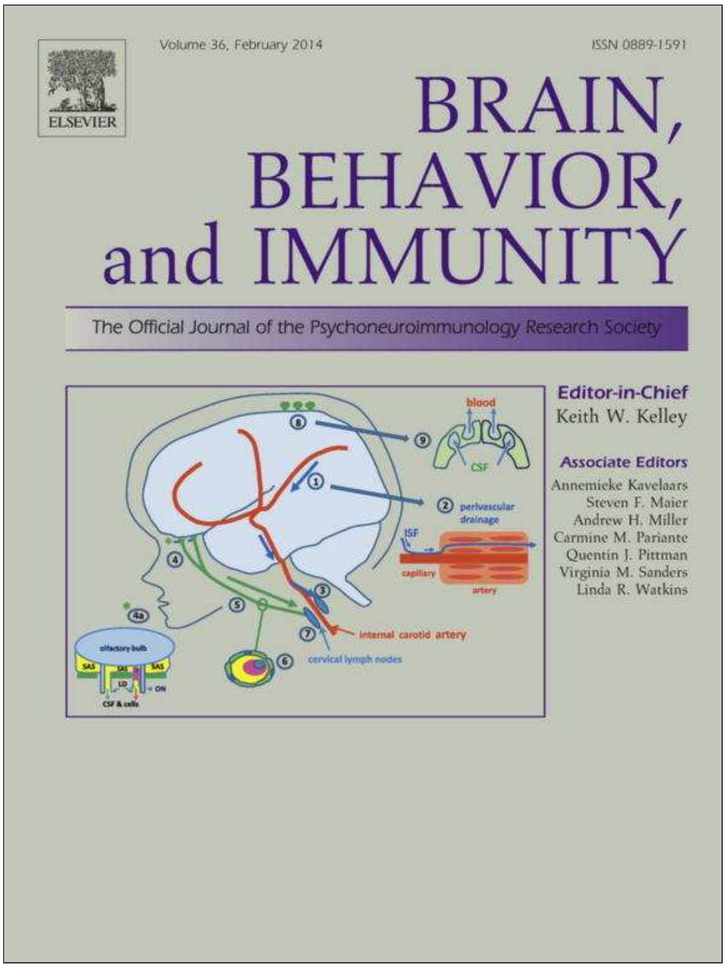
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Full Length Review

The psychoneuroimmunological effects of music: A systematic review and a new model

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ABSTRACT

There has been a growing interest over the past decade into the health benefits of music, in particular examining its psychological and neurological effects. Yet this is the first attempt to systematically review publications on the psychoneuroimmunology of music. Of the selected sixty-three studies published over the past 22 years, a range of effects of music on neurotransmitters, hormones, cytokines, lymphocytes, vital signs and immunoglobulins as well as psychological assessments are cataloged.

Research so far points to the pivotal role of stress pathways in linking music to an immune response. However, several challenges to this research are noted: (1) there is very little discussion on the possible mechanisms by which music is achieving its neurological and immunological impact; (2) the studies tend to examine biomarkers in isolation, without taking into consideration the interaction of the biomarkers in question with other physiological or metabolic activities of the body, leading to an unclear understanding of the impact that music may be having; (3) terms are not being defined clearly enough, such as distinctions not being made between different kinds of stress and 'music' being used to encompass a broad spectrum of activities without determining which aspects of musical engagement are responsible for alterations in biomarkers.

In light of this, a new model is presented which provides a framework for developing a taxonomy of musical and stress-related variables in research design, and tracing the broad pathways that are involved in its influence on the body.

1. Introduction

Research into the health benefits of music has rapidly expanded over the last decade, driven both by a desire to understand more about the inner workings of music on the brain and body and in order to see how music can be better applied in community, educational and, in particular, healthcare settings (MacDonald et al., 2012). The scientific study of music has gradually probed deeper into the mechanisms underlying the perception and processing of music, exploring the psychology of music (Hallam et al., 2008) and the cognitive neuroscience of music, sometimes referred to as 'neuromusicology' (Peretz and Zatorre, 2003). This depth of enquiry has included the neurological basis for music-induced emotions (e.g. Trainor and Schmidt, 2003; Juslin, 2009), the neurobiology of certain aspects of music such as harmony (e.g. Tramo et al., 2003) and the neuroanatomy of music performance (Parsons, 2003). And breadth of study has ranged from the perception of folk songs inside the womb (Lemos et al., 2011), to the performance of opera on concert platforms (Kenny et al., 2004), and the use of pop music in operating theatres (Pluyter et al., 2010).

Recently, there has been interest in the chemical and biological effects music, summarized in two reviews. Chanda and Levitin (2013) presented an overview of the neurochemical effects of music, in which they made reference to immunological changes. Their research has gained attention in the popular press as apparent evidence that music can boost the immune system and hold the key to wellbeing. However, their overview was not systematic and due to the focus specifically on neurochemical responses, it only reviewed half the studies pertaining to the psychoneuroimmunology of music and referred to a third of the immune biomarkers that have been tested with respect to music.

A second recent article, (Kreutz et al., 2012), overviewed the psychoneuroendocrinological effects of music in order to test the assumption 'that psychological processes associated with musical experiences lead to changes in the hormonal systems of brain and body' (Kreutz et al., 2012, p. 457); something they label as 'perhaps one of the most fascinating areas of future research'

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(Kreutz et al., 2012, p. 471). But as with the study by Chanda and Levitin (2013), their overview was not systematic and examines the impact of music on just five biomarkers (cortisol, oxytocin, testosterone, beta-endorphin and immunoglobulin A). And neither study discussed parallel physiological or psychological findings. This led Kreutz et al. (2012, p. 471) to conclude that 'much more research efforts should be undertaken to ascertain the emerging patterns of changes that were reported in the available literature'.

Consequently, a comprehensive systematic review into music and psychoneuroimmunology is timely. This would aim to consolidate key findings to date, compare theories concerning the mechanisms behind music's effect, and highlight gaps in current knowledge, helping to guide the focus of future studies. In particular, a systematic review could identify any challenges currently hindering the progress of research and, by presenting a new model, help overcome these obstacles.

As the term 'music' can be used broadly to refer to the materials and approaches used in a number of different interventions, it is relevant to define some of its parameters more specifically. This is because the style of music, the way it is delivered and personal attitudes to it may be crucial variables with the potential to alter psychoneuroimmunological responses. So as well as discussing these variables in relation to specific studies, it is useful for clarification to set them out up front.

