

The Power of Music on Alzheimer's Disease and the Need to Understand the Underlying Molecular Mechanisms

Carmela Matrone^{1*} and Elvira Brattico²

¹Institute of Biomedicine, Aarhus University, Bartholins Alle, 6, 8000 Aarhus, Denmark

²Center for Music in the Brain (MIB), Department of Clinical Medicine, Aarhus University & Royal Academy of Music Aarhus/Aalborg, Denmark

Abstract

Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disorder that leads to memory loss. The prevalence of AD varies among many different factors, including age, comorbidities, genetics, and education level. There is no way to definitively diagnose AD before performing an autopsy. There is no cure for AD, although large economical efforts are currently capitalized in promising research and development of new strategies. The purpose of this commentary is to review what we already know about the effects of music treatment on AD. Beside not curative of AD, the use of music seems to exert beneficial effects on Alzheimer's symptoms. In turn, we briefly summarize the accumulated evidence on the effects of music on brain plasticity, discussing the necessity to further investigate the molecular mechanisms governing this plasticity, with a particular focus on the brain derived neurotrophic factor (BDNF). We believe that a further comprehension of how music influences the molecular processes in the human neuronal network might open new perspectives to enhance quality of life for both the patient and his or her caregivers.

Introduction

As our population grows older, one of the most common chronic mental health conditions is dementia. According to a recent report the number of people living with dementia worldwide was 35,6 million in 2010 and it will nearly double in 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Alzheimer's Disease International, 2013). Given the increasing aging population, the overwhelming incidence of dementia will likely become a public health priority and one of the greatest social and economic challenges of our time [1-4].

Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for 60–80% of cases. AD is a progressive neurodegenerative disease, characterized by an early stage in which people experience a progressive memory loss and a decrease in thinking ability such as decision-making. Later the disease evolves in the incapacity to perform daily activities or to recognize loved ones [5-7]. Such behavioural changes are frequently associated to molecular changes in the brain, such as the development of amyloid beta plaques and neurofibrillary tangles. Accordingly, a disruption of balance between production and clearance of amyloid precursor protein is considered as a major cause of amyloid- β plaques formation, consequently leading to neural dysfunction, regional brain atrophy and finally dementia [8,9].

A rarely occurring form of AD (amounting to only 2% of AD cases) has a proven genetic background, namely a mutation on the gene coding for amyloid precursor proteins or presenilin 1 and 2, and it generally starts in early age [10]. The largest AD forms, normally appearing over 65 years of age, are instead defined as being of a sporadic nature because no precise cause has been established [9]. For the common AD forms, the strongest predictor of developing AD, aside from age, is the genetic risk factor apolipoprotein (apo) E4 [11,12]. Additionally, epidemiological studies strongly support associations between limited education, depression, hypertension, diabetes, high cholesterol, smoking, head trauma and AD [13]. Furthermore, an imbalance between blood and cerebrospinal fluid in growth factor levels, such as Brain Derived Neurotrophic factor (BDNF) and Nerve Growth factor (NGF), or alterations in their downstream signalling have been largely reported in patients with AD [14-17] (Table 1). Particularly, BDNF

Advancing age
Family history
Head trauma
Lack of mental stimulation
Down's syndrome
Environmental toxins: aluminum, mercury
Oxidative stress due to accumulation of free radicals and/or low antioxidant levels
Abnormal protein processing
Neurotransmitter deficit
Genetic polymorphism
Age-related reduction of sex hormones

Table 1: Risk factors in AD.

levels change during the progression of the disease with an increase in the early stages and then a decrease in the late stages, likely indicative of a different neuronal response to the insult. Accordingly, the increase of BDNF in the early stages might reflect a compensatory neuronal repair mechanism. Afterwards, with the progression of the neuronal degeneration, BDNF levels decrease as result of the increased neuronal loss and the severity of dementia [18].

