

Mozart, Music and Medicine

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Key Words

Music · Mozart effect · Neurobiology · Positron emission tomography · Functional magnetic resonance imaging · Emotion · Well-being

Abstract

According to the first publication in 1993 by Rauscher et al. [Nature 1993;365:611], the Mozart effect implies the enhancement of reasoning skills solving spatial problems in normal subjects after listening to Mozart's piano sonata K 448. A further evaluation of this effect has raised the question whether there is a link between music-generated emotions and a higher level of cognitive abilities by mere listening. Positron emission tomography and functional magnetic resonance imaging have revealed that listening to pleasurable music activates cortical and subcortical cerebral areas where emotions are processed. These neurobiological effects of music suggest that auditory stimulation evokes emotions linked to heightened arousal and result in temporarily enhanced performance in many cognitive domains. Music therapy applies this arousal in a clinical setting as it may offer benefits to patients by diverting their attention from unpleasant experiences and future interventions. It has been applied in the context of various important clinical conditions such as cardiovascular disorders, cancer pain, epilepsy, depression and dementia. Furthermore, music may modu-

late the immune response, among other things, evidenced by increasing the activity of natural killer cells, lymphocytes and interferon- γ , which is an interesting feature as many diseases are related to a misbalanced immune system. Many of these clinical studies, however, suffer from methodological inadequacies. Nevertheless, at present, there is moderate but not altogether convincing evidence that listening to known and liked music helps to decrease the burden of a disease and enhances the immune system by modifying stress.

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All colours in music come from emotional states.
Murray Perahia in 'Play It Again' by Alan Rusbridger

Introduction

Throughout the centuries, music has been used to raise the spirit of people. The power of music in eliciting mental and physical well-being was already recognized by the ancient Greeks. Pythagoras was intrigued by the fact that people appreciated consonant sounds. He discovered that

Prof. Pauwels dedicates this paper to Maestra Sonia Rubinsky, who helped him tremendously with her musical and pianistic interpretation of the sonatas of Mozart and Scarlatti.

harmonic music is able to soothe people and cure ailments of the spirit, body and soul. He believed that the mathematical nature of music influenced the mind and the body and termed it 'musical medicine'. In addition, he believed that the principles of harmony had the power to incite various emotions [1]. In *The Republic*, book III, Plato declared musical training a more potent instrument than any other because 'rhythm and harmony find their way into the inward places of the soul' [2]. In book 8 of Aristotle's *Politics*, it is argued that music has cathartic effects and that catharsis should be understood as a harmless release of emotions [3]. In modern times, a definite link was made between music and emotion, intuitively felt – and experimentally assessed by Goldstein [4] – as when one experiences chills and shivers while listening to preferred music. Recent papers confirm that listening to music for pleasure is related to a change in emotional arousal [5, 6]. In this way, music has a positive effect on psychological well-being, giving rise to a higher level of performance. It is likely that the so-called Mozart effect, first described in an article published in 1993 by Rauscher et al. [7] as comprising better spatial reasoning skills in normal subjects after listening to Mozart's piano sonata K 448, comes into this category. Subsequent multidisciplinary research in the music domain has attested that musical stimuli can activate physiological pathways that can modulate body responses [8]. Growing evidence shows that listening to preferred music shows beneficial effects in the areas of cardiac and neurological function [9, 10]. On this basis, it is plausible that listening to pleasurable music is suitable as an adjunctive therapeutic tool in the treatment of various heart- and brain-related diseases, a field known as 'music therapy' [11].

Examining recent studies, mostly not older than 5 years, this review will elucidate relevant neurobiological effects of music listening in adults, followed by some remarks on the above-mentioned Mozart effect. After this, the use of music for medical ailments will be illustrated, highlighting various beneficial aspects in adults. We like to emphasize that the effect of music on domains such as speech, language abilities and verbal intelligence is beyond the scope of this paper.

Neurobiological Studies and Music

Positron Emission Tomography and Functional Magnetic Resonance Imaging Studies

Modern imaging techniques [positron emission tomography (PET) and functional magnetic resonance im-

aging (fMRI)] suggest that a large bilateral cerebral area, known as the limbic (e.g. amygdala and hippocampus) and paralimbic structures (e.g. the orbitofrontal cortex, parahippocampal gyrus and temporal poles), is engaged when listening to music. Koelsch [12] has mapped the music-evoked areas that are repeatedly reported by various researchers. It appears that the amygdala, the nucleus accumbens and the hippocampus are frequently mentioned as activated structures, and this suggests that music is able to modulate activity in the core areas of emotion, among other regions. fMRI studies have also demonstrated that unpleasant irregular chords may elicit brain activity related to emotional processes, as evidenced by increased bilateral blood oxygen levels in the amygdala [13].

A number of studies have attempted to map the effects of tonality on neural activation. It has been observed that the minor keys activate larger areas of the brain than do major keys, which suggests that the two musical modes are processed differently [14]. When minor consonant chords are perceived as beautiful, the right striatum is strongly activated. This structure is known to be strongly involved in the processing of rewards and emotional processing. By contrast, major consonant chords induce activity in the left middle temporal gyrus, which is related to coherent information processing [15]. A recent study by Trost et al. [16] using fMRI confirmed that high-arousal joyful musical activity takes place in the left striatum and insula, whereas low-arousal nostalgic sad music activates the right striatum and orbitofrontal cortex. Other researchers have also demonstrated that distinct parts of the brain are activated by music as a function of tonality. For example, Pallesen et al. [17] demonstrated that the minor tonality, compared with the major one, showed a selective engagement of the amygdala, retrosplenial cortex, brain stem and cerebellum. On the other hand, Brattico et al. [18] found that sad music, often associated with the minor key, induced activity in the right caudal head and the left thalamus. Green et al. [19] revealed that minor tonalities cause an increased activity in the left parahippocampal gyrus, the left medial prefrontal cortex and the bilateral ventral anterior cingulate. From these imaging experiments, it is clear that various cerebral structures may be activated, which is ascribed to different factors in the classification of emotion and dissimilar neural activation [20, 21].