The degree of involvement of a participant in music can vary substantially. Passive involvement may consist of a participant sitting in silence to listen to either live or recorded music. Active involvement can range from music education (such as instrumental lessons), to participatory sessions (such as group workshops), to therapy (where music is used as a tool for communicating thoughts or emotions) (Ockelford, 2013). The music used in any of these interventions can be compositions in a wide range of genres (including classical, jazz or popular), specially composed (such as designer relaxation music) or improvised in different styles. It can be selected either by participants or investigators. Some music may be arousing, involving faster tempi, louder volume and disjunct melodic patterns. Other music may be inherently calming, involving slower tempi, a quieter volume and more even patterns (Scherer and Zentner, 2001).

Music can also influence our brains and bodies in different ways: aurally, via direct auditory perception; physically, through the movements of muscles and sensory experience of vibrations involved in the production and reception of music; socially, as many musical activities can bring with them additional psychosocial experiences such as increases in confidence, social participation and self-esteem; and personally, as music will be approached differently by each individual, depending on whether they like or dislike the music; whether they are familiar with the style, genre or work; or whether they feel any particular emotional connection to it (Juslin et al., 2001).

The effects of music will vary enormously depending on how it is employed. Consequently, it is necessary to be rigorous in identifying which of its features are responsible for sensitive psychological and biological changes. In light of this, more details on the nature of interventions are given when discussing the studies included in this review.

2. Methods

To assess the current state of research on the interactions between music and psychoneuroimmunology, systematic database searches were conducted of Cochrane, Web of Science, PubMed, PsychINFO, Science Direct and Sage Journals, as well as manual searches of personal libraries. These sources were chosen as they were felt to give a comprehensive overview of the subject area, including in their compass journals from the disciplines of psychology, immunology, music therapy, music psychology, neuroscience, medicine, life sciences, social sciences and nursing, among others. Searches were made using the keyword 'music' paired with other keywords pertaining to psychoneuroimmunology, including 'immune', 'psychoneuroimmunology', 'endocrinology', 'cortisol', 'cytokine(s)', 'lymphocyte(s)', 'immunoglobulin(s)', and 'interleukin(s)'. The search returned 1938 articles, ranging from 1953 to 2013. After removing 567 duplicate studies, a total of 1371 studies remained. (see Fig. 1).

Titles, abstracts and keywords were considered, and selection for inclusion in the review was made on the basis of five criteria. First, articles had to pertain to a new study. Reviews were read for their references which brought to light some additional relevant studies to be considered, but were not included themselves. Second, studies had to be controlled in order that the significance of alterations in biomarkers could be accurately assessed. Third, studies pairing music simultaneously with other stimuli such as exercise, progressive relaxation or guided imagery were only included if they also contained a test incorporating just music on its own, as it was felt that the other stimuli could confound results. Fourth, studies had to be testing for potential positive effects of music, even if their results were negative or nonsignificant. Studies were excluded if they deliberately tried to cause negative responses or distress through the use of noise, loud volumes or heavy beats. Finally, it was decided that studies involving animals rather than humans should be omitted from the review. Although working with animals can enable highly controlled trials to be undertaken and address specific research questions, as advocated by Rickard et al. (2005), even they acknowledge that extrapolating results from animal studies back to humans carries a number of limitations. Overall, this search was 'data-driven' in that a large number of keywords were included to identify a broad spectrum of studies, which were then scrutinized more closely against the inclusion criteria to assess their relevance to this review.

The selected studies that satisfied these criteria were then reviewed in full for key information including year of publication, country of origin, study design, sample size, biomarkers monitored, genre of music used, mode of music delivery, and depth of immunological discussion. There was a great deal of variation in the methods applied in these studies. In light of this, it was decided

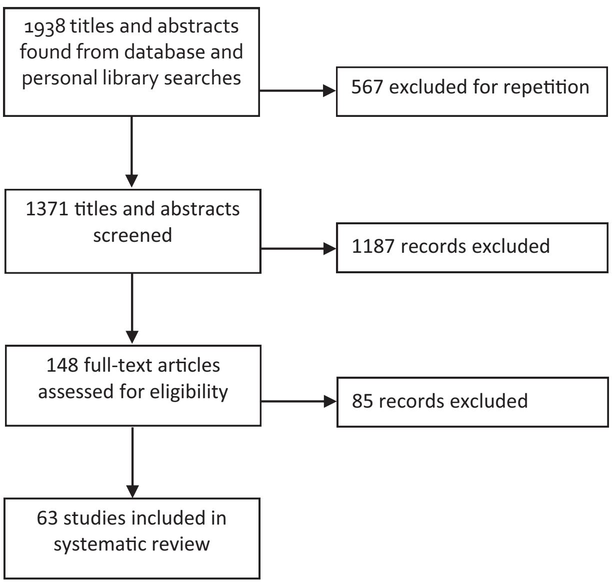

Fig. 1. Collection of studies for inclusion in systematic review.

that a meta-analysis aggregating the results of these studies was not possible, and instead a qualitative approach to assessing their findings was deemed to be more appropriate.

3. Results

We identified sixty-three studies for inclusion in this review, published from 1989 to 2013. This includes studies from North America ($n = 19$), Europe ($n = 18$), Asia ($n = 21$) and Australasia ($n = 1$) as well as four collaborative international studies. Despite some controversy about whether complementary therapies (such as music) should be tested in randomized controlled trials (as discussed by Mason et al., 2002) this review demonstrates a general willingness among researchers to follow scientific trial protocols, so in addition to all of the studies included in the review having control groups, forty-one studies were randomized. The psychological, neurological and immunological findings of these studies are broken down below.

3.1. Psychological responses

Twenty-eight of the studies in this review considered psychological responses to music, with twenty-five studies using validated psychological tests, five using self-report from participants, and two employing both methods. Twenty-one different psychological scales were used within the articles, with state-trait anxiety inventory (STAI) appearing most often, included in a quarter of psychological studies ($n = 7$). Six of the studies employed more than one psychological test, which gave a more comprehensive overview of the impact of music on participants.

Of the twenty-five studies involving psychological tests, twenty-two achieved statistical significance and found that psychological results aligned with results from biomarkers, such as that by Ventura et al. (2012), which found a parallel decrease in both state and trait anxiety scores and cortisol levels when listening to relaxing recorded music. Only three studies showed a lack of correlation between psychological and biological testing (Bittman et al., 2001; Field et al., 1998; Hirokawa and Ohira, 2003).

