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Title: **Neuroscience-informed music therapy as a neuroprotective intervention for pre-dementia populations**

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Abstract: Alzheimer's Disease (AD), the leading cause of dementia, deleteriously affects memory, cognitive function, and eventually leads to loss of motoric abilities and death (Alzheimer's Disease Fact Sheet, 2015). Most cases of AD occur later in life, with clinical symptoms appearing long after brain pathology begins. Drawing from neuroscience literature, we propose the relevance of music therapy interventions as a neuro-protective method for at-risk aging populations.

Summary:

Alzheimer's Disease (AD) and related dementias affect 44 million people globally (Alzheimer's Statistics, 2015). Disease diagnosis consists of three stages, the first being 'preclinical,' characterizing a state before noticeable symptoms, but with increasing brain pathology (Alzheimer's Association, 2014). Disease rates for this stage are yet unknown and challenging to estimate, but if this number were included among diagnoses, overall AD prevalence would be much higher. AD risk factors of interest in this paper include age, cardiovascular/cerebrovascular disease, and declining social/cognitive engagement. Lifespans continue to increase, creating a need for neuroprotective interventions in the vulnerable elderly population.

AD brain pathology includes intracellular and extracellular amyloid plaques, neurofibrillary tangles, neuronal and synaptic loss, and neurodegeneration (Alzheimer's Association, 2014; Nagele, Han et al. 2011), particularly in areas associated with

memory and cognition, including the hippocampus, entorhinal cortex, and tempoparietal lobes (Prestia et al., 2010). Current dementia models include the linkage between cerebrovascular health, namely blood-brain barrier (BBB) integrity (Clifford et al., 2007; Kapasi & Schneider, 2016; Raz, Knoefel, & Bhaskar, 2015; Saito & Ihara, 2016) and AD pathology, which, in progressed stages, produces cognitive and social deficits. Although early detection methods for AD elude us, we know the aging population is vulnerable to AD risk factors, and thus, early intervention is key in minimizing irreversible dementia-associated neurodegeneration.

Interventions that support both cognitive/social strength and cerebrovascular health provide promise in mitigating dementia outcomes. Music, as a very complex and dynamic experience, stimulates multiple areas of the brain, including those involved in cognition (Belfi, Karlan, & Tranel, 2015; Clark & Warren, 2015; El Haj, Antoine, Nandrino, Gely-Nargeot, & Raffard, 2015; Ferreri, Bigand, Bard, & Bugaiska, 2015; Janata, 2009; Raglio et al., 2015; Sikka, Cuddy, Johnsrude, & Vanstone, 2015; Vandervert, 2015; Zuk, Benjamin, Kenyon, & Gaab, 2014), emotion (Juslin, Barradas, & Eerola, 2015; Samson, Dellacherie, & Platel, 2009), movement (Large, Herrera, & Velasco, 2015; Vandervert, 2015) and autonomic function (Bernardi et al., 2009; Vlachopoulos et al., 2015), and may affect autonomic function in a way that supports cerebrovascular health (Vlachopoulos et al., 2015). Music engagement as a highly motivating activity also helps ensure participation and compliance in programs with non-musical goals, such as neuroprotective programs for the aging.

Mild cognitive impairment, such as memory deficit, is the most important feature in early-stage AD (Morris, Storandt, Miller, & et al., 2001). Through a systematic review of 13 journal articles, Wall and Duffy (2010) reported that music interventions may reduce levels of agitation, increase mood, and support socialization skills in persons with dementia. Bruer, Spitznagel, and Cloninger (2007) pointed out a term “cognition-enhancing music therapy” to inform the potential effect of music intervention in this population. They addressed the relationship between anxiety, cognition, and music and noted that the effect of reducing anxiety from music therapy may improve patients’ cognition.

LaGasse and Thaut (2013) proposed the effectiveness of music interventions by reviewing related empirical studies of music intervention and cognitive function. The interventions that may increase the cognitive function include: 1) using music to increase neuronal network synchronization, 2) through listening to assist the rehabilitation of attention due to the activation of cortical areas involved in attention, 3) through listening to increase verbal memory and focused attention skills, 4) through pairing with a rhythmic pattern to improve memory skills, and 5) using rhythmic and music exercises to improve executive functioning such as sequencing, decision making, problem solving, organizing, and planning.

Koelsch (2009, p. 375) proposed that music can be utilized to improve cognitive function through the mechanisms of memory processes related to music (such as encoding, storage, and decoding of musical information and of events associated with musical experiences), as well as the processes related to the analysis of musical syntax and musical meaning. He further suggested that the mechanisms of memory processes

in music might contribute to the effects of music therapy in the AD population. Similarly, Thaut et al. (2009) also stated that music may be utilized as a mnemonic device to enhance memory for nonmusical events (p. 407).

As mentioned above, memory and cognitive function are related to one other. Many studies have proposed that music interventions may play an important role in facilitating memory skills (Cuddy & Duffin, 2005; Legge, 2015; Moore, 2013; Thaut et al., 2009). In a clinical case report of an elderly woman with AD, Cuddy and Duffin (2005) demonstrated that the client responded to familiar melodies by singing along, usually with the words, and often continued to sing after the stimulus had stopped, but she never responded to the unfamiliar melodies. Researchers (Legge, 2015; Moore, 2013) have suggested that, through neurological perspectives, the human brain forms a route of associated memories while listening to familiar music. This route includes the left medial prefrontal cortex (linked to self-referential cognition), the ventrolateral prefrontal cortex (linked to cognitive control of semantic memories such as facts), and the lingual gyrus (linked to visual memories) (Legge, 2015, p. 6). Legge (2015) also assumed that music-induced autobiographical memories have a greater tendency to be emotionally positive.

Another neural mechanism that can be facilitated by musical stimulus is the motoric system. By perceiving rhythm, a person's premotor cortex, inferior frontal gyrus, superior temporal gyrus, and inferior parietal lobule may be activated (Levitin, 2013). Through music activities such as instrument playing and dancing to music, the sensory and motor cortices can be activated (Levitin, 2013) and lead to coordination of actions such as synchronization to a beat (Koelsch, 2014). Koelsch (2009) suggested that learning a new movement pattern can modulate a person's cognitive process. It also implies that improve a person's ability of movement may also facilitate one's cognitive function.

We intend to continue our critical literature review and further explore possibilities of neuroscience-informed music therapy interventions that not only support brain areas involved in cognitive function (including memory) and social engagement, but to also scour the literature, for music therapy interventions that support movement, and ultimately cerebrovascular health. We hope to support the value of music therapy interventions for aging persons at-risk for dementia, with the intention of intervening before clinical symptoms of AD appear, when it's too late.

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