Neurobiochemical Features of Music Listening

The biological mechanisms involved in music appreciation are far from understood, but some hypotheses based on experimental results are worth considering. Fukui and Toyoshima [22] mention that listening to music

lowers the secretion of cortisol and improves mood disturbances. This is a rewarding effect of listening to music. Furthermore, they hypothesize that these biological changes may facilitate neurogenesis as well as the regeneration and repair of cerebral nerves, possibly mediated by brain-derived neurotrophic factor [23]. The production of this factor as well as its receptor is increased by listening to music, as demonstrated by Angelucci et al. [24] in an experimental setting.

Another biochemical feature of listening to music is the increased secretion of the neurotransmitter dopamine. Using PET imaging with ¹¹C-radiolabeled raclopride, Salimpoor et al. [25] were able to demonstrate endogenous dopamine release in the striatum at peak emotional arousal while listening to music. It is known that increased levels of dopamine in healthy subjects improve executive functions, cognition and attention [26, 27]. Thus, improved performance may well be mediated by the dopaminergic system. Regarding the role of neurotransmitters, Evers and Suhr [28] found that during the perception of pleasant music, the platelet content of serotonin is higher than during the perception of unpleasant music. Recent genetic research has demonstrated that the serotonergic system is associated with music aptitude and creativity [29]. However, there have only been few studies in this area, and other mechanisms may be involved as well. One suggestion is that pleasurable music brings about enhanced glutamatergic neurotransmission and N-methyl-D-aspartic acid-mediated neural plasticity [30]. Another hypothesis is the effect of music-induced changes on attentional networks in the context of the noradrenaline system [31, 32], but little is known about a direct link between music and increased brain noradrenaline turnover in humans [33, 34].

The Mozart Effect: ‘Jubilate’ or ‘Lacrimosa’?

Soon after the publication by Rauscher et al. [7] on the so-called Mozart effect, a flurry of research activity focused on the notion that ‘music makes you smarter’. The effect on cognition has been replicated by Smith et al. [35], who showed a better spatial reasoning performance in young adults. Previous studies by Rideout and Laubach [36], Rideout et al. [37], Jausovec and Habe [38] and Jausovec et al. [39] confirmed that the first movement of Mozart sonata K 448 enhanced the learning of three-dimensional mental rotation tasks. Suda et al. [40] reported that this music enhanced cognitive performance in intelligence tests, compared with music by Beethoven or silence. These findings confirmed pioneering work by

Schellenberg [41], who studied 144 children and noticed intelligence enhancement in those taking music lessons compared with those in randomly assigned control groups receiving drama lessons or no lessons.

These intriguing findings inspired several other research groups to study the subject with different approaches. An interesting report by Chabris [42] deals with a meta-analysis to estimate the effect size. This author combined the results reported in 20 publications on Mozart-silence comparisons involving a total of 714 participants. The analysis yielded an average cognitive enhancement of 1.4 IQ points. The enhancement related to a single task of spatial-temporal processing amounted to 2.1 IQ points. In general, a single person’s IQ test comes with a 50% confidence interval of 4.5 IQ points. This made the author conclude that any cognitive enhancement is not translated into any significant change in IQ. If there were any, it would be restricted to the performance of one specific type of cognitive task in the field of spatial reasoning. This explicit finding is in line with results obtained by other researchers at later stages. McCutcheon [43] found no significant differences in the spatial reasoning performance of his study participants after listening to Mozart, jazz or silence. In an attempt to generalize the Mozart effect, Lints and Gadbois [44] demonstrated that enhanced spatial reasoning occurred following a variety of conditions and not just after listening to Mozart. Other investigators [45] replicated the Mozart effect but observed a Schubert effect as well. Moreover, participants who preferred listening to a narrated story rather than Mozart performed better on a spatial task after listening to the story. It is meaningful that the authors named their article ‘The Mozart effect: an artifact of preference’. Roth and Smith [46] investigated the effect of music or nonmusical auditory stimuli immediately prior to an examination in 72 undergraduate students. The obtained results did not support a Mozart-specific effect: individual elements of music (rhythm and melody) and traffic sounds provided similar effects. The authors explained their results in terms of physiological reactions evoked by heightened arousal. This may result in temporarily enhanced performance in many cognitive domains [47–51]. This arousal framework associated with music listening has paved the way for applications in music therapy.

Music and Medicine

Music may offer benefits to patients as it may divert their attention from unpleasant experiences and future interventions. The effect of listening to music can dimin-

ish or take away unpleasant thoughts in patients. In this sense, music therapy has been recognized as an allied medical intervention with evidence-based clinical benefits [52]. In the following, we will discuss the clinical application of music therapy in adults, but in view of the fact that many ailments find their origin in a misbalanced immune system, we will first dwell on the effect of music on the immune system.

Music and the Immune System

Many studies have documented that stress-induced immune dysregulation may produce changes in the humoral and cellular immune response, increasing health risks [53]. A meta-analysis by Segerstrom and Miller [53] based on effect sizes derived from 293 independent studies including 18,941 subjects showed that psychological stress affects the immune system. In their article, the authors described that time-limited stressors such as public speaking and mental arithmetic in healthy subjects were associated with the adaptive upregulation of natural immunity, evidenced by measurements of natural killer (NK) cells ($r = 0.43$), large granular lymphocytes ($r = 0.53$), neutrophil members ($r = 0.30$), IL-6 (r values not provided) and interferon (IFN)- γ (r values not provided) in peripheral blood. In healthy adults, brief naturalistic stressors such as examination changed the profile of cytokine production: decreased Th1 cytokine production resulted in a decrease in T cell proliferative response ($r = -0.19$ to -0.32) as well as NK cell cytotoxicity ($r = -0.11$). These changes were accompanied by increased antibody production, which is consistent with decreased cellular immunity and an enhancement of humoral immunity. With older age, decreases in NK cell cytotoxicity, T lymphocyte proliferation and the production of IFN- γ were more pronounced.

