10.3233/JAD-180183
Massoud, F., & Léger, G. C. (2011). Pharmacological Treatment of Alzheimer Disease. The Canadian Journal of Psychiatry, 56(10), 579–588. https://doi.org/10.1177/070674371105601003

Mateos, L., Persson, T., Kathozi, S., Gil-Bea, F. J., & Cedazo-Minguez, A. (2012). Estrogen protects against amyloid-β toxicity by estrogen receptor α-mediated inhibition of Daxx translocation. Neuroscience Letters, 506(2), 245–250. https://doi.org/10.1016/j.neulet.2011.11.016

Nilsen, J., Chen, S., Irwin, R. W., Iwamoto, S., & Brinton, R. D. (2006). Estrogen protects neuronal cells from amyloid beta-induced apoptosis via regulation of mitochondrial proteins and function. BMC Neuroscience, 7(1), 74. https://doi.org/10.1186/1471-2202-7-74

Pourhadi, N., Mørch, L. S., Holm, E. A., Torp-Pedersen, C., & Meaidi, A. (2023). Menopausal hormone therapy and dementia: Nationwide, nested case-control study. BMJ, 381, e072770. https://doi.org/10.1136/bmj-2022-072770

Raglio, A., Filippi, S., Bellandi, D., & Stramba-Badiale, M. (2014). Global music approach to persons with dementia: Evidence and practice. Clinical Interventions in Aging, 9, 1669–1676. https://doi.org/10.2147/CIA.S71388

Ragneskog, H., Bråne, G., Karlsson, I., & Kihlgren, M. (1996). Influence of Dinner Music on Food Intake and Symptoms Common in Dementia. Scandinavian Journal of Caring Sciences, 10(1), 11–17. https://doi.org/10.1111/j.1471-6712.1996.tb00304.x

Rosario, E. R., Chang, L., Head, E. H., Stanczyk, F. Z., & Pike, C. J. (2011). Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. Neurobiology of Aging, 32(4), 604–613. https://doi.org/10.1016/j.neurobiolaging.2009.04.008

Sakamoto, M., Ando, H., & Tsutou, A. (2013). Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. International Psychogeriatrics / Ipa, 25(5), 775–784. https://doi.org/10.1017/S1041610212002256

Satoh, M., Yuba, T., Tabei, K., Okubo, Y., Kida, H., Sakuma, H., & Tomimoto, H. (2015). Music Therapy Using Singing Training Improves Psychomotor Speed in Patients with Alzheimer's Disease: A Neuropsychological and fMRI Study. Dementia and Geriatric Cognitive Disorders EXTRA, 5(3), 296–308. https://doi.org/10.1159/000436960

Scheltens, P., Blennow, K., Breteler, M. M. B., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. The Lancet, 388(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1

Shumaker, S. A., Legault, C., Rapp, S. R., Thal, L., Wallace, R. B., Ockene, J. K., Hendrix, S. L., Jones III, B. N., Assaf, A. R., Jackson, R. D., Morley Kotchen, J., Wassertheil-Smoller, S., Wactawski-Wende, J., & for the WHIMS Investigators. (2003). Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal WomenThe Women's Health Initiative Memory Study: A Randomized Controlled Trial. JAMA, 289(20), 2651–2662. https://doi.org/10.1001/jama.289.20.2651

Svansdottir, H. B., & Snaedal, J. (2006). Music therapy in moderate and severe dementia of Alzheimer's type: A case–control study. International Psychogeriatrics, 18(4), 613–621. https://doi.org/10.1017/S1041610206003206

Takahashi, K., Rochford, C. D. P., & Neumann, H. (2005). Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. The Journal of Experimental Medicine, 201(4), 647–657. https://doi.org/10.1084/jem.20041611

Wang, M., Hu, S., Fu, X., Zhou, H., Yang, S., & Yang, C. (2024). Neurosteroids: A potential target for neuropsychiatric disorders. The Journal of Steroid Biochemistry and Molecular Biology, 239, 106485. https://doi.org/10.1016/j.jsbmb.2024.106485

Wang, S., Mustafa, M., Yuede, C. M., Salazar, S. V., Kong, P., Long, H., Ward, M., Siddiqui, O., Paul, R., Gilfillan, S., Ibrahim, A., Rhinn, H., Tassi, I., Rosenthal, A., Schwabe, T., & Colonna, M.

(2020). Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. The Journal of Experimental Medicine, 217(9), e20200785. https://doi.org/10.1084/jem.20200785

Wang, Y., Lin, Y., Wang, L., Zhan, H., Luo, X., Zeng, Y., Wu, W., Zhang, X., & Wang, F. (2020). TREM2 ameliorates neuroinflammatory response and cognitive impairment via PI3K/AKT/FoxO3a signaling pathway in Alzheimer's disease mice. Aging (Albany NY), 12(20), 20862–20879. https://doi.org/10.18632/aging.104104

Wharton, W., Baker, L. D., Gleason, C. E., Dowling, M., Barnet, J. H., Johnson, S., Carlsson, C., Craft, S., & Asthana, S. (2011). Short-term Hormone Therapy with Transdermal Estradiol Improves Cognition for Postmenopausal Women with Alzheimer's Disease: Results of a Randomized Controlled Trial. Journal of Alzheimer's Disease, 26(3), 495–505. https://doi.org/10.3233/JAD-2011-110341

Whitmer, R. A., Quesenberry, C. P., Zhou, J., & Yaffe, K. (2011). Timing of Hormone Therapy and Dementia: The Critical Window Theory Re-visited. Annals of Neurology, 69(1), 163–169. https://doi.org/10.1002/ana.22239

Zhong, L., Xu, Y., Zhuo, R., Wang, T., Wang, K., Huang, R., Wang, D., Gao, Y., Zhu, Y., Sheng, X., Chen, K., Wang, N., Zhu, L., Can, D., Marten, Y., Shinohara, M., Liu, C.-C., Du, D., Sun, H., … Chen, X.-F. (2019). Soluble TREM2 ameliorates pathological phenotypes by modulating microglial functions in an Alzheimer's disease model. Nature Communications, 10(1), 1365. https://doi.org/10.1038/s41467-019-09118-9