Only one of the studies selected involved a follow-up investigation to see whether changes in psychological state persisted in the weeks following an intervention. Sakamoto et al. (2013) showed promising evidence of the sustained impact of music, finding that improvements in the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) persisted for 3 weeks following the end of a 10-week intervention where patients listened to recorded music selected from memorable periods in their lives.

3.2. Physiological responses

Twenty studies reported recording vital signs including blood pressure, heart rate and respiratory rate. In nine of these, these were the only physiological measurements used. Several studies, including Sakamoto et al. (2013), used measurement of vital signs as evidence of a switch from sympathetic to parasympathetic systems, equating a change in immune function with a broader stress response (see Section 4.2). Relaxing music was shown to decrease blood pressure, heart rate and respiration rate in sixteen studies. Only four studies found no conclusive change.

Both valence and arousal of the music were found to be important variables. Sandstrom and Russo (2010) compared recorded music of four different tempi and moods, but only found a reduction in heart rate for peaceful, low tempo music. Yamamoto et al. (2007) found that although heart rate was decreased a little by high tempo music during a stressful task, there was a much greater effect with low tempo music. Respiratory rate was only decreased by low tempo music. Bernardi et al. (2006) found that when comparing six different tempo piece of music, blood pressure was not changed by calming music but was increased by fast tempo music.

Studies that incorporated more complex controls produced the most convincing results. For example, (Kibler and Rider (1983) reported that listening to Mozart had more of an impact on vital signs than a progressive relaxation session, and Berbel et al. (2007) found listening to relaxing recorded music to be as effective as diazepam in reducing vital signs of anxiety.

Three studies reported physiological measurements other than cardiac response, two of which achieved statistical significance. Sandstrom and Russo (2010) and Yamamoto et al. (2007) compared skin conductance levels before and after exposure to music. Sandstrom and Russo (2010) found a decrease in skin conductance, associated with a decrease in sympathetic stimulation, following peaceful music, but no change for agitated, happy or sad music. Yamamoto et al. (2007) found that skin conductance increased less in a group exposed to low-tempo music following a stressful situation than a group exposed to high-tempo music.

3.3. Neurological responses

This review revealed a total of fifteen studies examining neurological response to music [see Table 1]. McKinney et al. (1997) examined the effect of music on the opioid peptide neurotransmitter beta-endorphin, noting a decrease in response to relaxing recorded music. The same style of music produced an increase in mu-opiate receptor in a study by Stefano et al. (2004).

The monoamine neurotransmitters epinephrine and norepinephrine were tested in twelve studies. Seven of these reported no change in response to recorded music, including Hirokawa and Ohira (2003), who also found no change in levels of dopamine, another monoamine neurotransmitter, nor other biomarkers (see Section 3.5.1). However, three studies involving relaxing recorded music found a decrease in epinephrine and norepinephrine. And the same result was noted by Okada et al. (2009) in response to music therapy.

3.4. Endocrinological responses

A total of thirty-two studies examined the effect of music on hormones [see Table 2]. Of these twenty-nine included measurements of cortisol. Among these studies there was a general consensus that music reduced levels of cortisol ($n = 18$), whether through active participation or listening to recorded music. Only two studies noted the opposite tendency, (Escher et al., 1993; Uedo et al., 2004), but in both cases the increase in the music group was less than the increase in the control group. Escher et al. (1993) found that this pattern in cortisol was mirrored in their readings of adrenocorticotropic hormone levels; a smaller increase in the music group compared to the control group.

When investigators selected the music on behalf of participants, the majority of studies involving cortisol focused on the effects of relaxing music ($n = 11$). However, there were four studies that explored the effects of stimulating music, which produced conflicting results. Mockel et al. (1995) found a parallel decrease in cortisol for both relaxing and stimulating music, whereas Yamamoto et al. (2007) only found a decrease for relaxing music, and Gerra et al. (1998) actually found an increase for stimulating music. This last result was mirrored in the response of growth hormone and adrenocorticotropic hormone measured in the study, along with a similar response from epinephrine, which increased on exposure to stimulating music but was unchanged in response to relaxing music. These results demonstrate an apparent sensitivity of hormones to musical stimulation. More research will, however,

Table 1
Neurological responses to music.

Study	Activity details	E	NE	Dopamine	β-End	MOR
Active participation						
Okada et al. (2009)	Music therapy	↓	↓			
Recorded music – participant-selected (various styles)						
Wang et al. (2002)		–	–			
Lin et al. (2011)	(From a list)	–	–			
Chlan et al. (2007)	(From a choice of genres)	–	–			
Migneault et al. (2004)	(From a choice of genres)	–	–			
Schneider et al. (2001)	(From choice of genres)	–	–			
Mockel et al. (1995)	(From choice of genres)	↓ –[b]	↓ –[b]			
Escher et al. (1993)	(With a music therapist)	–	–			
Recorded music – experimenter-selected (relaxing)						
Conrad et al. (2007)		↓	–			
Brunges and Avigne (2003)		↓				
Stefano et al. (2004)						↑
McKinney et al. (1997)					↓	
Recorded music – experimenter-selected (stimulating)						
Field et al. (1998)						
Gerra et al. (1998)	Stimulating vs sedative	↑ –[a]	–		–	
Hirokawa and Ohira (2003)	Stimulating vs sedative	–	–	–		

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Dashes indicate no significant change. Blank fields indicate that the biomarker was not investigated. *Abbreviations:* E, Epinephrine; NE, Norepinephrine; β-end, beta-endorpin; MOR, μ-opiate receptor.
[a] The experimenters only found an increase with stimulating, not sedative music.
[b] The experimenters found a decrease with sedative but no change for stimulating music.

be needed to clarify which musical variables are responsible for the alterations in biomarkers.

Another variable in cortisol studies – patient vs experimenter selected music – was tested in only one study, (Leardi et al., 2007), which suggested that cortisol was most responsive to participant-selected music. However, as this is the only study considering this variable with cortisol, further studies would be needed to validate this finding.