One of the early indications of the relationship between the immune system and music has been found in a single trial experiment by Bittman et al. [54], who provided evidence that group drumming increased NK cell activity, lymphokine-activated killer cell activity and the dehydroepiandrosterone-to-cortisol ratio in normal subjects. Likewise, Koyama et al. [55] found that recreational music making modulates immunological responses in adults demarcated at the age of 65 years. Significant increases in the number of lymphocytes, T cells, CD4+ T cells and memory T cells as well as in the production of IFN- γ and IL-6 were observed. Contrary to what is expected with stress, increases in Th1 cytokine IFN- γ and unchanged Th2 cytokine IL-4 and IL-10 levels were noted. Similar results were obtained by Wachi et al. [56], who

studied the effects of recreational music making on the modulation of the immune response in healthy corporate employees. These investigators documented significant changes in NK cell activity and in the level of gene expression for IFN- γ and IL-10. A recent study by Bittman et al. [57] has confirmed the above-mentioned findings on a genetic level: their results support the hypothesis that different sets of genes play important roles in both stress and the relaxation response in humans. If these findings can be confirmed by other research groups, the implications may be of particular importance: they could provide a means for tailored music therapy by identifying the patients who would benefit the most from the clinical effect of music.

Cardiovascular Disorders

A direct physiological effect of classical music on the cardiac autonomic balance has been demonstrated by White [58, 59]. In patients recovering from acute myocardial infarction, a reduction in heart rate, respiratory rate and anxiety level was noticed when they were listening to classical music under restful circumstances as compared with a control group undergoing treatment as usual. The author's findings confirmed previous findings by Guzzetta [60], who studied 80 cases suspected of having acute myocardial infarction who were randomly assigned to relaxing music in a coronary care unit. The results demonstrated that apical heart rates were lower and peripheral temperatures were higher in the relaxation group than in a control group. Regarding the effect of music intervention on psychological and physiological responses in persons with coronary heart disease, a Cochrane Database (www.cochrane.org) analysis was published by Bradt and Dileo [61]. These two reviewers analyzed the data from 23 trials comprising 1,461 participants in whom music listening was the main intervention. It was concluded that music listening may have a beneficial effect on blood pressure, heart rate, respiratory rate, anxiety and pain, although the quality of the evidence was not strong.

Various studies have analyzed the effect of music listening on patients in intensive care units after cardiac surgery. A randomized controlled trial by Nilsson [62] comprising 58 patients who had undergone bypass grafting or aortic valve replacement revealed that listening to soft relaxing music (New Age style) was associated with significantly lower levels of serum cortisol, a measure of stress response. Other parameters including heart rate, respiratory rate, mean arterial pressure, arterial oxygen tension, arterial oxygen saturation, and subjective pain and anxiety levels were not significantly different between the

groups. The same author has reported on another randomized controlled study in 40 patients who had undergone similar surgery, in whom listening to music during bed rest had some effect on the relaxation system as regards oxytocin and subjective relaxation levels [63]. A recent review of 16 studies by Fredericks et al. [64] provided evidence that anxiety and depression in patients following heart surgery can be soothed by listening to music. A study published after this review aimed to investigate the effect on postoperative oxygen saturation and pain by listening to music of personal choice in 87 patients (including 43 patients in a control group) who had undergone open heart surgery. The authors reported a statistically significant increase in oxygen saturation and a lower pain score (both $p = 0.001$), which provides further evidence of the effectiveness of music listening for patients after open heart surgery [1, 65]. The highest benefit for health comes from classical (Bach, Mozart or Italian composers) and New Age music [66].

Music and Cancer Pain

In 2002, Evans [67] reviewed the effectiveness of music in the reduction of anxiety in hospital patients undergoing normal care. This meta-analysis was based on 19 studies and showed that music improves the mood and pain tolerance of patients. This knowledge has been applied to oncology patients, especially for cancer pain management. Igawa-Silva et al. [68] performed a comprehensive systematic evaluation of data-based literature and concluded that music reduces anxiety and, consequently, lessens the intensity of pain in chronic cancer patients. The authors of a Cochrane review came to a similar conclusion and stated that listening to music reduces pain intensity and opioid requirements [69]. This analysis, dating from 2006, was updated in 2011, comprising 30 trials with a total of 1,891 cancer patients. A moderate pain-reducing effect was found ($p = 0.0003$), together with small reductions in heart rate, respiration rate and blood pressure [70]. A compelling example of a beneficial effect of music in relieving pain in cancer patients has been published by Huang et al. [71]. These researchers carried out a randomized controlled trial in 126 hospitalized persons with cancer pain divided almost equally into an experimental group and a control group. The patients were allowed to listen to their preferred music for 30 min. Using an advanced pain assessment technique and appropriate statistical analysis, it turned out that the music listeners had significantly less posttest pain ($p < 0.001$). The fact that the patients were offered familiar, culturally appropriate music appeared to be a key element in the

intervention. Also, other authors showed that music has a more analgesic effect on pain if it is self-chosen and familiar [72, 73]. A recent paper by Villarreal et al. [74] provides evidence that familiarity with the music drives the emotional mechanisms to modulate pain. In case of unfamiliar music, the main analgesic mechanism may be of a cognitive nature rather than emotional.

