It is commonly believed among diverse nations and at different times that music impacts both the development of personality and our relationships with other human beings. The idea that music exerts power over human behavior can be traced back many centuries in China to two of the most substantial documents in Chinese musical philosophy: the *Yue Ji* (Record of Music, from Li Ji) and *Yue Shu* (Book of Music, from Shi Ji). Despite the fact that music can be used to adjust behavior, and hence, help to cultivate moral qualities, it was explicitly described in *Yue Shu* that music assists with the circulation of blood, which, in turn, activates various meridians (Wang, 2004). Throughout history, scientific and public interest in the mechanisms underlying how music is perceived and processed has promoted substantial advances in the field of music therapy. This particular health profession (i.e., using music to enhance human capabilities) facilitates an established method (Online Ref. 14). Thus, the question of how music heals arises.

**Music: therapeutic benefits for treating depression**

In 2011, research conducted in Finland and Norway showed that music therapy was efficient for treating depression among working-age people (Erkkilä et al., 2011). In that study, patients receiving music therapy showed significant improvement in their symptoms compared to those who received only standard treatment.

One of the most remarkable aspects of music is that it can trigger emotional response-related mechanisms by influencing the mesolimbic dopamine reward circuit in the brain (Online Ref. 15). In particular, a route beginning at the ventral tegmental area of the midbrain connecting to the limbic system via the nucleus accumbens, the amygdala (emotional response), and the hippocampus (memory processing) is involved in the emotional response to music. Listening to music, which is rated among the most rewarding stimuli available for humans, elicits pleasurable responses that are presumably similar to drug-taking, since both activities induce the release of dopamine in the brain (Salimpoor et al., 2009).

The very first evidence linking music listening with striatal (both the dorsal and ventral striatum) dopaminergic activation within the mesolimbic system was obtained (Salimpoor et al., 2011) by building on previous studies showing that music elicited pleasure, induced cerebral blood flow in reward-associated brain regions, and reduced activity in brain structures (amygdala) associated with negative emotions (Blood et al., 2001). Facilitated by multiple brain imaging techniques, this groundbreaking research conducted by Dr. Robert J. Zatorre and his research team successfully linked the pleasurable emotional responses elicited during music listening to activation of the stratum-based dopamine-rich area in the mesolimbic reward system. As pleasure experienced by individuals differs in qualitative ways, reasonable doubts might arise concerning the methods used to precisely quantify subjective emotional feelings. According to research published in *Nature Neuroscience*, a group of participants who constantly experienced intense pleasure (hereinafter referred to as chills) in response to self-provided music were recruited. As chills can be objectively verified by indexing stereotypical changes in physiological arousal, including changes in heart rate, electrodermal skin conductance, and respiration rate, the rating system is a reliable indicator. Participants underwent ligand-based positron emission tomography (PET) scanning accompanied by psychophysiological measurements of the autonomic nervous system while being exposed to self-selected pleasurable music or neutral music. The release of endogenous dopamine in the striatum at peak emotional arousal was identified from the PET results, indicating pleasure experienced during music listening.

It is premature to assume that the same pleasure-evoking mechanism can be applied to every patient with depression, as some patients may also suffer from other unknown defects in the reward

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circuit. However, the use of music therapy with different music stimuli and strategies to treat depression might have just found its greatest scientific support so far.

**Music: proposed mechanism involved in improving Parkinson’s movement disorder**

According to *US News & World Report*, American neurologists prescribed music therapy to patients with neurological diseases ranging from Parkinson’s to Alzheimer’s to aphasia (Online Ref. 16), which affirms the valuable role of music in treating real-life diagnostic problems.

A highly cited research study published in *Psychomomastic Medicine* (Pacchetti et al., 2000) purported a significant positive effect of music therapy on bradykinesia (extreme slowness of movement and reflex), which is a gait and balance disorder observed in patients with Parkinson’s disease, by utilizing choral singing, voice exercises, and free body movement. Although the neurophysiological process is not fully understood, this degenerative disorder of the central nervous system occurs when dopaminergic neurons located in a part of the midbrain called the substantia nigra (SN) die or become impaired.