As matter of fact, AD is a multifactorial disorder and each of these possible age-related causes provides little possibility in developing clinical prevention and therapies. For many years, the pharmacological treatment of AD has been symptomatic, focusing on the improvement of cognitive and behavioural symptoms in patients with moderate to

*Corresponding author: Carmela Matrone, Institute of Biomedicine, Aarhus University, Bartholins Alle, 6, 8000 Aarhus, Denmark, Tel: +45-87167252; E-mail: matrone@biomed.au.dk

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Symptomatic Treatments Acetylcholinesterase Inhibitors
NMDA-receptor Antagonists, Nicotinic-receptor Agonists
Disease-modifying Treatments:
Inhibition of amyloid formation: beta and gamma-secretase inhibitors Inhibition of Ab aggregation
Tau phosphorylation inhibitors
Other Therapies
Cholesterol-lowering therapies, Anti-inflammatory therapies
Therapies involving antioxidants: vitamin E and ginkgo biloba
Therapies involving neurotrophic factors: nerve growth factor (NGF) and estrogen
Alternative therapies: Diet control, Use of exercise, Stress control, Herbal remedies, Music
Psychotic Treatments: Antidepressants [depression], Anxiolytics [anxiety]
Antipsychotics [severe confusion, paranoia, and hallucinations]
Hormone replacement

Table 2: Pharmacological and non-pharmacological treatments of AD.

severe dementia. Those symptoms (frequently occurring in cluster and varying by time, severity, and diagnosis) mainly include hyperactivity cluster (agitation, aggression, euphoria, irritability, aberrant motor activity), psychosis cluster (hallucinations and delusions), mood liability cluster (depression and anxiety), and instinctual cluster (appetite disturbance, sleep disturbance, and apathy) [19]. Hence, in AD the main drugs used have been antipsychotic and anxiolytic, along with a limited number of drugs specifically approved for dementia, such as cholinesterase inhibitors and memantine. However, treatment effects are generally limited, and they only prevent symptoms from becoming worse for a limited time and/or partially help in controlling some behavioural symptoms (Table 2).

Moreover, some of the latest pharmacological treatments targeting the toxicity of amyloids or NMDA receptor antagonists acting on the glutamatergic system (memantine) are associated with increased morbidity and mortality in patients, particularly after long period of exposure [20-22]. As consequence, after a recent systematic review of all the results obtained by pharmacologically treating AD patient, it has been even recommended to avoid any pharmacological intervention [22-24]. Although restraining patients from taking medication is a very extreme position, it is evident that no pharmacological treatment can delay or halt the progression of the disease, and in too many cases, even symptomatic drugs have only limited efficacy. Conclusively, alternative approaches have been proposed and several non-pharmacological approaches have been developing, consisting in the regularly use of various cognitively stimulating leisure activities to help the cognitive and emotional capacity of the patients [25].

One such potential leisure activity is music. Other potential non-pharmacological interventions include cognitive training/stimulation, rehabilitative care, massage/touch, physical activity, education/training for professionals, and education and psychosocial support for informal caregivers. In this commentary we aim at providing a short overview of the findings on music-derived brain plasticity over the life span and in AD. Particular focus will be given to the potential connections between music and BDNF serum levels, and how that can be of help in AD. Finally, future perspectives on the use of musical activities as non-pharmacological therapy will be discussed.

Music in the Brain

Music is a powerful stimulator of the brain. In the simplest listening conditions in solitude at home or by means of mobile devices when

commuting, music consists of time-varying sound events characterized by a large number of acoustic features (in music information retrieval, more than a hundred of features can be computationally extracted from songs). Low-level features, such as the timbre of an instrument and pitch, are tracked by several regions of the brain, particularly the Heschl's gyrus and the right anterior part of the superior temporal gyrus, in which the primary and non-primary auditory cortices are located [26]. Also motor regions, like the supplementary motor area and the cerebellum are involved, if the listeners have an active musical background [27], due to the audio-motor transformations that are necessary for instrument playing.

Indeed, when music is played, score reading, fine movements of the limbs, haptic feedback, emotional arousal are all co-occurring and the related regions of the brain become activated [28,29] (Figure 1). The repetitive activation of these regions in professional musicians playing instruments for decades induces neuroplasticity that is clearly observable with modern neuroimaging techniques, e.g., magnetic resonance imaging (MRI). Increased grey matter volume of the Heschl's gyrus [30], primary motor cortex, premotor cortex [31,32], cerebellum [33] and hippocampus [34] have been found in musicians when compared with non-musicians.