Music and Depression

Depression is a widespread and disabling disease, and although psychotherapy and/or pharmacotherapy can be effective, it has been emphasized that conventional pharmacologic methods might result in dependence and an impairment of psychomotor and cognitive functioning [75]. Against this background, various reviews and meta-analyses have mentioned a positive clinical response in patients listening to music either combined with standard therapy or not [9, 76–78]. Recently, various randomized controlled trials have studied the effect of music as a monotherapy (including that by Chan et al. [79]) and as an addition to standard therapy (including those by Erkila et al. [80] and Fachner et al. [81]) in depressed individuals. Without exception, these studies show that music listening or music making reduces depression. The importance of music making as a social and pleasurable event has been stressed by Maratos et al. [82], who mentioned that music therapy may result in high levels of engagement in patient groups who are difficult to engage. Moreover, in patients with mild-to-moderate dementia and associated depression, group music making may have a beneficial effect. Chu et al. [83] performed a prospective randomized controlled study and showed that music therapy reduced depression, the effect occurring immediately after the onset of music making and lasting throughout the course of the therapy. Interestingly, cortisol levels, a measure of global mood state, are not significantly decreased after the therapy. To sum up, the results show that music therapy is an effective method for decreasing the burden of depression.

Music and Epilepsy

Epilepsy is clinically characterized by recurrent seizures. The patients are at an increased risk of comorbidities such as cardiovascular, respiratory and inflammatory diseases. Medication remains the best treatment, but drug resistance is an important clinical problem [84]. Non-pharmacological treatment may therefore be of benefit, and music therapy has been suggested as complementary treatment based on a pioneering case study by Hughes et al. [85], who found a significant decrease in epileptic ac-

tivity as demonstrated by EEG in 23 of 29 patients (even when in coma) listening to Mozart's sonata K 448. Hughes and Fino [86] investigated whether the effect was specific to this music and found a similarity between the music of Mozart and that of Bach but not between the music of Mozart and the minimalist music of Philip Glass, which 'may not resonate within the cerebral cortex'. A reduction in seizures has also been reported in case studies by Lahiri and Duncan [87] and by Lin et al. [88]. Recently, a randomized controlled clinical study on the antiepileptiform effect of specific music has been carried out by Bodner et al. [89]. The reduction in, or even prevention of, seizures was investigated through auditory cortical stimulation by Mozart's sonata K 448 from sustained passive nightly exposure. This CONSORT study consisted of 73 randomized patients assessed for eligibility, of whom 48 were allocated to receive the musical stimulation. The remaining 25 subjects served as a control group and received only regular antiepileptic drug treatment. After 3 years, 25 patients in the treatment group and 11 patients in the control group could be included in the final analysis. This investigation revealed that a significant ($p = 0.024$) treatment effect was present: exposure to the music was likely to result in a remarkable reduction in seizure rate of 24%. Furthermore, it was noted that 24% (6 patients) of the treatment group exhibited a complete absence of seizures during treatment. Moreover, during the posttreatment follow-up year, a reduced average seizure rate of 33% was maintained after cessation of the therapy, indicating a long treatment effect in these 6 patients. Such a long-term effect had previously been observed by Lin et al. [90] in a case study on children in which epileptiform discharges decreased ($71.6 \pm 45.8\%$) 6 months after listening to Mozart's sonata K 448. A recent publication by the same research group provided evidence that Mozart music stimuli induce a parasympathetic activation which leads to a reduction in seizure rate [91].

Music and Dementia

With the aging of the world population, the growing incidence and prevalence of dementia have become more and more apparent [92]. Apart from cognitive enhancers for mild cognitive impairment such as Alzheimer's dementia, no treatment has been established for patients with vascular and frontotemporal dementia [93]. Of particular risk is antipsychotic medication, as cerebrovascular events and cases of death have been reported following this therapy [94]. These and other safety concerns regarding psychopharmacological medication [95] have been the impetus to search for nonpharmacological methods

for improving the quality of life. A recent meta-analysis of the effect of music interventions on patients with various degrees of dementia revealed that many studies indicate large positive effects on behavioral, cognitive and physiological main outcome measures and medium effects on affective measures, assessed in both subjective (e.g. well-being and/or reasoning abilities) and objective ways (decreased blood pressure and/or increased oxygen uptake), the overall effect size ranging from 0.04 to 4.56 (mean: 1.04). The fact that studies with undefined measuring methods and patients with various degrees of dementia were included in this meta-analysis may explain the large range of measured overall effects [96]. Other systematic reviews and meta-analyses [97–101] have confirmed these beneficial effects but have also indicated that the study designs were diverse and that randomized controlled trials need to confirm the outcome. One prospective randomized controlled study in 104 elderly persons with dementia by Chu et al. [83] made clear that music therapy delayed the deterioration in cognitive functions. A randomized controlled crossover trial in 42 participants with dementia by Ridder et al. [102] showed that agitation disruptiveness increased during standard care and decreased during music therapy. This is not in agreement with a previous randomized controlled crossover study by Cooke et al. [103], who found no effect of music therapy on the degree of agitation in 24 patients who attended more than 50% of the music sessions, although improvements in self-esteem and depressive symptoms were registered. The contrasting findings between these two studies may be due to the geographical difference between the two study groups, which makes a racial and socioeconomic background very likely. An additional difference between the Danish [102] and the Australian study [103] is that the former is a crossover study, whereas the latter uses a control group.

A Critical Note

It is remarkable that many studies regarding music therapy have been published in specialized journals, the contents of which are not easily retrievable. It should be stressed that it is not always clear whether, for these articles, an independent peer review process had been carried out and in how far only papers with beneficial results were published. Another remark concerns methodological inadequacies which are present in various studies mentioned throughout the section Music and Medicine, as only 11 of the 21 included studies are randomized con-

trolled trials. Of these, only 8 [62, 63, 71, 75, 80, 81, 102, 103] describe the methods of measuring effects, randomization and statistical analysis and report details on patient selection, dropouts and exclusion. Thus, a risk of bias is present not only in the remaining case and case-control studies but also in the randomized trials, which may limit the strength of the evidence. A further examination of the patient studies reveals limitations regarding their sample size: only 2 randomized controlled trials [71, 83] and 1 case study [54] based their statistical analysis on data assessed in more than 50 patients and 50 controls. Also Cochrane Database systematic reviews noticed the low methodological quality of some of the studies, including the poor categorization of diseases and inhomogeneity of the study groups, which diminishes the evidence and the generalizability of their conclusions [62, 69, 77, 104, 105].