The link between structural changes in the SN and Parkinson’s disease was demonstrated by Bártová et al. (2010); Among the 115 Parkinson’s patients assessed by transcranial sonography, an enlarged SN was found in 84% of the patients with bilateral rigidity and 85% of the patients suffered from bilateral bradykinesia. As music therapy improved bradykinesia and the enlarged SN found in patients with bradykinesia; therefore, it is reasonable to assume that music therapy can influence nigrostriatal cell regeneration and the restoration of related dopaminergic pathways.

Moreover, researchers have identified accumulations of iron in the SN of patients with Parkinson’s disease, a phenomenon that appears to occur in the iron-chelating neuromelanin found in dopamine-releasing neurons (Zecca et al., 1994). This catecholamine-originating amorphous pigment differs from other known melanins and has been proposed to be involved in the protective mechanisms triggered by an unknown reaction during the early developmental stages of Parkinson’s disease (Zecca et al., 2006). Related research further suggested that neuromelanin attenuates the progression of Parkinson’s disease by irreversibly scavenging neurodegradation-promoting endogenous metals, quinones-derived adducts, and reactive metabolites (Zecca et al., 2003).

Although neuromelanin biosynthesis is an area of ongoing research, Sulzer et al. (2000) purported that SN-based neuromelanin is derived from dopamine-precursors via L-DOPA mediated biosynthetic pathways catalyzed by both Fe^{3+} and aromatic acid decarboxylase (AADC), providing insight into a possible route for neuromelanin synthesis through the dopaminergic pathway.

In this report, I proposed a detailed model of a novel enzymatic biosynthetic pathway incorporating the existing model to address the influence of an unknown cytosolic protein in the neuromelanin synthetic pathway. In my proposed model, an unknown enzyme is suggested to serve as a dopaminergic synthesis-promoting factor in the existing metabolic pathway.

Under normal conditions, the protein associates with AADC to maintain a normal dopamine level and neuromelanin formation in cells. The accumulation of neuromelanin ensures the continued reduction of toxic materials and known quinone-derived adducts within the system. Upon the depletion or loss of protein function due to unknown reasons, the formation of neuromelanin is interrupted, resulting in the excess accumulation of toxic material in cells that may eventually lead to neurodegeneration (Zhang et al., 2011) (Fig. 2) and SN enlargement. This proposed model is consistent with previous findings showing a low dopamine level and enlarged SN in patients with Parkinson’s disease.

Furthermore, the potential role of music stimuli in assisting restoration of the unknown protein function is demonstrated in Fig. 3. Because exposure to music is reported to promote regulatory cell proliferation in mice with heart transplants (Uchiyama et al., 2012), the reactivation of DNA and protein synthesis in other injured cells (e.g., neurons) may be possible. Studies demonstrating the positive effect of music on motor rehabilitation in patients with Parkinson’s disease (Pacchetti et al., 2000) might also be helpful in supporting my hypothesis that music stimulation helps to recover the dopamine-derived neuromelanin biosynthetic pathway.
Figure 1. Proposed model demonstrating the role of an unknown enzyme facilitating neuromelanin formation and prevents dopaminergic neurodegeneration in patients with Parkinson’s disease. Blue dots represent toxic materials and known quinone-derived adducts.

Figure 2. Degeneration of the unknown protein results in decreased dopamine synthesis, which reduces neuromelanin formation. The insufficient amount of neuromelanin causes the cellular accumulation of toxic materials (e.g., reactive metabolites). These toxic materials, which presumably trigger neurodegradation, might also stimulate abnormal cell growth, resulting in enlargement of the substantia nigra (SN). Red arrows indicate abnormal cell proliferation possibly caused by toxic materials.

Figure 3. Model describes the recovery of the neuromelanin synthesis via functional restoration of the proposed unknown enzymatic protein due to music stimulation. The outcome is slow, as the rehabilitation of damaged brain cells is a time-consuming process.

Although the key element determining the interplay between music stimulation and neuron death in Parkinson’s disease remains in obscurity, with a growing amount of evidence explicating clinical application of music therapy in treating numerous neurological and psychiatric disorders, it is to my belief that a better understanding of the mechanism underlying these neurologic diseases will be unveiled in the very near future.
References:


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