



Music facilitate the neurogenesis, regeneration and repair of neurons

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Summary Experience has shown that therapy using music for therapeutic purposes has certain effects on neuropsychiatric disorders (both functional and organic disorders). However, the mechanisms of action underlying music therapy remain unknown, and scientific clarification has not advanced.

While that study disproved the Mozart effect, the effects of music on the human body and mind were not disproved. In fact, more scientific studies on music have been conducted in recent years, mainly in the field of neuroscience, and the level of interest among researchers is increasing. The results of past studies have clarified that music influences and affects cranial nerves in humans from fetus to adult. The effects of music at a cellular level have not been clarified, and the mechanisms of action for the effects of music on the brain have not been elucidated.

We propose that listening to music facilitates the neurogenesis, the regeneration and repair of cerebral nerves by adjusting the secretion of steroid hormones, ultimately leading to cerebral plasticity. Music affects levels of such steroids as cortisol (C), testosterone (T) and estrogen (E), and we believe that music also affects the receptor genes related to these substances, and related proteins.

In the prevention of Alzheimer's disease and dementia, hormone replacement therapy has been shown to be effective, but at the same time, side effects have been documented, and the clinical application of hormone replacement therapy is facing a serious challenge. Conversely, music is noninvasive, and its existence is universal and mundane. Thus, if music can be used in medical care, the application of such a safe and inexpensive therapeutic option is limitless.

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Introduction

In the history of mankind, music and medicine have always maintained a close relationship. This remains true with hunter-gatherer cultures that are thought to reflect primitive human forms as clarified by cultural anthropological and ethnomusico-

logical studies. Interestingly, music has been used for the treatment of neuropsychiatric disorders in hunter-gatherer cultures.

However, in westernized societies in the 21st Century, no established therapy exists for neuropsychiatric disorders such as stress disorders, mood disorders (depression) and dementia. Experience has shown that therapy using music for therapeutic purposes has certain effects on neuropsychiatric disorders (both functional and organic disorders),

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and music therapy is currently being administered mainly in the United States and Europe in clinical and welfare settings. However, the mechanisms of action underlying music therapy remain unknown, and scientific clarification has not advanced.

Various studies have examined the effects of listening to music on the brain [1,2]. The study by Rauscher et al. [3] on the Mozart effect is one of the most famous studies and has had both positive and negative impacts on music therapy and music education, since the article was published, it received a lot of attention. However, many subsequent studies have questioned the reliability of the results, and Chabris et al. [4] also published a study disproving the Mozart effect. While that study disproved the Mozart effect, the effects of music on the human body and mind were not disproved. In fact, more scientific studies on music have been conducted in recent years, mainly in the field of neuroscience, and the level of interest among researchers is increasing [5,6]. The results of past studies have clarified that music influences and affects cranial nerves in humans from fetus to adult [7].

The most important discovery by such studies has been that music enhances synaptic plasticity in the brain. In other words, studies comparing musicians and non-musicians and music learners and non-learners have clarified that music brings about cerebral plasticity. Music affects neuronal learning and readjustment (response of brain cells to sound and music stimuli, and changes in cell counts), and this effect lasts for a long period of time [7]. For example, even when neurodegenerative diseases such as Alzheimer's disease causes memory loss, patients can still remember music from the past, and listening to music can facilitate the recovery of other memories. Music listening during the early post-stroke stage can enhance cognitive recovery and prevent negative mood [8].

This type of memory recovery is accompanied by the reconfiguration of existing neuron networks, and it may allow access to long-term memory. However, most past studies have been based on brain imaging modalities such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). The effects of music at a cellular level have not been clarified, and the mechanisms of action for the effects of music on the brain have not been elucidated.

Hypothesis

We propose herein that listening to music facilitates the neurogenesis, the regeneration and repair

of neurons by adjusting the secretion of steroid hormones in both directions (increase and decrease), ultimately leading to cerebral plasticity. Music affects levels of such steroids as cortisol (C), testosterone (T) and estrogen (E), and we believe that music also affects the receptor genes related to these substances, and related proteins.

Evaluation of the hypothesis

Plastic effects of steroids on the brain have been documented in many animal species. For example, vocal communication is a common characteristic among many vertebrates, and steroid hormones are closely involved in the formation of neural mechanism for vocal behaviors in fish, amphibians, birds and mammals (including primates) [9]. In anurans, androgen and E are involved in the expression of vocal behaviors by controlling vocal organ formation, advertisement calling and release calling [10]. The most well-known relationship between steroids and cerebral plasticity is vocal (singing) behaviors in birds. The development of vocal behaviors in singing birds involves complicated processes including neurons and muscles, and steroid hormones (T and E) are involved during many steps, such as neuron organization, neuron survival and neural song-system formation [11,12].