Implications

Auditory stimulation with music evokes emotions which are often accompanied by physiological reactions such as changes in heart rate, respiration, skin properties and hormone secretion [106–109]. These reactions are linked to heightened arousal [47], resulting in temporarily enhanced performance in many cognitive domains including spatial reasoning [44], attention [24, 28], information processing [110] and recognition memory [111] in healthy subjects. Thus, the overall positive effect of listening to pleasurable music can serve as a stimulant that enhances cognitive performance. This strongly suggests that the Mozart effect is explained by a complex interplay between music, arousal and intellectual performance. It is hardly conceivable that it is an isolated phenomenon typically associated with specific Mozart music. Rather, it is an example of a wide range of stimulating circumstances.

In this context, it is plausible that music therapy can affect the autonomous nervous system and diminish stress and stress-related health issues [112], rebalancing the immune system, especially when the music is known and liked [31, 35]. It is the aim of the music therapist to optimize the effect of music therapy by registering the degree of enjoyment and the hedonic response. This is important, since preferences are based on numerous individual factors [113].

Apart from the effect of pleasurable music on cognition, the esthetic value as experienced by the patient adds to the management of pain and anxiety, e.g. in cardiovas-

cular and surgical patients. Indeed, a growing body of evidence suggests that making music and listening to preferred music is a valuable adjunct to medical practice.

It should be noted, however, that little is known about the neural substrates and psychological mechanisms that are the basis of the esthetic emotion evoked by music [114, 115], nor do we know enough about the duration of each single effect and the total of effects as follow-up studies in adult patients are missing. These follow-ups and other factors, including cognitive mastering of the musical experience and the perception of musical emotions as suggested by Brattico and Pearce [116], are important issues for further research in music therapy, a noble endeavor to promote the health of patients.

Conclusions

From neurobiological investigations, it is apparent that preferred music may evoke emotions that are associated with heightened arousal, which results in temporarily enhanced performance in many cognitive domains. This positive effect is not necessarily confined to Mozart's piano sonata K 448, as was suggested by some studies performed in the 1990s.

The arousal phenomenon is successfully being applied in various clinical settings. However, many clinical studies in this area suffer from methodological inadequacies limiting their scientific quality. This urges the need for well-designed prospective randomized studies, if possible in a blinded mode, to establish the efficacy under clinical circumstances. Nevertheless, present knowledge suggests that there is moderate but not altogether convincing evidence that listening to known and liked music, a regular feature in music therapy, leads to a decreased disease burden and increased well-being as well as less tension in patients suffering from cardiovascular disease, cancer pain, epilepsy, depression and dementia. It would be worthwhile to investigate a genetically, individually increased predisposition to respond emotionally to music as this would open pathways to tailored music therapy.

Disclosure Statement

The authors declare no conflict of interest whatsoever with regard to this article.

