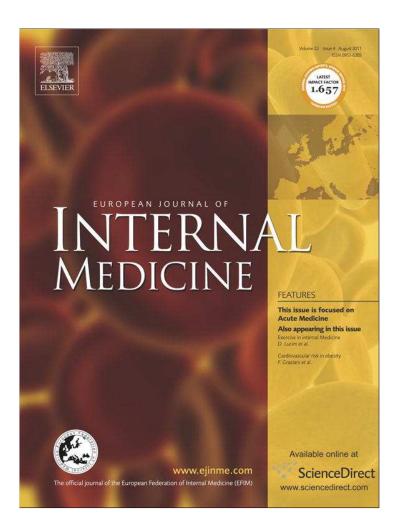
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Reflections in Internal Medicine

From music-beat to heart-beat: A journey in the complex interactions between music, brain and heart

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ABSTRACT

Although the potential influence of music in eliciting organic reactions has been appreciated since the ancient Assyrian and Greek cultures, its relationship with body responses has been believed for long to belong to the field of magic. Growing experimental evidence now attests that some kind of music might indeed modulate several cardiac and neurological functions, as well as trigger biochemical measurable stress-reducing effects in certain individuals, mostly depending on their subjective musical education. On this basis, music has been increasingly used as a therapeutic tool in the treatment of different diseases in healthy and ill subjects over recent years (e.g., the so called "Mozart effect"), although the underlying scientific background is still poorly understood. The aim of this article is to review the current scientific evidences about the complex and multifaceted interactions between music and human biology.

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1. Introduction

Humans discovered the effects of the music on their own wellness at the dawn of the pre-historical age, i.e., during the Cro-Magnon and the Neanderthalian cave cultures. Charles Darwin hypothesized that music may have been a protolanguage in ancient times. Under a cultural perspective, the definition of music is subtle and not well established, since it has varied through history, in different regions, and within societies. The fifteenth edition of the Encyclopædia Britannica describes that "while there are no sounds that can be described as inherently unmusical, musicians in each culture have tended to restrict the range of sounds they will admit". In his 1983 book, Music as Heard: A Study in Applied Phenomenology, Thomas Clifton affirms that "music is the actualization of the possibility of any sound whatever to present to some human being a meaning which he experiences with his body—that is to say, with his mind, his feelings, his senses, his will, and his metabolism" [1]. On the other hand, the French musicologist Jean-Jaques Nattiez has affirmed that "the border between music and noise is always culturally defined — which implies that, even within a single society, this border does not always pass through the same place; in short, there is rarely a consensus.... By all accounts there is no single and intercultural universal concept defining what music might be" [2] (Table 1).

Some authors believe that the first ancient musical rituals, such as wooden-drums beating, vocalizing (either as animal voice imitation,

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or as an extension of spoken language) and body swaying and shaking, may represent the oldest form of religion and perhaps of medicine, searching and often obtaining a sense of depersonalization and well-being [3,4]. The power of the music in eliciting physical reactions has been known probably since the ancient Assyrian and Greek cultures, although the relationship between music and body responses was at that times believed to belong to the field of magic. During the Olympic Games in ancient Greece, musicians were paid for playing flute and kithara (a harp-like string instrument) with the aim of improving athlete's performance [3]. In that era, Pythagoreans were the first to disclaim the mathematical relationships of musical notes, and Plato, in "The Republic", wrote that "Music is most sovereign because rhythm and harmony find their way to the inmost soul and take strongest hold upon it, imparting grace, in one is rightly trained". Music was mostly based on three distinct "modes" (dorian, lydian, and phrygian) in ancient Greece, each further subdivided in two or three sub-modes, representative of different musical scales. This organization was strongly related to the feeling, each "mode" being characterized by specific properties (e.g., to arouse pity, or fear, or enthusiasm – this last word having itself a mystic connotation: εv τηεοσ (én Theos), meaning, according to the majority of authors, "having a God inside", or "being in a God-like state") and sometimes allowing to "heal and purify the soul" (Aristotle) [3]. In ancient Rome, Plinius reported that Cato recalled a melody specific for the treatment of muscular distractions, and Varro another one for the treatment of gout [3]. In the Middle Ages there was an "epidemic of dances": choreic patients were used to dance continuously for several hours, in the belief that this might heal them. The southern-Italy dance "tarantella" was also thought to cure some tarantula-spider (Lycosa tarantula, Latrodectes tredecimguttatus and other species) bites [5,6].

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 Table 1

 Words of one of the most important living musicians.