The relationship between steroids and cerebral plasticity has been confirmed in humans. It is well known that the nervous system is a target for steroids (peripheral glands and neurosteroids which are synthesized by nerve cells). Even if those steroids varies its origin, both are neuroactive [13]. They regulate important functions such as reproduction, feeding behavior, brain development, neurogenesis, neuroprotection, cognition and memory [14,15]. Particularly, trophic and neuroprotective functions of steroids have recently attracted a great deal of attention [16–24]. For example, corticosteroid (C) is a substance that modifies stress in many ways, and while C acts on the hippocampus (for long-term potentiation (LTP)), amygdaloid complex and frontal lobe, high levels of C damage neurons. E and T are also involved with the expression, regeneration, repair and protection of nerve cells via gene expression regulation and non-genomic circuits. Within the genomic system, E is involved with the regulation of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and within the non-genomic system, E is involved with nerve signal transmission and amyloid beta suppression [25–30]. T also elevates NGF and p75-nerve growth factor receptors to decrease amyloid beta [31,32].

In humans, primates, rodents and birds, steroids (C, T and E) influence cognitive abilities (spatial perception and cognition; visual (object recognition) and spatial memory (object placement and radial arm maze)). Particularly in birds, steroids (17beta-estradiol (E2)) improve spatial cognition (memory) [33,34]. In rats and mice, many studies have reported that steroid hormones improve spatial perception and cognition (learning and memory) [35,36].

In humans, steroid hormones are involved in spatial perception and cognition. The relationship between T and cognitive abilities is negative in men and positive in women [37–42]. In women, the balance of T and E associated with the menstrual cycle alters cognitive abilities [41,43]. Furthermore, in women, age-related decreases in E are thought to be involved in cognitive dysfunction, memory disorder, learning disorder, depression and mood disorder. Numerous studies have also examined the relationship between E and Alzheimer's disease accompanying marked cognitive dysfunction. The level of E is lower for Alzheimer patients than for healthy individuals, and this decrease in E may hasten the progression of Alzheimer's disease and facilitate amyloid beta accumulation, which is one of the causes of characteristic disorders such as memory disorders. Tissue experiments using test tubes and postmortem brains have shown that E suppresses amyloid beta elevation and deposition to prevent nerve cell damage [44–47]. Moreover, T administration to elderly men reportedly improves cognitive function [48].

The correlation between musical ability and spatial cognition has long been known [49–51]. Many studies have investigated the relationship of musical ability to spatial perception and cognition in humans. The assumption that some correlation exists between musical ability and steroid hormones also appears reasonable. In fact, Hassler discovered that the relationship between T and musical ability (music composition) resembled that between T and other forms of spatial perception and cognition [50,52].

Furthermore, the relationship between music and steroid hormones is not limited to musical ability. In the field of behavioral endocrinology and neuroendocrinology, many studies have documented that musical stimulation (listening) affects various biochemical substances [53–55]. In particular, many studies based findings on C. Experience has shown that listening to music is effective in alleviating and relieving stress. In many studies, stress reduction due to music listening has been attributed to reductions in C [56,57]. Listening to music also reportedly alters levels of T (increase

and decrease) [58,59]. The research reported that musical activities (listening and playing) adjust steroid secretion in elderly individuals and are likely to alleviate psychological states such as anxiety and tension. Furthermore, levels of steroids changed in both directions, increasing in subjects with low hormone levels and decreasing in subjects with high hormone levels [60].

Conclusion

Music listening and playing altered steroid levels agrees with the results of various previous studies that have documented strong correlations between steroids and spatial perception and cognition and the effects of music listening on steroid secretion. Summarizing these results, the hypothesis that listening to music adjusts the steroid hormone cascade and facilitating the neurogenesis, regeneration and repair of neuron appears highly plausible. At this point, the effects of music on steroids are unclear, but music appears to be involved with steroid production via the pathway from the auditory system to the auditory area, particularly the neural pathway (emotion circuits) mediated by the cerebral limbic system (hypothalamic-pituitary-adrenal axis and amygdaloid complex).

In recent years, the possible involvement of nerve damage in neuropsychiatric disorders has been suggested, and musical activities may enable the protection, repair and even regeneration of human cerebral nerves. In the prevention of Alzheimer's disease and dementia, hormone replacement therapy has been shown to be effective [46,61], but at the same time, side effects have been documented, and the clinical application of hormone replacement therapy is facing a serious challenge [62]. Conversely, music is noninvasive, and its existence is universal and mundane. Thus, if music can be used in medical care, the application of such a safe and inexpensive therapeutic option is limitless.

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