References

- 1 Pratt RR, Jones RW: Music and medicine: a partnership in history; in Spintge R, Droh R (eds): *Music in Medicine*. Berlin, Springer, 1987, pp 377–388.
- 2 Whitfield S: Music: its expressive power and moral significance. *Musical Offerings* 2010;1: 11–19.
- 3 Ford A: Catharsis: the power of music in Aristotle's *Politics*; in Murray P, Wilson P (eds): *Music and the Muses: The Culture of 'Mousike' in the Classical Athenian City*. Oxford, Oxford UP, 2004.
- 4 Goldstein A: Thrills in response to music and other stimuli. *Physiol Psychol* 1980;8:126–129.
- 5 Salimpoor VN, Benovoy M, Longo G, et al: The rewarding aspects of music listening are related to degree of emotional arousal. *PLoS One* 2009;4:e7487.
- 6 van den Bosch I, Salimpoor VN, Zatorre RJ: Familiarity mediates the relationship between emotional arousal and pleasure during music listening. *Front Hum Neurosci* 2013;7:534.
- 7 Rauscher FH, Shaw GL, Ky KN: Music and spatial task performance. *Nature* 1993;365:611.
- 8 DeNora T: 'Time after time': a Quali-T method for assessing music's impact on well-being. *Int J Qual Stud Health Well-being* 2013;8: 20611.
- 9 Lin ST, Yang P, Lai CY, et al: Mental health implications of music: insight from neuroscientific and clinical studies. *Harv Rev Psychiatry* 2011;19:34–46.
- 10 Zatorre RJ, Salimpoor VN: From perception to pleasure: music and its neural substrates. *Proc Natl Acad Sci USA* 2013;100 (suppl 2):10430–10437.
- 11 Cervellin G, Lippi G: From music-beat to heart-beat: a journey in the complex interactions between music, brain and heart. *Eur J Intern Med* 2011;22:371–374.
- 12 Koelsch S: Towards a neural basis of music-evoked emotions. *Trends Cogn Sci* 2010;14: 131–137.
- 13 Koelsch S, Fritz T, Schlaug G: Amygdala activity can be modulated by unexpected chord functions during music listening. *Neuroreport* 2008;19:1815–1819.
- 14 Nemoto I, Fujimaki T, Wang LQ: fMRI measurement of brain activities to major and minor chords and cadence sequences. *Conf Proc IEEE Eng Med Biol Soc* 2010;2010:5640–5643.
- 15 Suzuki M, Okamura N, Kawachi Y, et al: Discrete cortical regions associated with the musical beauty of major and minor chords. *Cogn Affect Behav Neurosci* 2008;8:126–131.
- 16 Trost W, Ethofer T, Zentner M, et al: Mapping aesthetic musical emotions in the brain. *Cereb Cortex* 2012;22:2769–2783.
- 17 Pallesen KJ, Brattico E, Bailey C, et al: Emotion processing of major, minor, and dissonant chords: a functional magnetic resonance imaging study. *Ann NY Acad Sci* 2005;1060: 450–453.
- 18 Brattico E, Alluri V, Bogert B, et al: A functional MRI study of happy and sad emotions in music with and without lyrics. *Front Psychol* 2011;2:308.
- 19 Green AC, Baerentsen KB, Stodkilde-Jorgensen H, et al: Music in minor activates limbic structures: a relationship with dissonance? *Neuroreport* 2008;19:711–715.
- 20 Riby LM: The joys of spring. *Exp Psychol* 2013;60:71–79.
- 21 Green AC, Baerentsen KB, Stodkilde-Jorgensen H, et al: Listen, learn, like! Dorsolateral prefrontal cortex involved in the mere exposure effect in music. *Neurol Res Int* 2012; 2012:846270.
- 22 Fukui H, Toyoshima K: Music facilitate the neurogenesis, regeneration and repair of neurons. *Med Hypotheses* 2008;71:765–769.
- 23 Noble EE, Billington CJ, Kotz CM, et al: The lighter side of BDNF. *Am J Physiol Regul Integr Comp Physiol* 2011;300:R1053–R1069.
- 24 Angelucci F, Ricci E, Padua L, et al: Music exposure differentially alters the levels of brain-derived neurotrophic factor and nerve growth factor in the mouse hypothalamus. *Neurosci Lett* 2007;429:152–155.
- 25 Salimpoor VN, Benovoy M, Larcher K, et al: Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci* 2011;14:257–262.
- 26 Dang LC, O'Neil JP, Jagust WJ: Dopamine supports coupling of attention-related networks. *J Neurosci* 2012;32:9582–9587.
- 27 Dang LC, Donde A, Madison C, et al: Striatal dopamine influences the default mode network to affect shifting between object features. *J Cogn Neurosci* 2012;24:1960–1970.
- 28 Evers S, Suhr B: Changes of the neurotransmitter serotonin but not of hormones during short time music perception. *Eur Arch Psychiatry Clin Neurosci* 2000;250:144–147.
- 29 Ukkola-Vuoti L, Kanduri C, Oikkonen J, et al: Genome-wide copy number variation analysis in extended families and unrelated individuals characterized for musical aptitude and creativity in music. *PLoS One* 2013; 8:e56356.
- 30 Xu J, Yu L, Cai R, et al: Early auditory enrichment with music enhances auditory discrimination learning and alters NR2B protein expression in rat auditory cortex. *Behav Brain Res* 2009;196:49–54.
- 31 Jiang J, Sclaro AJ, Bailey K, et al: The effect of music-induced mood on attentional networks. *Int J Psychol* 2011;46:214–222.
- 32 Sara SJ: The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci* 2009;10:211–223.
- 33 Panksepp J, Bernatzky G: Emotional sounds and the brain: the neuro-affective foundations of musical appreciation. *Behav Processes* 2002;60:133–155.
- 34 Lin PC, Lin ML, Huang LC, et al: Music therapy for patients receiving spine surgery. *J Clin Nurs* 2011;20:960–968.
- 35 Smith A, Waters B, Jones H: Effects of prior exposure to office noise and music on aspects of working memory. *Noise Health* 2010;12: 235–243.
- 36 Rideout BE, Laubach CM: EEG correlates of enhanced spatial performance following exposure to music. *Percept Mot Skills* 1996;82: 427–432.
- 37 Rideout BE, Dougherty S, Wernert L: Effect of music on spatial performance: a test of generality. *Percept Mot Skills* 1998;86:512–514.
- 38 Jausovec N, Habe K: The influence of Mozart's sonata K 448 on brain activity during the performance of spatial rotation and numerical tasks. *Brain Topogr* 2005;17:207–218.
- 39 Jausovec N, Jausovec K, Gerlic I: The influence of Mozart's music on brain activity in the process of learning. *Clin Neurophysiol* 2006; 117:2703–2714.
- 40 Suda M, Morimoto K, Obata A, et al: Cortical responses to Mozart's sonata enhance spatial-reasoning ability. *Neurol Res* 2008;30:885–888.
- 41 Schellenberg EG: Music lessons enhance IQ. *Psychol Sci* 2004;15:511–514.
- 42 Chabris CF: Prelude or requiem for the 'Mozart effect'? *Nature* 1999;400:826–827, author reply 827–828.
- 43 McCutcheon LE: Another failure to generalize the Mozart effect. *Psychol Rep* 2000;87: 325–330.
- 44 Lints A, Gadbois S: Is listening to Mozart the only way to enhance spatial reasoning? *Percept Mot Skills* 2003;97:1163–1174.
- 45 Nantais KM, Schellenberg EG: The Mozart effect: an artifact of preference. *Psychol Sci* 1999;10:370–373.
- 46 Roth EA, Smith KH: The Mozart effect: evidence for the arousal hypothesis. *Percept Mot Skills* 2008;107:396–402.
- 47 Sarkamo T, Soto D: Music listening after stroke: beneficial effects and potential neural mechanisms. *Ann NY Acad Sci* 2012;1252: 266–281.
- 48 Hirokawa E: Effects of music listening and relaxation instructions on arousal changes and the working memory task in older adults. *J Music Ther* 2004;41:107–127.
- 49 Mammarella N, Fairfield B, Cornoldi C: Does music enhance cognitive performance in healthy older adults? The Vivaldi effect. *Aging Clin Exp Res* 2007;19:394–399.
- 50 Lesiuk T: The effect of preferred music on mood and performance in a high-cognitive demand occupation. *J Music Ther* 2010;47: 137–154.
- 51 Angel LA, Polzella DJ, Elvers GC: Background music and cognitive performance. *Percept Mot Skills* 2010;110:1059–1064.
- 52 Kemper KJ, Danhauer SC: Music as therapy. *South Med J* 2005;98:282–288.
- 53 Segerstrom SC, Miller GE: Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004;130:601–630.

