

Music and Steroids – Music Facilitates Steroid-Induced Synaptic Plasticity

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1. Introduction

Music and medicine have always been closely related. This remains true even in hunter-gatherer cultures that are thought to reflect primitive human forms, as clarified by cultural anthropological and ethno-musicological studies (Lee & Daly, 2005; Merriam & Merriam, 1964). Interestingly, music has also been used for the treatment of neuropsychiatric disorders in hunter-gatherer cultures (Lee & Daly, 2005; Merriam & Merriam, 1964). However, in westernized societies, no established music therapy exists for neuropsychiatric disorders such as stress disorders, mood disorders (depression), and dementia. Experience has shown that music has certain therapeutic effects on neuropsychiatric disorders (both functional and organic disorders), and music therapy is currently being used in the United States and Europe in clinical and welfare settings. However, the mechanisms of action underlying music therapy remain unknown.

Various studies have examined the effects of listening to music on the brain (Bermudez & Zatorre, 2005; Nan et al., 2008). The study by Rauscher et al. on the “Mozart effect” is one of the most famous studies and has had both positive and negative impacts on music therapy (Rauscher et al., 1993). However, many subsequent studies have questioned the reliability of those results, and Chabris et al. published a study disproving the Mozart effect (Chabris, 1999). However, the fact that music affects the human body and mind was 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 (Zatorre, 2003; Zatorre & McGill, 2005). Results of past studies have clarified that music influences and affects cerebral nerves in humans from fetuses to adults (Abbott, 2002).

The most significant finding has been that music enhances synaptic changes 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 (Abbott, 2002). For example, even when neurodegenerative diseases such as Alzheimer’s disease cause memory loss, patients can still remember music from the past, and listening to music can facilitate the recovery of other memories. This type of memory recovery is accompanied by the reconfiguration of existing neuron networks, which may allow access to long-term memory. However, most 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.

The effects of steroids on changes in the brain have been documented in many animal species. For instance, vocal communication is a common characteristic among many vertebrates, and steroid hormones are implicated in the formation of neural mechanisms of vocal behavior in fish, amphibians, birds, and mammals (including primates) (Bass, 2008). The most fully known relationship between steroids and cerebral plasticity is vocal (singing) behavior in birds. The development of vocal behavior in singing birds involves complicated processes including neurons and muscles, and steroid hormones (testosterone and 17 β -estradiol) are involved during many steps, such as neuron organization, neuron survival, and neural song-system formation (Fusani & Gahr, 2006; Nottebohm, 1981).

In humans, steroid hormones are associated with spatial perception and cognition. The relationship between testosterone and cognitive abilities is negative in men and positive in women (Gouchie & Kimura, 1991; Grimshaw et al., 1995a; Grimshaw et al., 1995b; Kimura & Hampson, 1994; O'Connor et al., 2001; Silverman et al., 1999). In women, the equilibrium of testosterone and 17 β -estradiol associated with the menstrual cycle alters cognitive abilities (Silverman et al., 1999; Silverman & Phillips, 1993). Furthermore, in women, age-related decreases in 17 β -estradiol are thought to be involved in cognitive dysfunction, memory disorder, learning disorder, depression, and other mood disorders. Numerous studies have also examined the relationship between 17 β -estradiol and Alzheimer's disease accompanied by marked cognitive dysfunction (Gillies & McArthur, 2011; Wharton et al., 2001). The level of 17 β -estradiol is lower for Alzheimer patients than for healthy individuals, and this decrease in estrogen level may lead to the progression of Alzheimer's disease and facilitate amyloid beta accumulation, one of the causes of memory disorders. Furthermore, testosterone administration to elderly men reportedly improves cognitive function (Gruenewald & Matsumoto, 2003).

The correlation between musical ability and spatial cognition is well recognized (Cupchik, 2001; Hassler, 1992; Hassler & Birbaumer, 1984). Many studies have investigated the relation between musical ability and 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 testosterone and musical ability (music composition) corresponded to that between testosterone and other forms of spatial perception and cognition (Hassler, 1991, 1992).