All we can do is speak about our own reaction to music and life. If I attempt to speak about music, it is because the impossible has always attracted me more than the difficult, because the impossible has not only a feeling of adventure, but a feeling of activity which I find highly attractive. I will therefore attempt the impossible and try to draw some connection between the inexpressible content of music and the inexpressible content of life.

Daniel Barenboim

Robert Burton wrote in his "Melancholy's Anatomy" in 1632: "music is the more grateful and effective remedy for sadness, fear and mood disorders". Peter Lichtenthal, an Austro-Hungarian scientist and musician, wrote in his "Dissertation About the Influence of Music on the Human Body" (1811): "Worthy of the experiment of a physician is, in my opinion, research into the impact of music on man and, led by philosophical reasoning, use it in the treatment of illnesses". The great German surgeon C.A.T. Billroth (also a good violin and cello player), in his "Wer ist musikalish?" published in 1894, attempted first to correlate musical abilities with the anatomy and physiology of the brain [6]. It was only in 1899, however, that "The Lancet" published an article by J.T.R. Davison, entitled "Music in Medicine", leading to the now growing field of scientific investigation in music and health [7]. In 1914 E. O'Neil Kane published in JAMA the first experiment describing the effects of music in medical procedures, demonstrating that the use of a phonograph within operating and recovery room was able to decrease the need for pharmacological analgesia and reduce anxiety of patients undergoing "horrors of surgery" [8]. In 1918 Hyde and Scalapino reported, in the first technology-based experiment in this field (e.g., EKG recording), that minor tones increased pulse rate and lowered blood pressure, whereas stirring music increased both blood pressure and heart rate [9]. In recent years, music has been increasingly used as a therapeutic tool in the treatment of different diseases, although the physiological basis in healthy and ill subjects is still poorly understood.

This article is mainly focused on Western music, since the vast majority of available literature regards this fundamental chapter of Western culture.

2. The neurophysiologic bases of music perception

According to a neurophysiologic perspective, music is elaborated in a primary acoustic projection center localized in areas 41 and 42 of the temporal lobes, whereas the adjacent area 22 is the secondary auditory projection center [10,11]. A tonotopical organization, beginning from the cochlea and maintained in the acoustic nerve, has been described within these areas, resembling the somatotopical organization of other cortical regions [12]. It is well known, moreover, that there is some interaction between visual and acoustic systems, and that the enjoyment of music is more complete when one person looked at the playing and/or singing musicians. Newer neuroimaging techniques, such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (MRI), enable to visualize the cerebral areas which are activated in response to musical stimuli and reveal the pathway which allows the perception of music and evokes emotions in the different cerebral regions. Even the hemispheric dominance shows different patterns, depending on the musical education of the subjects. As such, PET-based studies demonstrate that listening to the music activates the right hemisphere (thought to be the more "intuitive" part of the brain) in inexpert listeners, whereas the left hemisphere, the "rational" side, is instead activated in musicians. Moreover, the right hemisphere perceives timbre and melody, whereas the left one analyzes rhythm and pitch, the "mathematical" and "syntactical" face of music, strictly interacting with the language areas [13-15]. There is no doubt that the same Mozart's Symphony is perceived with a different way and different depth when listened to by a naïve listener or by a Mozart's lover, or by a great Mozart's conductor such as Claudio Abbado. It has been demonstrated that the naïve listener only exhibits a "gestaltic" perception of music [16]. Mozart himself helps our understanding with some of his letters: "In my work music is for all kind of listeners..." (to his father, December 1780) and, writing about his Piano Concerts K 413, 414 and 415 "They are a compromise between the too difficult and the too easy: they are very brilliant, pleasant to the ear, natural without falling into the trap of emptiness, here and there only experts can gain satisfaction but even non experts will feel pleasure without knowing why" (to his father, December 1782) [17].

Herbert von Karajan, one of the greatest conductors in music history, was observed by telemetry during the recording of the Ouverture "Leonore Nr.3" by L. van Beethoven. His heart rate was doubled during the most intense emotional passages, independently from physical involvement. The same reaction was reproduced while he listened to the music just recorded. He was also observed by telemetry while piloting his jet, and a minimal heart rate variations could only be observed [18]. This behavior cannot be generalized to everybody, rather understandably. Nearly 4% of the general population suffers from amusia (sometimes in a heritable form), not being able to recognize and distinguish unison, the octave and pitch. This disorder was first described in 1752 by the great French composer J.P. Rameau, who reported a typical case of amusia in a young singer male pupil, although the medical term "amusia" was firstly introduced by A. Knoblauch in 1888 [5,19–22]. Amusia is occasionally a consequence of brain damage, and is often coupled with aphasia. It is notable in the case of the Russian composer V.Y. Shebalin (1902-1963), who continued to compose after a left-hemisphere stroke causing hemiplegia and severe aphasia. Shebalin's case was studied in 1948 by the great Russian neuropsychologist A.R. Luria [23], and D. Shostakovich considered Shebalin's 5th Symphony, composed after the stroke, "a creation of a great master".