Of the other hormones tested, Nilsson (2009) found an increase in oxytocin when participants listened to relaxing recorded music. Bittman et al. (2001) found an increase in the dehydroepiandrosterone-to-cortisol ratio when participants took part in group drumming, whilst Conrad et al. (2007) found a decrease when patients listened to relaxing recorded music, along with an increase in growth hormone. When participants selected their own recorded music, Migneault et al. (2004) found an increase in testosterone for men, but a decrease for women. There were no significant changes in the other four biomarkers tested in this study, which included cortisol, adrenocorticotropic hormone, epinephrine and norepinephrine. The study by Suzuki et al. (2005) found that music therapy sessions decreased levels of chromogranin A, which was accompanied by an immune response (see Section 3.5c).

3.5. Immunological responses

3.5.1. Leukocytes

Six studies examined the effect of music on leukocytes [see Table 3a]. Bittman et al. (2001) found that natural killer cells increased, which was accompanied by an endocrine response (see Section 3.4) when participants took part in stimulating group drumming sessions. In contrast, Leardi et al. (2007) found that for relaxing recorded music, natural killer cell levels decreased, with the most marked results noted when patients selected their own music. Cai et al. (2001) found that participatory music therapy sessions prevented levels of natural killer cells along with CD4+ T cells, CD3, and the ratio of CD4 to CD8 cells from dropping.

Other tests measuring numbers of CD4 and CD8 cells were carried out by Hirokawa and Ohira (2003) and Staricoff et al. (2002). Stimulating recorded music, studied by Hirokawa and Ohira (2003), was found to increase levels of CD4+ T cells in plasma. But there were no significant results noted for CD8+ T cells, nor a range of other leukocyte and endocrine measurements. On the other hand, Staricoff et al. (2002) found that levels of CD4+ T cells did not rise high enough to achieve significance, but CD8+ T cells did in the presence of live music. Koyama et al. (2009) found an increase in CD4+ T cell counts among older adults who took part in group drumming workshops, along with an increase in lymphocyte and memory T cell counts (and other immune biomarkers; see Section 3.5.2), but these results were not found in younger adults.

3.5.2. Cytokines

Eight studies reported the investigation of cytokines [see Table 3b], although Lai et al. (2013) found no results due to the breakdown of cytokines in plasma before they could be analyzed. Of the remaining seven studies, interleukin-6 showed the greatest levels of responsiveness, changing significantly in four out of the five studies in which it was tested. Okada et al. (2009) and Conrad et al. (2007) both found a reduction in response to music therapy sessions and relaxing recorded music respectively. Both studies also found the same changes as each other in neurotransmitters (see Section 3.3). A decrease in interleukin-6 was also found by Stefano et al. (2004) among older adults exposed to relaxing recorded music. Although there were no significant changes found in this study for interleukin-1-beta or interleukin 10, there was a neurological biomarker change reported (see Section 3.3). The fourth decrease in interleukin-6 was found by Koyama et al. (2009) during group drumming exercises. But this was only found in younger adults. For older adults, it increased, along with increases in levels of interferon-gamma, and was accompanied by a significant leukocyte response (see Section 3.5.1). However, for this same study levels of interleukins 2, 4 and 10 remained unchanged in participants of all ages (Koyama et al., 2009).

Among other cytokine responses, Bartlett et al. (1993) found an increase of interleukin-1 when patients selected their own recorded music, which was matched by an endocrine response (see Section 3.4). And Kimata (2003) found that the music of Mozart down-regulated levels of interleukins 4, 10 and 13 (Th2 type cytokines) and up-regulated levels of interferon-gamma and interleukin-12 (Th1 type cytokines) in patients undergoing an allergic

Table 2
Endocrinological responses to music.

Study	Activity details	CORT	ACTH	CRH	DHEA	PRL	GH	OT	Test	CgA
Active participation										
Bittman et al. (2001)	Group drumming				↑[b]					
Lindblad et al. (2007)	Instrumental music lessons	↓								
Suzuki et al. (2005)	Music therapy									↓
Recorded music – participant-selected (various styles)										
Chlan et al. (2012)		–								
Lai and Li (2011)		↓								
Wang et al. (2002)		–								
Milukkolasa et al. (1994)		↓								
Bartlett et al. (1993)		↓								
Lin et al. (2011)	(From a list)	–								
Schneider et al. (2001)	(From choice of genres)	^								
Chlan et al. (2007)	(From a choice of genres)	–		–[a]						
Mockel et al. (1995)	(From choice of genres)	↓[f]								
Migneault et al. (2004)	(From a choice of genres)	–	–						↓↑[c]	
Ventura et al. (2012)	(From choice of genres)	↓								
Leardi et al. (2007)	(From choice of genres vs new age)	↓[g]								
Escher et al. (1993)	(With a music therapist)	↑[e]	↑[e]							
Recorded music – experimenter-selected (relaxing)										
Nilsson et al. (2005)		↓								
Uedo et al. (2004)		↑[e]								
Nilsson (2009)		↓								
Nilsson (2009)								↑		
Khalfa et al. (2003)		↓								
Tabrizi et al. (2012)		^								
Conrad et al. (2007)		–	–		↓	–	↑			
Knight and Rickard (2001)		↓								
Kar et al. (2012)		↓								
Urakawa and Yokoyama (2004)		–								
Fukui and Yamashita (2003)		↓								
Berbel et al. (2007)		↓								
Recorded music – experimenter-selected (stimulating)										
Koelsch et al. (2011)		↓	–							
Field et al. (1998)		↓								
Yamamoto et al. (2007)	Stimulating vs sedative	↓[h]								
Gerra et al. (1998)	Stimulating vs sedative	↑↓[d]	↑↓[d]			–	↑↓[d]			

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Arrows (v or ^) indicate that without music (i.e. in control groups), levels decreased or increased, but with music levels remained constant. Dashes indicate no significant change. Blank fields indicate that the biomarker was not investigated. *Abbreviations:* CORT, Cortisol; ACTH, Adrenocorticotropic Hormone; CRH, Corticotropin-releasing Hormone; DHEA, Dehydroepiandrosterone; PRL, Prolactin; GH, Growth Hormone, OT, Oxytocin; Test, Testosterone; CgA, Chromogranin A.
[a] The experimenters found an increase, but it was not significant.
[b] The experimenters found an increase in the DHEA-cortisol ratio.
[c] The experimenters found an increase for men and a decrease for women.
[d] The experimenters found an increase with stimulating music and decrease with sedative music.
[e] The experimenters found increase, but it was less in the music group than the control group.
[f] The experimenters found a decrease for both stimulating and relating music.
[g] Although cortisol levels decreased in both groups compared to controls, the experimenters found a significantly greater decrease in the group where patients selected their music from one of four styles compared to the group who listened to new age music.
[h] The experimenters found a decrease only following low tempo music.

response. These cytokine patterns were in direct contrast to the direction of up- and down-regulation noted when these patients were made more stressed. In the presence of the more stimulating music of Ludwig van Beethoven and Franz Schubert, reported relaxation was lower and immunological results were not significant (Kimata, 2003).