Furthermore, the relationship between music and steroid hormones is not confined to musical ability. Many studies in the field of behavioral endocrinology and neuroendocrinology have documented that musical stimulation (listening) affects various biochemical substances (Hassler et al., 1992; Kreutz et al., 2004; VanderArk & Ely, 1993).

2. Music and human physiology

The fact that music has an effect on the human body, particularly on stress and easing pain or anxiety, has been generally known since the Greeks (Aristoteles). Music influences the endocrine system to keep the body normal, as shown by many studies (e.g., Gardner et al., 1960; Logan & Roberts, 1984; Maslar, 1986; Standley, 1986; Hodges, 1996). Musical behavior is believed to invigorate several parts of the nervous system, as auditory information passes through the limbic and paralimbic systems including the thalamus, the hypothalamus, and amygdala, to the neocortex, and influences the pituitary gland; as a result, various

physiological effects are induced. Much research has been done regarding the physiologic effects of music, with results showing increases or decreases in respiration, heart rate, blood pressure, skin temperature, GSR (galvanic skin response), and electroencephalogram findings (Hodges, 1996). However, because of problems with experimental methods, results are inconsistent. Unfortunately, there is still no unified concept regarding the physiological effects of music, although the fact that music causes physiological effects in the human body is well accepted. Enormous advances have been made in recent years toward an understanding of the brain structures involved in music. Using the brain imaging techniques of PET, fMRI, and magnetoencephalography, the brain structures and activity related to music were clarified (Koelsch, 2010; Zatorre, 2003). Interestingly, these structures (limbic and paralimbic structures) are involved in the initiation, generation, detection, maintenance, regulation, and termination of emotions that have survival value for the individual and the species (Koelsch, 2010). Needless to say, emotions are deeply affected by steroids (Garcia-Segura, 2009).

3. Effects of steroids on auditory and musical behavior

Recently, endocrinologic research on human behavior has progressed. Evidence to date suggests that hormones not only have organizational effects but also affect cognition, perception, and other behaviors. Because the endocrine and nervous systems do not function in isolation but as an integrated whole, many aspects of neuronal functioning are affected by hormones (gonadal steroids). However, we still lack data regarding the effect of music on hormones. In addition, although knowledge regarding endocrinologic function and music has begun to accumulate, results are contradictory. Some studies indicate that music influences humans endocrinologically and other studies indicate that hormones influence musical behavior. Below we will review the substances that have been examined thus far and explore the physiological function of music.

Many reports support the correlation between hormones and hearing or vocal behaviors. The fact that testosterone influences growth of the larynx is well known. It is believed that testosterone also influences the auditory sense and the vocal organ (Kelley & Brenowitz, 1992; Marler et al., 1988; Silver, 1992). Reports also indicate that the utterance of song birds is influenced by testosterone (Nottebohm, 1972; Marler et al., 1988) and point to the existence of similarities between the vocal tract of song birds and humans (Bridgeman, 1988). The fact that the auditory sense of the human females undergoes cyclical changes affected hormones has been reported (Wynn, 1971). Moreover the female voice is also influenced by 17 β -estradiol (Abitbol et al., 1989). The hypothesis that the perception of sound is influenced by hormones is based on the idea that hormones influence dorsal division and reticular formation in the auditory pathways.

Testosterone influences the development of the neural pathways of the brain and stimulates cerebral lateralization (Geschwind & Galaburda, 1985). As Lovejoy said, this provides males with right brain superiority, which results in making him proficient in spatial ability, such as securing food and adapting to the environment (Lovejoy, 1981). Other reports also show that spatial ability is influenced by sex hormones; for example, men with lower testosterone levels performed better than men with higher testosterone levels whereas women with higher testosterone levels performed better than women with lower testosterone levels on spacial ability tests (Gouchie & Kimura, 1991; Hampson & Kimura, 1992; Nyborg, 1983). Further a relation between spatial ability and musical ability has been reported (Hassler et

al., 1985), and listening to music has been shown to improve spatial ability (IQ) (Rauscher et al., 1993).