- 54 Bittman BB, Berk LS, Felten DL, et al: Composite effects of group drumming music therapy on modulation of neuroendocrine-immune parameters in normal subjects. *Altern Ther Health Med* 2001;7:38–47.
- 55 Koyama M, Wachi M, Utsuyama M, et al: Recreational music-making modulates immunological responses and mood states in older adults. *J Med Dent Sci* 2009;56:79–90.
- 56 Wachi M, Koyama M, Utsuyama M, et al: Recreational music-making modulates natural killer cell activity, cytokines, and mood states in corporate employees. *Med Sci Monit* 2007;13:CR57–CR70.
- 57 Bittman B, Croft DT Jr, Brinker J, et al: Recreational music-making alters gene expression pathways in patients with coronary heart disease. *Med Sci Monit* 2013;19:139–147.
- 58 White JM: Music therapy: an intervention to reduce anxiety in the myocardial infarction patient. *Clin Nurse Spec* 1992;6:58–63.
- 59 White JM: Effects of relaxing music on cardiac autonomic balance and anxiety after acute myocardial infarction. *Am J Crit Care* 1999;8:220–230.
- 60 Guzzetta CE: Effects of relaxation and music therapy on patients in a coronary care unit with presumptive acute myocardial infarction. *Heart Lung* 1989;18:609–616.
- 61 Bradt J, Dileo C: Music for stress and anxiety reduction in coronary heart disease patients. *Cochrane Database Syst Rev* 2009; 2:CD006577.
- 62 Nilsson U: The effect of music intervention in stress response to cardiac surgery in a randomized clinical trial. *Heart Lung* 2009;38: 201–207.
- 63 Nilsson U: Soothing music can increase oxytocin levels during bed rest after open-heart surgery: a randomised control trial. *J Clin Nurs* 2009;18:2153–2161.
- 64 Fredericks S, Lapum J, Lo J: Anxiety, depression, and self-management: a systematic review. *Clin Nurs Res* 2012;21:411–430.
- 65 Ozer N, Karaman Ozlu Z, Arslan S, et al: Effect of music on postoperative pain and physiologic parameters of patients after open heart surgery. *Pain Manag Nurs* 2013;14:20–28.
- 66 Trappe HJ: Role of music in intensive care medicine. *Int J Crit Illn Inj Sci* 2012;2:27–31.
- 67 Evans D: The effectiveness of music as an intervention for hospital patients: a systematic review. *J Adv Nurs* 2002;37:8–18.
- 68 Igawa-Silva W, Wu S, Harrigan R: Music and cancer pain management. *Hawaii Med J* 2007; 66:292–295.
- 69 Cepeda MS, Carr DB, Lau J, et al: Music for pain relief. *Cochrane Database Syst Rev* 2006; 2:CD004843.
- 70 Bradt J, Dileo C, Grocke D, et al: Music interventions for improving psychological and physical outcomes in cancer patients. *Cochrane Database Syst Rev* 2011;8:CD006911.
- 71 Huang ST, Good M, Zauszniewski JA: The effectiveness of music in relieving pain in cancer patients: a randomized controlled trial. *Int J Nurs Stud* 2010;47:1354–1362.
- 72 Mitchell LA, MacDonald RA, Brodie EE: A comparison of the effects of preferred music, arithmetic and humour on cold pressor pain. *Eur J Pain* 2006;10:343–351.
- 73 Roy M, Peretz I, Rainville P: Emotional valence contributes to music-induced analgesia. *Pain* 2008;134:140–147.
- 74 Villarreal EA, Brattico E, Vase L, et al: Superior analgesic effect of an active distraction versus pleasant unfamiliar sounds and music: the influence of emotion and cognitive style. *PLoS One* 2012;7:e29397.
- 75 Chan MF, Chan EA, Mok E: Effects of music on depression and sleep quality in elderly people: a randomised controlled trial. *Complement Ther Med* 2010;18:150–159.
- 76 Maratos AS, Gold C, Wang X, et al: Music therapy for depression. *Cochrane Database Syst Rev* 2008;1:CD004517.
- 77 Gold C, Solli HP, Kruger V, et al: Dose-response relationship in music therapy for people with serious mental disorders: systematic review and meta-analysis. *Clin Psychol Rev* 2009;29:193–207.
- 78 Chan MF, Wong ZY, Thayala NV: The effectiveness of music listening in reducing depressive symptoms in adults: a systematic review. *Complement Ther Med* 2011;19:332–348.
- 79 Chan MF, Wong ZY, Onishi H, et al: Effects of music on depression in older people: a randomised controlled trial. *J Clin Nurs* 2012;21: 776–783.
- 80 Erkkila J, Punkanen M, Fachner J, et al: Individual music therapy for depression: randomised controlled trial. *Br J Psychiatry* 2011; 199:132–139.
- 81 Fachner J, Gold C, Erkkila J: Music therapy modulates fronto-temporal activity in rest-EEG in depressed clients. *Brain Topogr* 2013; 26:338–354.
- 82 Maratos A, Crawford MJ, Procter S: Music therapy for depression: it seems to work, but how? *Br J Psychiatry* 2011;199:92–93.
- 83 Chu H, Yang CY, Lin Y, et al: The impact of group music therapy on depression and cognition in elderly persons with dementia: a randomized controlled study. *Biol Res Nurs* 2014;16:209–217.
- 84 Das N, Dhanawat M, Shrivastava SK: An overview on antiepileptic drugs. *Drug Discov Ther* 2012;6:178–193.
- 85 Hughes JR, Daaboul Y, Fino JJ, et al: The 'Mozart effect' on epileptiform activity. *Clin Electroencephalogr* 1998;29:109–119.
- 86 Hughes JR, Fino JJ: The Mozart effect: distinctive aspects of the music – a clue to brain coding? *Clin Electroencephalogr* 2000;31:94–103.
- 87 Lahiri N, Duncan JS: The Mozart effect: encores. *Epilepsy Behav* 2007;11:152–153.
- 88 Lin LC, Lee WT, Wang CH, et al: Mozart K 448 acts as a potential add-on therapy in children with refractory epilepsy. *Epilepsy Behav* 2011;20:490–493.
- 89 Bodner M, Turner RP, Schwacke J, et al: Reduction of seizure occurrence from exposure to auditory stimulation in individuals with neurological handicaps: a randomized controlled trial. *PLoS One* 2012;7:e45303.
- 90 Lin LC, Lee WT, Wu HC, et al: The long-term effect of listening to Mozart K 448 decreases epileptiform discharges in children with epilepsy. *Epilepsy Behav* 2011;21:420–424.
- 91 Lin L, Chiang CT, Lee MW: Parasympathetic activation is involved in reducing epileptiform discharges when listening to Mozart music. *Clin Neurophysiol* 2013;124:1528–1535.
- 92 Hurd MD, Martorell P, Langa KM: Monetary costs of dementia in the United States. *N Engl J Med* 2013;369:489–490.
- 93 Schwarz S, Froelich L, Burns A: Pharmacological treatment of dementia. *Curr Opin Psychiatry* 2012;25:542–550.
- 94 Mittal V, Kurup L, Williamson D, et al: Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. *Am J Alzheimers Dis Other Demen* 2011;26:10–28.
- 95 Brandt NJ, Pythtla J: Psychopharmacological medication use among older adults with dementia in nursing homes. *J Gerontol Nurs* 2013;39:8–14.
- 96 Vasionyte I, Madison G: Musical intervention for patients with dementia: a meta-analysis. *J Clin Nurs* 2013;22:1203–1216.
- 97 Koger SM, Chapin K, Brotons M: Is music therapy an effective intervention for dementia? A meta-analytic review of literature. *J Music Ther* 1999;36:2–15.
- 98 Wall M, Duffy A: The effects of music therapy for older people with dementia. *Br J Nurs* 2010;19:108–113.
- 99 McDermott O, Crellin N, Ridder HM, et al: Music therapy in dementia: a narrative synthesis systematic review. *Int J Geriatr Psychiatry* 2013;28:781–794.
- 100 Raglio A, Bellelli G, Mazzola P, et al: Music, music therapy and dementia: a review of literature and the recommendations of the Italian Psychogeriatric Association. *Maturitas* 2012;72:305–310.
- 101 Ueda T, Suzukamo Y, Sato M, et al: Effects of music therapy on behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. *Ageing Res Rev* 2013;12:628–641.
- 102 Ridder HM, Stige B, Qvale LG, et al: Individual music therapy for agitation in dementia: an exploratory randomized controlled trial. *Aging Ment Health* 2013;17:667–678.
- 103 Cooke M, Moyle W, Shum D, et al: A randomized controlled trial exploring the effect of music on quality of life and depression in older people with dementia. *J Health Psychol* 2010;15:765–776.
- 104 Bradt J, Dileo C: Music therapy for end-of-life care. *Cochrane Database Syst Rev* 2010; 1:CD007169.