3.5.3. Immunoglobulins and other immune responses

Thirteen studies examined the effect of music on immunoglobulins [see Table 3c]. Immunoglobulin A (IgA) was the most researched antibody ($n = 12$). Of these studies, eight reported an increase in the level of IgA following a range of musical interventions with a wide variety of styles and genres. Only one study showed a significant decrease in IgA levels (Nomura et al., 2004). It is notable that this study also reported an increase in IgA following a stressful task; the opposite of the anticipated reaction. As these results have not been replicated, there is a need for further investigation. IgA increases were found to be greatest when music was liked and when participants were actively involved in its production (McCraty et al., 1996; Kuhn, 2002).

Two studies investigated music and allergy response. Following consumption of allergenic food, music was found to reduce levels of histamine release (Kejr et al., 2010). And for patients experiencing a reaction to latex, Kimata (2003) found that the music of Mozart reduced levels of immunoglobulin E. The author attributes this reduction to a broader decrease in stress response inferred from cytokine measurements (see Section 3.5.2).

4. Discussion

4.1. Findings

The aim of this review was to assess systematically the published studies dealing with the psychoneuroimmunological effects of music. The findings of these studies revealed that there are some markers which have now been studied in depth, allowing us to

Table 3a
Immunological responses to music: leukocytes.

Study	Activity details	NK	CD4+ T	CD8+ T	CD4/CD8 ratio	CD16	CD3	lymphocytes	Memory T
Active participation									
Bittman et al. (2001)	Group drumming	↑							
Koyama et al. (2009)	Group drumming		↑[a]					↑[a]	↑[a]
Cai et al. (2001)	Music therapy	v	v		v		v		
Live music – experimenter-selected (various styles)									
Staricoff et al. (2002)			–	↑					
Recorded music – participant-selected (various styles)									
Leardi et al. (2007)	(From choice of genres vs new age)	↓[c]							
Recorded music – experimenter-selected (stimulating)									
Hirokawa and Ohira (2003)	Stimulating vs sedative	–	↑ –[b]	–		–			

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Arrows (v or ^) indicate that without music (i.e. in control groups), levels decreased or increased, but with music levels remained constant. Dashes indicate no significant change. Blank fields indicate that the biomarker was not investigated. *Abbreviations:* NK, Natural Killer cell count; CD4+ T, T helper cells; CD8+ T, cytotoxic T cells.
[a] The experimenters found an increase only in older, not younger patients.
[b] The experimenters found an increase only for stimulating music, not sedative.
[c] Although cortisol levels decreased in both groups compared to controls, the experimenters found a significantly greater decrease in the group where patients selected their music from one of four styles compared to the group who listened to new age music.

Table 3b
Immunological responses to music: cytokines.

Study	Activity	IL-1	IL-1-beta	IL-2	IL-4	IL-6	IL-10	IL-12	IL-13	IL-γ	TNF-α	IFN-γ
Active participation												
Bittman et al. (2001)	Group drumming			–						–		
Koyama et al. (2009)	Group drumming			–	–	↑↓[d]	–					↑
Okada et al. (2009)	Music therapy					↓						
Recorded music – participant-selected (various styles)												
Bartlett et al. (1993)		↑										
Recorded music – experimenter-selected (relaxing)												
Conrad et al. (2007)						↓						
Stefano et al. (2004)			–			↓ –[b]	–					
Kimata (2003)					↓[a]		↓[a]	↑[a]	↓[a]			↑[a]
Recorded music – experimenter-selected (stimulating)												
Lai et al. (2013)	Stimulating vs sedative					[c]	[c]				[c]	

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Dashes indicate no significant change. Blank fields indicate that the biomarker was not investigated. *Abbreviations:* IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma.
[a] The experimenters found results only in the presence of music by Mozart, not Beethoven.
[b] The experimenters found a decrease in older adults, not younger adults.
[c] The experimenters found tried to test 3 interleukins, but levels were all undetectable in the plasma due to breakdown.
[d] The experimenters found an increase for older adults and a decrease for younger adults.

Table 3c
Immunological responses to music: other immune responses.

Study	Activity	IgA	IgE	Histamine
Active participation				
Suzuki et al. (2005)	Music therapy	↑		
Lane (1994)	Music therapy	↑		
Kuhn (2002)	Singings vs listening to singing	↑[a]		
Recorded music – participant-selected (various styles)				
McCraty et al. (1996)	(From choice of genres)	↑ – [b]		
Recorded music – experimenter-selected (relaxing)				
Nilsson et al. (2005)		–		
Urakawa and Yokoyama (2004)		↑		
Knight and Rickard (2001)		↑		
Kimata (2003)			↓	–
Kejr et al. (2010)		–		↓
Nomura et al. (2004)		↓		
Charnetski et al. (1998)		↑		
Recorded music – experimenter-selected (stimulating)				
Koelsch et al. (2011)		↑		
Hirokawa and Ohira (2003)	Stimulating vs sedative	–		

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Dashes indicate no significant change. Blank fields indicate that the biomarker was not investigated. *Abbreviations:* IgA, Immunoglobulin A; IgE, Immunoglobin E.
[a] The experimenters found the increase to be greater for active rather than passive involvement.
[b] The experiments found an increase when the music was liked, but no change if patients disliked it.

note consistent patterns. Immunoglobulin A has been revealed to be particularly responsive to music, increasing following exposure to a range of styles of music, including both relaxing and stimulating music, as well as for both active involvement and simply listening to recorded music. Similarly, strong patterns can be noted with respect to cortisol, which repeatedly decreases in response to relaxing recorded music. There also appear to be patterns in the response of epinephrine and norepinephrine, which have been shown to decrease in response to relaxing recorded music. However more studies will be needed to confirm this pattern as other studies have not managed to achieve statistical significance.