4. Musical behavior and steroids

4.1 Cortisol

Psychological and physiological stress affects testosterone and cortisol levels in both sexes. Generally, cortisol levels increase significantly in the presence of stress. It has been reported that music eases stress responses psychologically, physiologically, and endocrinologically. It is well known that listening to music reduces uneasiness (Gerdner & Swanson, 1993; Kaminski & Hall, 1996), depression, and fatigue (Field et al., 1997; Hanser & Thompson, 1994), changes mood (Cadigan et al., 2001; Gfeller & Lansing, 1991; McCraty et al., 1998; Sousou, 1997), and suppresses pain (Allen et al., 2001; Browning, 2000; Maslar, 1986). However, some reports that compare listening to music with other relaxation methods show no differences in alleviation of anxiety, depression, and fatigue (Field et al., 1997; Hanser & Thompson, 1994) or reduction of heart rate (Guzzetta, 1989; Scheufele, 2000). In addition, some authors have reported that there is differences in psychological and physiological responses among different genres of music (classical, hard rock, "favorite music," "relaxation music") (Allen & Blascovich, 1994) and others have reported no such differences (Burns, 1999).

Most of these studies have been on the stress-reducing effects of listening to music, and listening to music has been reported to cause a reduction in the cortisol levels. Cortisol is involved in many vital functions such as glucose metabolism and immune function, but in cases of chronic stress, it has been known to induce symptoms such as hypertension and impaired cognitive function (Lundberg, 2005). In addition, increasing cortisol levels with age may lead to a decline in memory or progression of Alzheimer's disease (Huang et al., 2009). Thus, the reduction of cortisol through the passive activity of listening to music may be useful for the treatment and prevention of diseases and disabilities.

Listening to music for short periods could lower cortisol regardless of the subject's mental state (Field et al., 1998; Möckel et al., 1994), and music has been shown to significantly lower (Escher et al., 1993; Miluk Kolasa et al., 1994; Rider et al., 1985) or suppress cortisol levels (Schneider et al., 2001) even during surgery. Other papers reported that not only listening to music but also playing music (percussion instruments) lowered cortisol levels (Bittman et al., 2001; Burns et al., 2001). In addition, studies have shown that cortisol responses differed by music experience, such as (Vander Ark & Ely, 1992, 1993) and the subject's preference (Gerra et al., 1998). However, so far results are contradictory and there is no consensus regarding the relation between cortisol and music category or preference. However, judging from published research results, listening to one's favorite music decreases cortisol levels (Fukui, 1996).

4.2 Testosterone

Contrary to cortisol, several investigations have been conducted on the relationship between music and testosterone.

Testosterone has been shown to influence musical ability (Hassler, 1991), and its effects produce discrepancies between the sexes (Schumacher & Balthazart, 1986). Hassler hypothesized the existence of an optimal testosterone level in proportion to musical ability. Reports also discuss the existence of a correlation between hormone levels (testosterone)

and musical ability in puberty (Durdin-Smith & Simone, 1983; Hassler, 1987; Hassler and Birbaumer 1987). Another report indicates that during puberty, children show poor results in music tests because of low testosterone levels at this stage (Serafine, 1988). Moreover, there is a report that composition has a seasonality that might be influenced by the circannual rhythm of testosterone (Fukui, 1995). In addition, most composers are male, and composers tends to show a low level of testosterone compared with control (Hassler et al., 1990). Further reports show that musicians have a tendency to demonstrate relatively low levels of sex-role stereotyping (Kemper, 1990), which again, may be related to testosterone levels. The point is that testosterone influences musical ability.

Regarding musical ability and testosterone, there is a high positive correlation between spatial cognitive ability and musical ability (talent) (Rauscher et al., 1993). A high correlation is also found between spatial cognitive ability and testosterone (Nyborg, 1983). Furthermore, these correlations differ between males and females. Hassler reported that male composers had relatively low testosterone levels, and that testosterone values increased as musical ability increased in female composers (Hassler, 1991).