Many studies document the efficacy of music in increasing some cognitive functions such as memory, executive functions, speech, and attention in both adults and children [35-38]. Effects on verbal intelligence, positively correlated with activity in prefrontal brain regions, have been documented in preschool children even after short-term music training [39]. In adults, larger brain activity in the hippocampus and the dorsolateral prefrontal cortex, strongly related to cognitive control abilities [40]. Overall, these findings demonstrate the relevance of music for brain plasticity in the cortex and the hippocampus, making musicians a good model for non-invasively studying neuroplasticity processes in humans [41,42].

In elderly professional musicians, musical practice seems to preserve the volumes of the neuronal fibers of the arcuate fasciculus, connecting the supratemporal lobe with the inferofrontal regions of the brain, hence halting the apoptosis related to normal aging [43]. Additionally, in adults music is a reliable elicitor of memories, including autobiographical ones. Janata presented subjects to songs from the rock/pop charts of the years when subjects were between 7 and 19 years old [44]. The songs that were rated by subjects as familiar and

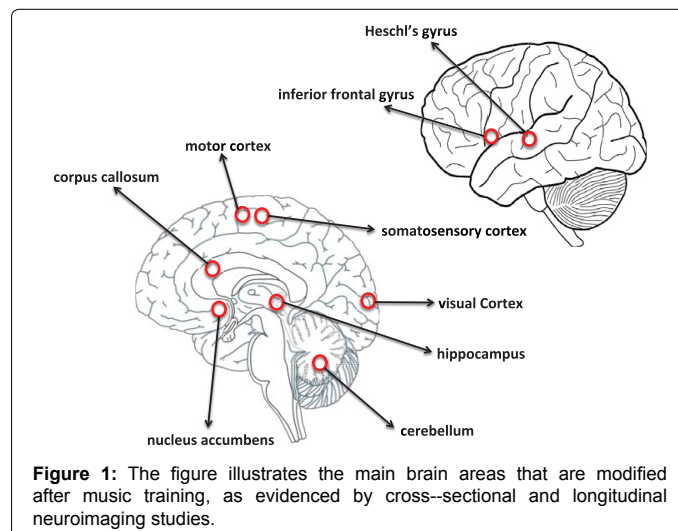


Figure 1: The figure illustrates the main brain areas that are modified after music training, as evidenced by cross-sectional and longitudinal neuroimaging studies.

autobiographically salient activated the dorsomedial prefrontal cortex, previously associated with self-referential processes and integration of sensory information with self-knowledge. The repetition of motifs in a musical piece also activates the prefrontal cortex and the hippocampus [45], further supporting the links between music listening and memory processes [46].

Music In Alzheimer's Disease

In recent years, music has been introduced as a treatment modality for several central nervous system (CNS) pathologies extending from disturbed behaviour caused by senile dementia [46,47] to schizophrenic-like disorders [48] and AD [49]. In addition, recent findings have reported beneficial effects of music in Parkinson's disease (PD) [50] cerebral ischemia [51], pain [52], autism [53], anxiety and depression [54]. Furthermore, it also has been shown that music can change the pattern of brain electrical activity in electroencephalography recordings [55,56]. Interestingly, neuroimaging studies show that rhythm perception activates basal ganglia that are compromised to varying degrees in PD [57].

Music therapy has the ability to alleviate some symptoms of dementia [58], by providing access to lost memories or enhancing affective state and communicative skills [59-62]. Although some criticisms and some methodological limitations have been pointed out [63,64], most part of the studies have showed the benefits of music therapy in AD patients. Music has been reported to improve healthy cognition in healthy adults, such as autobiographical memory [60-62], semantic memory [65], language ability and cognitive function [59], or in neuropsychiatric symptoms, such as agitation [59,66] apathy [67], depression, and anxiety [68,69]. Moreover, regular musical activities, such as singing, improve the well-being and cognitive functions in healthy older persons [37,70-74] reducing the risk of developing dementia [75]. In a recent study 10 weeks singing practice by both the patients and the caregivers positively affected not only the short-term and working memory of patients but even the quality of life of caregivers [76].