With regards to participant vs experimenter-selected music, changes are being noted in studies involving either scenario, suggesting that immune response is not entirely dependent on personal choice. However, two studies have demonstrated greater responses when participants selected their own music (Leardi et al., 2007 and McCraty et al., 1996 for cortisol and immunoglobulin A respectively). Similarly, there have not been clear differences in immune responses to stimulating vs relaxing music yet. Where studies have compared responses, there have been some preliminary suggestions that stimulating music can cause the reverse reactions to relaxing music in certain biomarkers (e.g. Yamamoto et al., 2007; Gerra et al., 1998; Hirokawa and Ohira, 2003). But this will need to be isolated in studies to ascertain the true significance of this variable, as studies so far have not only changed the tempo of the music to distinguish between stimulating and sedative music, but have actually employed completely different genres of music which brings with it a conflicting variable of personal taste (e.g. Gerra et al., 1998, testing techno vs classical music), the influence of which has not yet been properly examined.

A final point of interest is that changes have been observed across various biomarkers of immune response, including leukocytes, cytokines and immunoglobulins, as well as hormones and neurotransmitters associated with immune response. This pervasive influence of music highlights that there is still much more to be explored as the vast majority of hormones, neurotransmitters and immune cells that are possibly involved in music-activated endocrine and immune pathways have yet to be examined. Overall, the trend towards positive findings of the effect of music on psychoneuroimmunological response strongly supports further investigation in this field.

4.2. Music, psychoneuroimmunology and stress

Another intriguing pattern that has emerged from this research is that fifty-six of the sixty-three studies included in this review discussing the psychoneuroimmunological effects of music linked this to stress response. Stress is certainly a central area of research in psychoneuroimmunology. A major meta-analytic study by Segerstrom and Miller (2004) drew together over 30 years of research and helped to consolidate key findings, modeling pathways between stress and the immune system and cataloguing the effects of different types of stress on immune biomarkers. In considering the significance of stress on health, Cohen et al. (2007) have since linked it to the onset and progression of chronic diseases such as cancer. In exploring counterbalances to the effects of stress, Esch et al. (2003) have outlined the molecular mechanisms underlying the efficacy of relaxation to demonstrate its significance in the treatment of stress-related diseases.

Evidence of the use of music as a method of stress relief exists from 4000 BC and is estimated to stretch back as far as Palaeolithic times (West, 2000), and many people turn to music to alleviate their stress without feeling the need for scientific reasoning. But in recent decades, music has begun to be taken seriously in healthcare settings as research findings have started to link the beneficial effects of music on stress to a wider effect on health (Haake, 2011). Many of the studies included in this review link the psychoneuroimmunological effects of music into this larger dialogue on music and stress.

Indeed, music and stress have been the subject of several systematic reviews, (e.g. Avers et al., 2007; Austin, 2010; Dileo, 2008). However, the knock-on implications that a reduction of stress can have on immune function are clearly not a part of the mainstream dialogue on music and stress, as none of these reviews even mentioned immune response. Consequently, the links that the articles in this review are making are important in their contribution to the literature not just on music and psychoneuroimmunology but also music and stress. In particular a few articles stand out for their particularly insightful examinations of the stress pathways and mechanisms involved in psychoneuroimmunological response to music.

For example, an interesting debate is between the theories of Bittman et al. (2005) and both Conrad et al. (2007) and Tabrizi et al. (2012). Bittman et al. (2005) argue for an approach to stress response that considers each individual as being unique: instead of specific genes being up- or down-regulated in response to stress or relaxation, all humans will have their own unique genetic response to situations. The authors explain, "this assumption challenges the notion that the human stress response is characterized by the uniform modulation of each gene in a specific direction" (Bittman et al., 2005, p.39). They demonstrate their theory through showing different alterations in genetic stress response from thirty-two participants all involved in group recreational music making.

In contrast, both Conrad et al. (2007) and Tabrizi et al. (2012) propose neurohumoral stress pathways common to all humans in response to relaxing recorded classical music. Focusing on growth hormone and cortisol respectively, they draw up maps detailing the influence that these hormones have within the body, and then test some of the biomarkers that should be affected if their theories are correct. Following relaxing recorded music interventions, both are then able to point to which path they believe is dominant within these maps, exerting the greatest impact on subsequent biomarkers, as well as identify which biomarkers are least affected, either due to a lack of force from the activating hormone or the interference of another hormone shutting off the system (Conrad et al., 2007; Tabrizi et al., 2012). A compromise between the theories of Bittman et al. (2005) and Conrad et al. (2007)/Tabrizi et al. (2012) seems the most likely reality, whereby certain pathways are often affected by stress or music-induced relaxation, but the sensitivity of these pathways and how quickly they are activated may depend on the individual. Alternatively, it could be that the pathways are common to all, but what constitutes the strength and type of stress or relaxation to switch them on and off differs between people; something that Bittman et al. (2005) concede may have affected their results.

Another interesting debate relating to music, stress and psychoneuroimmunology is between Han et al. (2010) and Koelsch et al. (2011) regarding cardiac responses. Han et al. (2010), claim that music reduces stress by working to entrain outer symptoms such as breathing and blood flow, which in turn lead up a chain of action and cause decreased sympathetic activity. This is a reversal of the normal 'top-down' sequence of events, as discussed by Koelsch et al. (2011), who argue that psychological effects of music are channeled through various neurological pathways such as the mesolimbic dopaminergic system and the central nucleus of the amygdala before they then exert an influence on hormones, cells and physiological measures such as blood pressure. The theories of Koelsch et al. (2011) are more commonplace, and Han et al. (2010) do not provide enough of a challenge to displace these dominant theories. However, if more can be explained about the neurological pathways that cause the entrainment of breathing and blood flow in response to music, perhaps we will discover that a bi-directional model is at play here: for example, whilst neurons are carrying messages through the brain and stimulating the release of neurotransmitters and hormones that activate the parasympathetic system, causing our heart rates to slow, it could also be that motor signals in the cortex are causing our heart rates to entrain, which helps us to switch from the sympathetic to parasympathetic systems, which switches off the release of catecholamines and inhibits their neurological feedback.

The studies in this review propose intriguing links between music, stress and psychoneuroimmunology which have the potential to change how music and stress are researched. Certainly, this is a promising avenue for future research, and it will be important to ascertain in future studies whether the psychoneuroimmunological effects of stress are always linked to stress pathways.

However, this discussion leads us onto some of the challenges to research into music and psychoneuroimmunology which can be noted from these articles. Given the growing interest in this topic evidenced by the number of articles written, it is pertinent to explore these challenges in approach and methodology to current research which are emerging from the literature and affecting studies in this field, to see how they can be addressed and future research facilitated. Three challenges in particular have been noted and will be discussed in more detail.