On the other hand, only one report is available on sex-related differences in testosterone responses associated with music playing or listening. Fukui examined testosterone level changes between before and after listening to a wide variety of music, including favorite music, pop, jazz, and classical, in male and female students, and showed sex-related differences (Fukui, 2001). Specifically, testosterone values decreased in males and increased in females after listening to music, regardless of genre. Interestingly, the sex-related difference in testosterone levels while listening to music were the same as sex-related differences in stress responses. Grape et al. compared between patients with irritable bowel syndrome who took part in singing in a choir with those who took part in a group discussion and found that testosterone levels decreased in the singing group (Grape et al., 2010).

So far, there is no research investigating music and estrogen.

5. Hypothesis and the study

We propose that listening to music facilitates the regeneration and repair of cerebral nerves by adjusting the secretion of steroid hormones in both directions (increase and decrease), ultimately leading to cerebral plasticity. Music affects levels of cortisol, testosterone, and 17β -estradiol, and we believe that music also affects the receptor genes related to these substances and related proteins.

5.1 Methods

Subjects were recruited from healthy elderly women aged 60 or older who were participating in a 90 min. singing group (choir) as part of disease prevention and health-promoting activities hosted by the local government. The session was taught by a music therapist. Inclusion criteria were as follows: attended all four sessions (once a month); healthy; and not taking any medications such as steroids that could affect endocrinologic factors. A total of 50 volunteers (8 males and 42 females) were enrolled, however because of missing value, male's data was not possible to use. Finally, 42 female volunteers were enrolled. Mean age was 72.9 years (range: 64-83 years).

After obtaining informed consent, subjects participated in four choral sessions, once a month for 4 consecutive months. The sessions took place at a facility owned by the local

government. The flow of the experiment was as follows: first, health status and medication were checked. Then a saliva sample was collected before and after each session (about 90 min). Saliva samples were stored at -20°C in the freezer immediately after collection, and cortisol, testosterone, and 17β -estradiol levels were measured by enzyme immunoassay. Intra- and inter-assay coefficients of variation ranged between 3.35–3.65% and 3.75–6.41% for cortisol, 2.5–6.7% and 7.9–8.6% for testosterone, and 6.3–8.1% and 6.0–8.9% for 17β -estradiol.

The musical preference of subjects was ascertained before the study, and several pieces of music were selected for the session. The contents of all four sessions were the same.

To assess depression and anxiety as psychological states, the Japanese version of the Profile of Mood States (POMS) as executed before and after the session (Yokoyama & Araki, 1994). The POMS is a highly reliable test that is often used in studies on mood states and the test we used were revised for use by the elderly in terms of terminology and style. In the present study, of the six subscales of POMS ("tension/anxiety" (TA), "depression/dejection" (DD), "anger/hostility," "vitality," "fatigue," and "confusion," the DD and TA subscales were used.

Cognitive tests were carried out at the same time as the POMS. Tests performed were as follows: 1) Digit Symbol-Coding (WAIS: Wechsler Adult Intelligence Scale III) memory task (Silverman and Eals' Object Location Memory Task), and 3) mental rotations test (Vandenberg and Kuse Mental Rotations test "3-dimensional").

5.2 Results

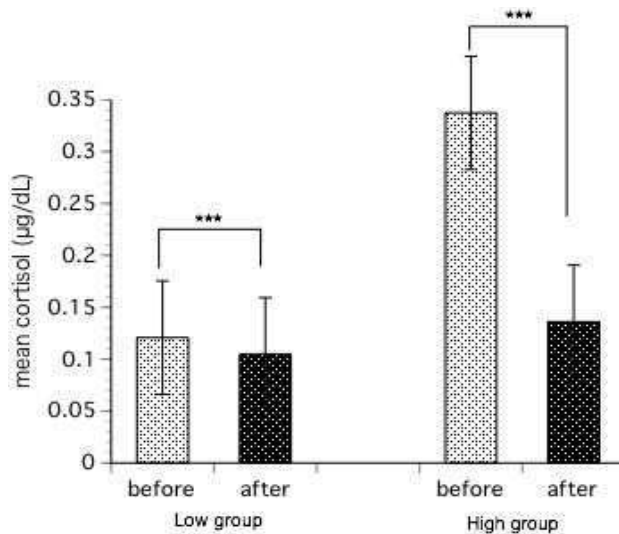
Cortisol, testosterone, and 17β -estradiol levels for subjects were biphasic, and subjects were divided into two groups (high and low) with respect to pre-session median values. Mean hormone levels prior to the choral session were $0.2243\ \mu\text{g}/\text{dL}$ for cortisol, $66.0579\ \text{pg}/\text{mL}$ for testosterone, and $6.1332\ \text{pg}/\text{mL}$ for 17β -estradiol.