3. Scientific evidences on the effects of music on human biology

The vast majority of clinical studies dealing with the effects of music on different diseases has been carried out in the neurological field, and the positive effects of music on the motor parameters in patients affected by Parkinson's disease, Alzheimer's disease, multiple sclerosis, ataxia or spasticity, have been clearly demonstrated [5,24–27]. In elderly people with gait impairment, music-based multitask training prolonged for six months was able to improve gait and balance, and significantly reduced both the rate of falls as well as the risk of falling [28].

Surgery is another field of comprehensive investigation, with the main aim to decrease pre- and postoperative stress and possibly reduce the dosing of the drugs. Nillson et al. analyzed 40 patients undergoing bypass grafting or aortic valve replacement (20 patients listened to music prior to surgery, 20 served as controls). After surgery, improved values of oxytocin and PaO2 were observed in the music group as compared with controls (p<0.05) [29]. The same authors analyzed the follow-up of 58 patients after cardiac surgery. Patients exposed to at least 30 min of music the day after surgery displayed significantly lower values of plasma cortisol as compared with the control group (p<0.02), thereby reflecting a potential reduction of stress [30]. The perceived stress of ambulatory surgery in geriatric patients is associated with a clinical hypertensive and tachycardiac response which might be improved by self-selected perioperative music and also decreases perceived stress and increases patients' sense of personal control and well-being [31]. Music has hence been proposed as a nursing technique in selected settings [32], whereas no effects have been observed when music was administered during surgery under general anesthesia [33]. A recent systematic Cochrane review concluded that there is a weak evidence that music listening may have a beneficial effect on heart rate, respiratory rate, and anxiety in mechanically ventilated patients [34].

Bernardi et al. studied 12 practicing musicians and 12 matched controls, presenting six musical pieces in a random order and in different musical styles (Indian Raga; "Adagio molto e cantabile" from Beethoven's 9th Symphony; a dodecaphonic music by Anton Webern; a rap music by Red Hot Chili Peppers; a techno music by Gigi d'Agostino and the "presto" from Vivaldi's "Summer"), with a two minute pause randomly inserted. It was observed that ventilation, blood pressure, and heart rate increased, whereas mid-cerebral artery flow velocity (trans-cranial Doppler) and baroreflex decreased in association with faster tempi and simpler rhythmic structures, as compared with the baseline. The introduced silence pause reduced heart rate, blood pressure and ventilation even below the baseline, showing that silence between music had the most profound relaxating effect. Regardless of music style, a progressive reduction in mid-cerebral artery flow velocity was also observed. Moreover, the two groups performed in a similar manner, but musicians had greater respiratory sensitivity to the music tempo than did nonmusicians [35]. The same authors subsequently evaluated 12 musicians (choristers) and 12 nonmusician controls, by presenting five different pieces of classical music in a random order ("Adagio molto e cantabile" from Beethoven's 9th Symphony; "Nessun dorma" from Puccini's Turandot; "Gott soll allein mein Herze haben" from Bach's Cantata BWV 169; "Va pensiero" from Verdi's Nabucco and "Libiam nei lieti calici" from Verdi's La Traviata), and a randomly interposed period of silence. They found that almost every music crescendo or emphasis induced progressive skin vasoconstriction, along with increases in blood pressure and heart rate. More interestingly, it was also observed that specific music phrases (frequently at a rhythm of 6 cycles/min, like in famous arias by Verdi) could synchronize inherent cardiovascular rhythms, thus modulating cardiovascular control. Once again, musicians and nonmusicians showed comparable qualitative responses, although the musicians exhibited closer and faster cardiovascular and particularly respiratory modulation induced by the music [36].

Some of the relaxing properties of music – in this case some slow movements from Mozart's piano sonatas – can also elicit biochemical measurable stress-reducing effects, such as reduction of inflammatory markers and improved activation of the immune system natural killer cells [37,38]. A group of Japanese scientists, working in a geriatric nursing hospital, observed a decrease in biochemical parameters such as cytokine and catecholamine levels, as well as a decrease in congestive heart failure events, in a group of 87 elderly patients with cerebrovascular disease and dementia [39].