4.3. Challenges facing research

4.3.1. The mechanisms of music

Studies such as Bittman et al. (2005) Conrad et al. (2007), Tabrizi et al. (2012), Han et al. (2010) and Koelsch et al. (2011) are amongst a small minority that actually discuss precise pathways possibly involved in the psychoneuroimmunological response to music. Instead, this review has highlighted a general lack of discussion on the neuroimmunological mechanisms behind the effects of music. This could account for the confusion voiced by certain researchers, such as Gillen et al. (2008), who expressed skepticism about the 'adequacy of theories in this area' (Gillen et al., 2008, p.24). Only eighteen articles included in this review discuss the pathways by which music might have achieved its neurological and biological impact. Of these, two merely quote theories from other studies without using their results to expand the knowledge base (Kreutz et al., 2004; Lai and Li, 2011). And one contains non-specific theories, which are neither expanded nor tested (Stuhlmiller et al., 2003, which also contains a misquotation of Boso et al., 2006). Lai et al. (2013) propose a model of cytokine circuits in the body, but unfortunately cytokine levels were undetectable in the samples taken, which means they were unable to confirm or negate their theory. (It should be noted that their study is also not, as it claims, the first study of the effects of music on cytokines; see Conrad et al. (2007)). This leaves just fifteen articles, including the five already discussed, exploring the mechanisms behind music's impact, in varying levels of detail.

Moving forwards, future research should focus more on tracing some of these pathways, as it is new theories and insights into the mechanisms of music that drive understanding forward, as they give a deeper explanation of the effect of music on the brain and the immune system. This in turn helps both in considering the extent of the impact that music is able to have, and in guiding the design of music projects in healthcare settings to enable this impact to be felt to maximum effect.

4.3.2. Singular approaches

This challenge is possibly tied into another challenge regarding the way that the psychoneuroimmunological effects of music are being approached. Despite there being sixty-three studies into the effect of music on immune markers, only twenty-two of the articles actually discussed the immunological significance of the biomarkers being tested in any detail. Of the remaining studies, thirteen just referenced that the biomarkers they were testing were components of the immune system without any explanation of the significance of the biomarkers tested; how they are produced or what effects they have on the rest of the body. And twenty-eight other studies made no mention of immune function at all, and simply cited their biomarkers as stress markers.

As an example, this is clearly seen in discussions of cortisol, the most common biomarker investigated. Twenty-one of the twenty-nine studies in cortisol consider it without any reference to how it is produced in the body, what chain of events its increase or decrease triggers, or its impact on the immune system. It is simply cited as a stress hormone. These studies are clearly approaching cortisol from an angle of wanting to explore the impact of music on stress in more detail rather than from the angle of wanting to examine the psychoneuroimmunological effects of music. The studies are valid in their assessments and certainly contribute to our knowledge of music's stress-relieving properties. But by omitting any mention of the endocrine or immune systems, they fail to contextualize the full significance of their results.

A more in-depth understanding of the immune functions of different biomarkers would add another dimension to studies simply using them as a stress marker, as it would help to show the impact that a change in their levels can have on the body and highlight the importance of using music to achieve this effect. This could be facilitated by a greater awareness of the psychoneuroimmunological effects of music. Indeed, there is evidence that this is happening, as of the twenty-two articles that have explicitly explored the psychoneuroimmunological effects of music, sixteen have been within the last decade and ten of those within the last five years. And seventeen studies examined biomarkers on different levels (neurotransmitters, hormones, immune cells and chemicals) in conjunction. This is promising, since research of this nature demonstrates an understanding of the complex neurological processes required to produce an endocrinological or immunological effect and shows an increasing tendency towards a multidisciplinary approach to research in this field.

4.3.3. Definition of terms

A final but crucial challenge to future research is with regards to the way terms are being defined and tested. For example, where it is mentioned, stress is not always being precisely discussed. In particular distinctions are generally not being made between acute and chronic stress. This is despite the fact that these two types of stress can have very different effects on the immune system (e.g. Dhabhar and McEwen, 1997; Kudielka and Wüst, 2010), and despite the fact that research has demonstrated that the specific way stress is perceived (e.g. visual, sensory or auditory) and the method of coping used (e.g. active vs passive coping strategies) can alter biological response (Lei and Chen, 2009; Keay and Bandler, 2001). Future studies will need to take this into consideration in the formulation of their hypotheses and study design.

With regards to the way music is used in these studies, this review demonstrates a tremendous breadth of modes of musical intervention ranging from recorded music to live concerts, music therapy, individual music lessons and group workshops. However, there is a prevailing tendency in these studies simply to categorize the activity as 'recorded music' or 'music making', for example, as though the activity can be taken as a single entity. This approach means that the simple term 'music' is in fact hiding a number of key variables any one of which could be responsible for psychoneuroimmunolooical changes, such as musical content, physical engagement, social involvement and personal response.

Furthermore, a number of articles categorize activities incorrectly. For example, Conrad et al. (2007), Peng et al. (2009) and White (1992) among others apply the term 'music therapy' to the use of pre-selected recorded music. In fact, music therapy is defined by the World Federation of Music Therapy as psychotherapeutically oriented: 'the use of music and/or musical elements *by a qualified music therapist* with a client or group ... to facilitate and promote communication, relationships, learning, mobilization, expression, organization and other therapeutic objectives' (Wigram et al., 2002, p. 30, italics added).

Only four articles attempt to compare different modes of delivery. Kreutz et al. (2004) found a greater relaxation response when a choir actively sang a piece in contrast to simply listening to a recording of it. Both Lai et al. (2012a) and Burns et al. (2001) compared listening to recorded music with music therapy interventions, finding almost identical results between the two groups in terms of blood pressure and STAI, and immunoglobulin A and cortisol respectively. However, it is not known whether other biomarkers would have been affected differently. The most thorough comparison, carried out by Kuhn (2002), found significantly higher immunoglobulin A measurements for active participation rather than passive listening. She theorizes, in line with Bartlett et al. (1993), that, during active participation, the music produced takes on a more personal significance, triggering a greater emotional response and consequently greater endocrine changes.

Further studies comparing different forms of musical intervention could help to clarify the neurological pathways being activated, enabling researchers to trace the course of the psychoneuroimmunological response. Furthermore, if future studies carry out more thorough comparisons of the extent of the psychological and immunological effects of various music interventions (e.g. live vs recorded vs therapy vs education) against one another, this could have important implications for how health settings such as hospitals decide to implement music programs. If results continue to point towards active participation as the most effective, it may even help provide an incentive for the financial investment in participatory music interventions in healthcare settings.