Analysis of variance (ANOVA) was conducted on changes in cortisol, testosterone, and 17β -estradiol levels before and after each session, between the high and low groups, and between each session.

In terms of cortisol levels, the main effect of cortisol changes before and after the choral session was significant ($F(1,122)=28.16$, $p=0.0000$). In addition, the main effect between the high and low groups ($F(1,122)=35.05$, $p=0.0000$) was significant. Cortisol significantly decreased after each session in both the high and low groups (Fig. 1).

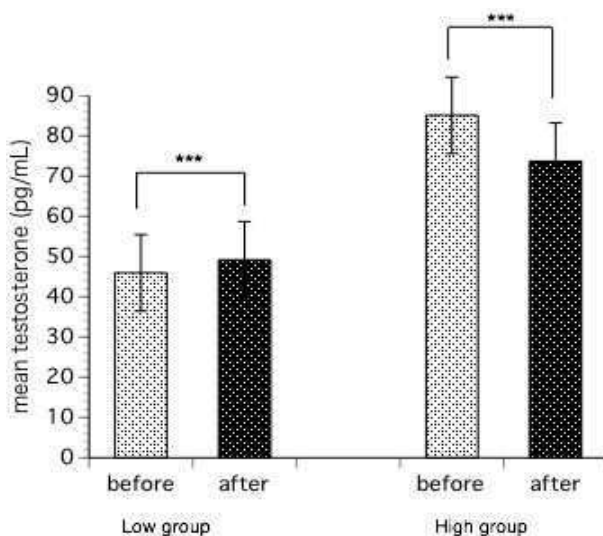
The main effect of testosterone changes before and after the choral session ($F(1,284)=4.26$, $p=0.0399$), the main effect between the high and low groups ($F(1,284)=289.99$, $p=0.0000$), and the interaction between testosterone changes and the high and low groups ($F(1,244)=15.04$, $p=0.0001$) were significant. In the high group, testosterone levels significantly decreased after the choral session; in contrast, in the low group, testosterone levels increased significantly after the session (Fig. 2).

The main effect of 17β -estradiol changes ($F(1,244)=23.23$, $p=0.0000$), the main effect between the high and low group ($F(1,244)=193.72$, $p=0.0000$), and the interaction between 17β -estradiol changes and the high and low groups ($F(1,244)=58.27$, $p=0.0000$) were significant. In the high group, 17β -estradiol levels significantly decreased after the choral session. Conversely, in the low group, 17β -estradiol levels significantly increased after the session (Fig. 3).



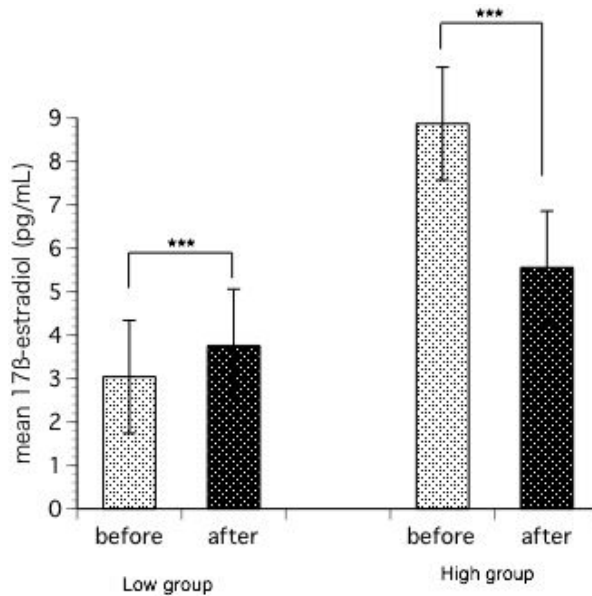
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Fig. 1. Cortisol levels of 42 female subjects