AD causes the impairment of episodic and autobiographical memories, and difficulties in interaction between the self and the world. Music seems to mostly alleviate the negative effect of AD by affecting autobiographical memory. In a pioneering study, Foster and Valentine [77] asked AD patients to complete an autobiographical adaptation of the Mini-Mental State Examination [78] while listening to the famous Vivaldi's Four Seasons, unfamiliar music, cafeteria noise, or in silence. They reported different autobiographical performance among the patients analysed as compared to controls, but, in general, AD patients remembered significantly better in the sound conditions than in silence, and while listening to music than in the cafeteria noise. Afterwards, these outcomes were replicated and confirmed by others [60-62,79]. This result pattern has been attributed to several different factors associated with music listening, such as arousal enhancement [77], anxiety reduction [79], involuntary recall, and verbal narration enhancement [60-62]. Overall, the effects of music on brain functions (musical memory) seem to be carried out via the neural circuits in both limbic and neocortical regions of the brain [80,81]. However, it is still unclear whether these areas are preserved in demented patients.

Although some reports have described impaired music memory in AD [82], and defects in musical episodic memory [83], most of the studies indicate that musical memory remains relatively intact even in the advanced stages of the illness [84,85]. If it is true, it means that these areas have a great potential in designing rehabilitation or therapeutic

strategies and might provide promising prospects for clinical interventions. In this regard, Jacobsen and colleagues have recently provided an important contribution by demonstrating that the anterior cingulate and the ventral pre-supplementary motor areas are both responsible in translating musical memory and show minimal cortical atrophy and minimal disruption of glucose metabolism in young adult AD patients [86].

Music and BDNF

BDNF and NGF are believed to be involved in several CNS pathologies, including AD [15,87] and PD [88,89] schizophrenia and depressive disorders [90,91]. In addition the loss of BDNF levels is likely related to the degenerative processes of Huntington's Disease [92]. These proteins also play an important role in cerebral recovery after ischemic damage [93] and are able to stimulate neurogenesis in the hippocampus [94] and influence the behavioural performance of rats [95]. In various mouse, rat, and primate models, BDNF administration has reversed synaptic damage, partially normalized genetic errors, improved cell signaling, partially rescued learning, memory deficits and cognitive decline, and reduced oxidative stress and cell death [96]. In addition, there is indication demonstrating the potential neuroprotective effect of BDNF against A β -induced neurotoxicity [97]. Compelling evidence supports the idea that reduced BDNF levels in serum and plasma predispose and associate to the severity of depression [98,99], a potent risk factor for dementia and neurodegenerative disease. In addition, a decrease in BDNF levels has been largely associated to stress, which plays an important role in suicidal behaviour and constitutes a major risk factor for depression [100-102]. Stress and depression can also be related to dysregulated neuroinflammation reactions [103]. In relation to this, neuroinflammation is associated to a decrease in BDNF levels in specific brain areas, such as the hippocampus and prefrontal cortex [104]. While a direct link between BDNF levels in depressed humans and music intervention has not been established yet, human and animal evidence exists that music has a beneficial effect in alleviating stress symptoms and depression [105-107], and it is capable of influencing the neuroinflammation response by reducing the number and the activity of natural killer cells and controlling cytokine production [103,108].

A major problem for the therapeutic use of BDNF is that the molecule is too large to penetrate the blood-brain barrier resulting in the failure of its action in brain and its consequent accumulation in blood [109]. When BDNF is taken by routes common for other drugs, such as orally or injections into the body, it cannot reach the brain where it is needed. Although in vitro and animal data are promising, it is unlikely that BDNF therapy will be feasible in the next coming future.

Initial experimental data on animal models indicate that exposure to music can influence brain function, probably through modulation of neurotransmitters and/or other neuronal mediators. In the mouse, music exposure differentially alters the levels of BDNF and NGF in the hypothalamus and hippocampus [110,111]. Some studies have shown the effect of Mozart's music on hippocampal content of BDNF in prenatal/postpartum and adult exposed animals [110-114]. Moreover, it has been reported that perinatal exposure of mice to music has an influence on BDNF/TrkB level and its intracellular signaling [115]. These data have been obtained by studying post mortem the BDNF levels in mice hippocampus and hypothalamus slices. In humans, the measurement of BDNF levels can be done in vivo only via blood serum. While the accurate localization of the changes in BDNF expression in the central nervous system cannot be obtained non-invasively in humans, the systemic changes of BDNF levels could still

be established before and after music intervention in future studies.