- 105 Bradt J, Dileo C, Shim M: Music interventions for preoperative anxiety. *Cochrane Database Syst Rev* 2013;6:CD006908.
- 106 Grewe O, Nagel F, Kopiez R, et al: How does music arouse 'chills'? Investigating strong emotions, combining psychological, physiological, and psychoacoustical methods. *Ann NY Acad Sci* 2005;1060:446-449.
- 107 Baltes FR, Avram J, Miclea M, et al: Emotions induced by operatic music: psychophysiological effects of music, plot, and acting - a scientist's tribute to Maria Callas. *Brain Cogn* 2011;76:146-157.
- 108 Miu AC, Baltes FR: Empathy manipulation impacts music-induced emotions: a psychophysiological study on opera. *PLoS One* 2012;7:e30618.
- 109 Suda M, Morimoto K, Obata A, et al: Emotional responses to music: towards scientific perspectives on music therapy. *Neuroreport* 2008;19:75-78.
- 110 Ro T, Friggel A, Lavie N: Musical expertise modulates the effects of visual perceptual load. *Atten Percept Psychophys* 2009;71:671-674.
- 111 Green CM BP, Soto D: Interplay between affect and arousal in recognition memory. *PLoS One* 2010;5:e11739.
- 112 Pereira MA, Barbosa MA: Teaching strategies for coping with stress: the perceptions of medical students. *BMC Med Educ* 2013;13:50.
- 113 Palmer SE, Griscorn WS: Accounting for taste: individual differences in preference for harmony. *Psychon Bull Rev* 2013;20:453-461.
- 114 Koelsch S: A neuroscientific perspective on music therapy. *Ann NY Acad Sci* 2009;1169:374-384.
- 115 Brattico E, Bogert B, Jacobsen T: Toward a neural chronometry for the aesthetic experience of music. *Front Psychol* 2013;4:206.
- 116 Brattico E, Pearce M: The neuroaesthetics of music. *Psychology of aesthetics, creativity and the arts. Neuroaesthet Cogn Neurobiol Aesthet Exp* 2013;7(special issue):48-61.