The main effect of testosterone changes before and after the choral session ($F(1,284)=4.26, p=0.0399$), the main effect between the high and low groups ($F(1,284)=289.99, p=0.0000$), and the interaction between testosterone changes and the high and low groups ($F(1,244)=15.04, p=0.0001$) were significant. In the high group, testosterone levels decreased after the choral session; in contrast, in the low group, testosterone levels increased after the session.

Fig. 2. Testosterone levels of 42 female subjects

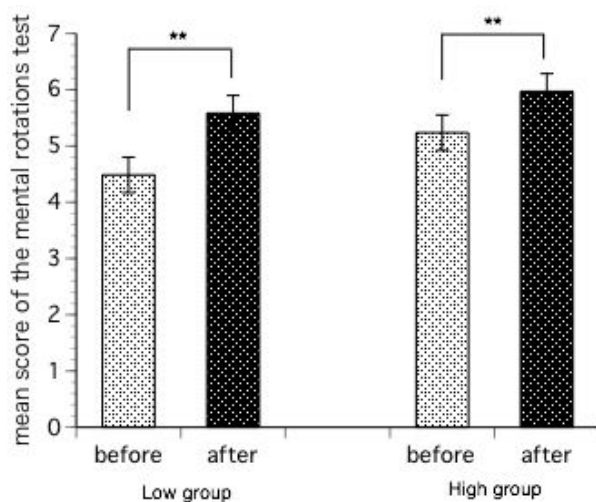


The main effect of 17 β -estradiol changes ($F(1,244)=23.23, p=0.0000$), the main effect between the high and low group ($F(1,244)=193.72, p=0.0000$), and the interaction between 17 β -estradiol changes and the high and low groups ($F(1,244)=58.27, p=0.0000$) were significant. In the high group, 17 β -estradiol levels decreased after the choral session. Conversely, in the low group, 17 β -estradiol levels increased after the session.

Fig. 3. 17 β -estradiol levels of 42 female subjects

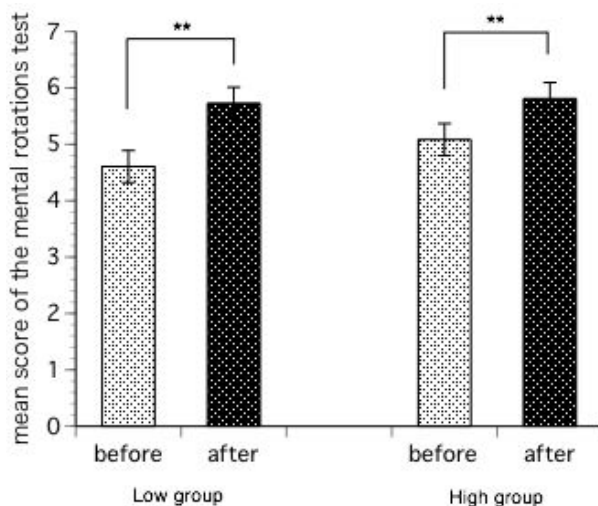
ANOVA was conducted on changes in cortisol, testosterone, and 17 β -estradiol levels before and after each session, between the high and low groups, and between each session. No significant difference was found in any factor of the TA scores. The main effect of the DD scores was significant for cortisol ($F(1,122)=4.02, p=0.0473$), testosterone ($F(1,117)=3.70, p=0.05$), and 17 β -estradiol ($F(1,119)=4.25, p=0.0414$). The scores of high and low groups significantly decreased after the session.