Music has also been thought to improve some intellective performances. In a group of students, listening to the Mozart's fourhands Piano Sonata K 448, but not Brahms's 5th Hungarian Dance, enhanced the learning of spatio-temporal rotation tasks (a tool used for determining spatial IQ), by activating task-relevant brain areas, as shown by EEG recording. However, a still unsolved issue concerns the kind of specific characteristics of Mozart's Sonata K 448 that might have had elicited the described changes in brain activity. There is also uncertainty on what kind of music pieces might be more beneficial for specific cognitive processes [40]. Albert Einstein, who was also a good violin, viola and piano player, affirmed while writing about one of his discoveries: "It occurred to me by intuition, and music was the driving force behind that intuition. My discovery was the result of musical perception". Different effects can in fact be provoked by major and minor tones. For example, listening to the music in major keys significantly reduces the levels of cortisol in the salivary glands during mental fatigue, whereas minor keys are mostly ineffective [41].

Intense music can elicit strong emotional responses, up to ecstatic "chill" experiences, and these strong psychological reactions are often accompanied by measurable bodily reactions, such as goose pimples or shivers. Grewe et al. reported that chills are rare events, and

occurred mainly during defined semantic musical structures, thus reflecting at least partially the personal degree of musical education. The subjects studied exhibited the most intense and reproducible reaction while listening to the 4th movement "Urlicht" from Mahler's 2nd Symphony [42]. Conversely, emotional disorders such as major depression seem to impair the processing of emotions elicited by the music [43].

A new recreational use of repetitive, beating, atonal tracks listened to at a high volume through headphones is now becoming very popular among teenagers. Formerly called "digital drugs", the trendy name for this tool is "I-dosing", and many of the downloadable "musical" simulations borrow their names from prohibited recreational drugs. At present, the scientific evidence on the effects and/or the potential harms (taking for granted the damage of the acoustic system) of this new form of "drug" is almost completely lacking [44]. Nevertheless, the phenomenon of digital drugs or I-dosing has not been comprehensively analyzed as yet, so that the presumption that these can be a potential danger to the consumer must be considered as plausible.

Mozart's music is the most frequently used, both in experiments on music-brain relationships and in music therapy, so that some authors have suggested that this music yields the best and most permanent outcomes, the so-called Mozart effect [45,46]. In our opinion, the extraordinary popularity of several Mozart's compositions, the limited musical culture of many physicians, and some intrinsic characteristics of most of his production (but not all — we are doubtful on the relaxing effects of some passages of the Requiem K 626, or the Piano Concert K 466, or the String Quintet K 516 since they are intrinsically dramatic and able to trigger a wide variety of feelings, but not relaxation at all) are the main determinants of the *probably-non-existing* Mozart effect. The music effects do exist however, noticeably varying with the different characteristic of the music itself. Overwhelming evidence seems to indicate that the effects are rather widespread, but somehow depending on the musical education of the subjects.

A final issue is whether animals do have music perception. This is a truly difficult question to be answered, with many potentially different answers. Some studies showed at least a rudimental music perception in definite species, most notably apes, monkeys and birds [47,48], while others failed to reach a similar conclusion [49]. There is a large literature on song learning in some birds. Birds move through a series of stages with increasing precision, learning from a teacherbird, finally reaching the ability to faithfully reproduce the crystallized song [50]. It has also been demonstrated that blood pressure and heart rate spontaneously decreased in hypertensive rats while listening to Mozart's 40th Symphony, and vice-versa the same parameters increased while listening to Ligeti's String Quartet Nr.2 (a dissonant, post-dodecaphonic composition). Conversely, white noise at the same 75 dB level produced no effect [51].

Once again, it seems that the Mozart effect does exist really, even in non-primate mammalians, but not surprisingly only if Mozart's music is matched with dodecaphonic music. What about a musical-physiological challenge between Mozart and Bach, Vivaldi, or Haydn?

4. Learning points

- The potential influence of music in eliciting organic reactions has been appreciated since the ancient Assyrian and Greek cultures.
- Growing experimental evidence attests that some kind of music might modulate cardiac and neurological functions and elicit biochemical stress-reducing effects in individuals according to their musical education.
- Music is also increasingly used as a therapeutic tool in the treatment of different diseases in healthy and ill subjects.
- The scientific background underlying the beneficial influence of music on human health is still poorly understood.

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Conflict of interest

The authors have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, this work.

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