The effectiveness of Mozart's sonatas on behaviour has been demonstrated in humans in a study performed on three groups of college students before taking an intelligence quotient (IQ) test. The first group listened to a Mozart sonata. The second group listened to a relaxation tape before their test. The third group did not listen to anything before the test. The first group had the highest score [116,117]. This finding, baptized the "Mozart effect" by the mass media, was erroneously interpreted as the power of classical music to make people smarter simply by listening to it. Subsequent behavioural studies did not replicate the effect of music listening but provided consistent proof of the impact of long-term music training on cognitive abilities, such as working memory, spatial cognition, second language phoneme acquisition, discrimination of prosody, and mathematic skills [118,119].

In the field of dementia, many studies document the efficacy of music in increasing some cognitive functions such as memory, executive functions, speech, and attention [35-38]. As mentioned above effects on verbal intelligence, positively correlated with activity in prefrontal brain regions, have been documented in preschool children even after short-term music training [39]. Larger brain activity in attention and cognitive control-related networks [120], especially in the dorsolateral prefrontal cortex, strongly related to cognitive control abilities, but also in the hippocampus, middle cingulate cortex, motor and auditory areas [40].

Whether or not BDNF production might underlie the cognitive and neural effects of music training in younger and elderly population is an intriguing aspect that should be speculated. Indeed, studies carried out in BDNF Met/Met mutated mice suggest that music exposure induces a relaxing and anxiolytic effect by increasing BDNF levels in hippocampus [121].

Hence, the increase in the BDNF concentration via music exposure and the activation of BDNF downstream signaling, if confirmed in humans, might provide a molecular explanation for the role played by music in dementia. Additionally, understanding the molecular mechanisms behind music effects on brain plasticity and AD might provide a solid ground for increasing the use of music for alleviating the symptoms and improving the life quality of demented patients.

Music and Sex Hormones

An alternative molecular mechanism that might explain the beneficial effects of music on AD can be searched from sex hormones. Aging seems to affect sex hormone levels. In particular, a reduction in sex hormones have been associated to various symptoms in the elderly, including diminished cognitive function, disturbance of memory, mood depression, and climacteric disturbance [122-125]. In AD, the aging-related reductions in sex hormones, especially estrogen, represent a critical risk factor [126,127]. In vitro studies indicate that estrogen decreases β amyloid peptide content and protects neurons from neuronal death [128]. In addition to these effects on amyloid metabolism, estrogen improves cognitive function and delays the onset of dementia by increasing cholinergic activity in the brain, stimulating axonal budding and dendrite formation and retarding cerebral arteriosclerosis [122-125].

Hormone replacement therapies (HRT) are frequently used to normalize sex hormone levels and even though the issue is largely debated, HRT is also indicated to treat some symptoms in AD patients [129-131]. Interesting recent studies indicate that music can be effective in the treatment of AD, by increasing the secretion of 17-estradiol and

testosterone [132]. A link between musicality and musical creative behaviour and vasopressin (acting in synergy with testosterone) receptor gene variations has been recently made [133,134]. Hence, sex hormones might mediate the positive effects of music in AD, although the interaction with the neural processes involved is most likely separated from the processes involved in BDNF mediated effects.

Conclusions

Music is something that most people will take for granted, but it has demonstrated effects on the quality of life *via* emotion regulation in everyday life [135] and on cognitive and motor abilities through daily instrumental practice [136]. As mentioned above, these effects are observable in the behavior and in the brain. Furthermore, evidence from several studies suggests that music therapy effectively reduces some behavioral features of AD patients and, besides some skepticism, overall there is a large assent in considering music therapy at least as an effective supplemental non-pharmacological strategy in AD.

This commentary has not the purpose to provide a reliable ground on which to justify the use of music therapy as a treatment for dementia, but rather to encourage further research on determining the scientific reasons for music effects on AD. In conclusion, we highlight the need for a deeper comprehension of the molecular mechanism linking music benefits to brain functions in demented patients.

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