ANOVA was conducted on changes in cortisol, testosterone, and 17 β -estradiol levels before and after each session, between the high and low groups, and between each session. No significant difference was found in any factor of the Digit Symbol-Coding. For the memory task, only the main effect of high and low groups for 17 β -estradiol was significant ($F(1,120)=10.85, p=0.0013$). The main effect of the mental rotations test was significant for cortisol ($F(1,123)=9.16, p=0.0030$), testosterone ($F(1,116)=8.48, p=0.0043$), and 17 β -estradiol ($F(1,120)=9.03, p=0.0032$). The scores of high and low groups significantly increased after the session (Fig. 4, 5, 6).



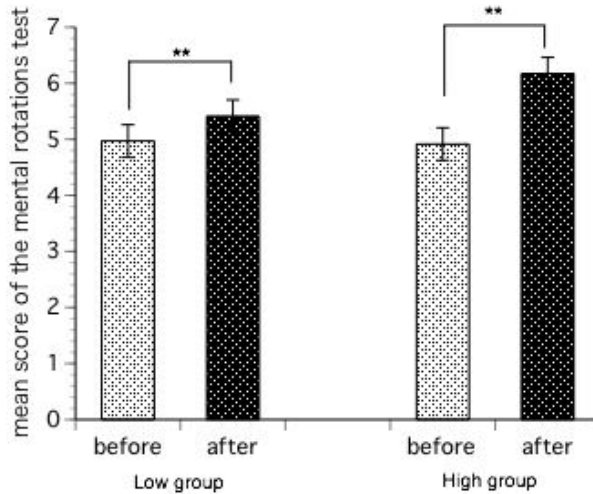
The main effect of the mental rotations test was significant for cortisol ($F(1,123)=9.16, p=0.0030$). The scores of high and low groups increased after the session.

Fig. 4. Mean score of the mental rotations test in cortisol levels



The main effect of the mental rotations test was significant for testosterone ($F(1,116)=8.48, p=0.0043$). The scores of high and low groups increased after the session.

Fig. 5. Mean score of the mental rotations test in testosterone levels



The main effect of the mental rotations test was significant for 17β -estradiol ($F(1,120)=9.03$, $p=0.0032$). The scores of high and low groups increased after the session.

Fig. 6. Mean score of the mental rotations test in 17β -estradiol levels

6. Discussion

Cortisol, testosterone, and 17β -estradiol were affected by musical behavior (chorus). Cortisol levels decreased after each choral session, whereas changes in testosterone and 17β -estradiol levels were dependent on the subject's baseline hormone level. After all sessions, testosterone and 17β -estradiol levels increased in the low groups and decreased in the high groups.

Anxiety and depression score (POMS) decreased after all sessions. The interesting finding was a result of the cognitive test (mental rotations test). The score increased regardless of the initial hormone level. Mental rotation involves spatial ability and is localized to the right hemisphere and is associated with intelligence (Hertzog & Rypma, 1991); Johnson, 1990; Jones & Anuza, 1982). It has been documented that music training improves verbal, mathematical, and visuo-spatial performance in children and adults (Brochard, 2004; Ho et al., 2003). However, no study has investigated music and mental rotation beside the "Mozart effects," especially in elderly people (Cacciafesta, et al., 2010). Our study is the first report to show that music improved mental rotation ability in elderly women.

Results of this study clarified that musical activities affect steroid secretion in elderly women 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. Thus, the hypothesis that listening to music affects the steroid hormone cascade and facilitates neurogenesis, regeneration, and repair of neuron appears highly plausible.

This study has several limitations, including the fact that only data obtained from a small number of elderly women were analyzed. However, the finding that musical behavior (chorus in this study) altered steroid levels agrees with results of previous studies that have documented strong correlations between steroids and spatial perception and cognition and the effects of listening to music on steroid secretion.

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.

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.

7. Acknowledgment

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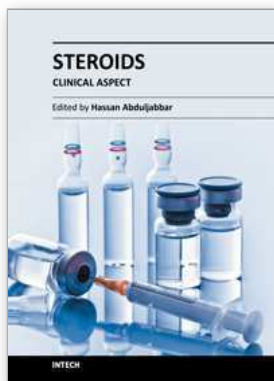
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