5. A new model

This discussion highlights three challenges which may hinder research into the psychoneuroimmunology of music. As is evident, not all studies are facing all three challenges, and many are navigating between them very successfully. Nevertheless, it is suggested that a new model may be of use as a working framework for future research with the aim of helping more studies overcome potential methodological problems.

In light of the relatively few articles discussed in Section 4.2.1 that have proposed precise pathways connecting our perception and reaction to music, it would be premature to suggest a model that attempts to catalog in detail the relevant psychological, neurological and immunological mechanisms involved. Instead, the results of this review suggest that two things would be of benefit from this new model:

1. A way of giving more specific details of the variables involved in studies in terms of both the mode of music delivery and perception and the types of stress being experienced by participants.
2. A broader view of how systems including the nervous, endocrine, and immune systems interact when a person is exposed to music, encouraging studies to situate their findings within the context of the body, identify the systems involved, and consider the pathways and mechanisms being activated.

We would like to propose a model to serve these purposes, presented in Fig. 2. The connections drawn in this model have all been demonstrated in research studies (see notes to Fig. 2). However, because the model draws together information from a number of fields, these connections have not, to the authors' knowledge, been synthesized in a single diagram before. It is this synthesis that it is hoped will aid the design of future studies and facilitate the analysis of their results.

5.1. Independent variables

The model proposes that the inputs or variables of each study should be more specifically cataloged and terms such as 'music' and 'stress' need to be broken down.

There are two suggested categories for the types of stress experienced by participants in studies; either naturally-occurring or induced for the purposes of the study (Pastorino and Doyle-Portillo, 2011; Lamb, 1979):

- Psychological stress (including social, personal or environmental changes, daily/microstressors and ambient stressors).
- Physiological stress (both within the body, such as viruses and bacteria, and outside the body, including exercise, injury, surgery, changes in outside temperature, exposure to chemical's etc.).

These two categories are then further subdivided into acute and chronic stress, following research demonstrating a difference in biological effect (e.g. Dhabhar and McEwen, 1997; Kudielka and Wüst, 2010).

The model then proposes four different categories for how music can affect us (Peretz and Zatorre, 2003; Hallam, 2010; Hodges, 2008):

- The sound of music, as it is perceived by our auditory system. (Studies should specify key details that may be relevant, such as the tempo of pieces of music, their tonality and their instrumentation).
- Physical involvement (including the bodily actions required to produce the sound, as in singing or playing an instrument, as well as any strong musical vibrations that may have been perceived by participants).
- Social engagement (including whether participants socialized with others as part of the study, or reported an increase in confidence, pride or self-esteem).
- Personal response (including whether participants were familiar with the music; whether they liked or disliked it; or whether it elicited an emotional response).

5.2. Dependent variables

The central part of the model linking together various neurological, psychological and physiological systems draws on research in the field of psychoneuroimmunology from the last decade (references provided in the figure). In line with findings of Solomon (1987), among others, these links have been modeled as bidirectional. The aim of this part of the model is to facilitate the study of psychological, neurological and biochemical pathways involved in the processing of and response to music.

This could involve guiding the design of future studies to consider how music is being chosen and delivered to participants in studies and encourage the inclusion of a range of tests (both psychological and biological). It could also make it possible to compare whether specific systems within the body are particularly sensitive to the effects of music and allow researchers to compare which independent variables (stress and music) produce which results.

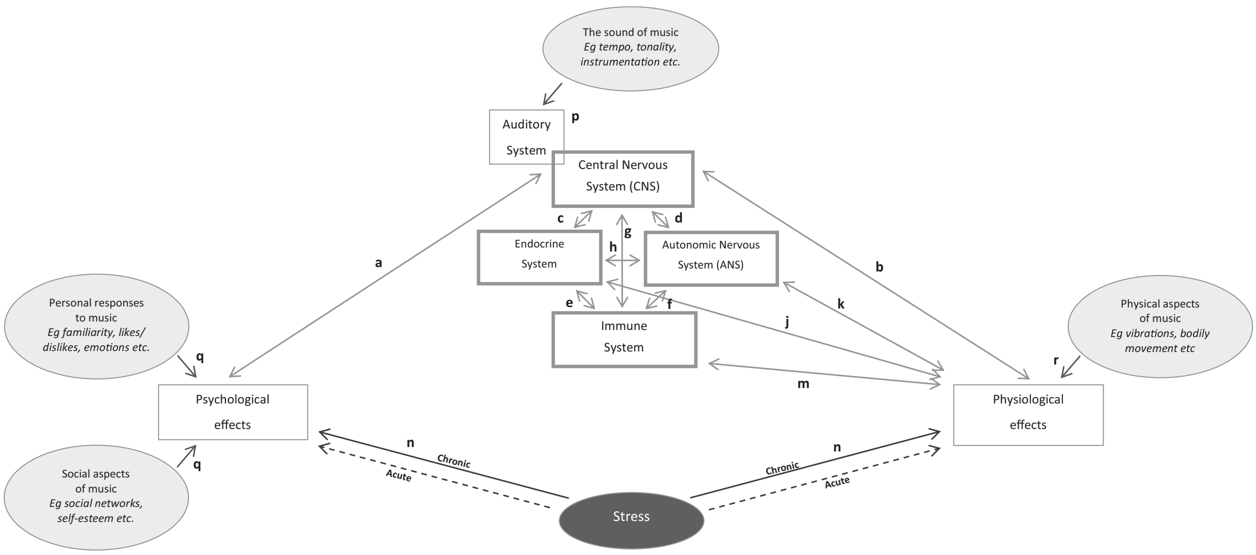

Fig. 2. A model of the system interactions involved in the psychoneuroimmunological response to music. *Note*: [a]Cacioppo and Decety (2009); [b]Andreassi (2013); [c] Asterita (1985); [d]Critchley (2005); [e]Besedovsky and Rey (1996); [f]Nance and Sanders (2007); [g]Sternberg (2006); [h]Ulrich-Lai and Herman (2009); [j]Turner (1994); [k]Jänig (1989); [m]Kelley (2004); [n]Lamb (1979); [p]Peretz and Zatorre (2003); [q]Hallam (2010); [r]Hodges (2008).

Sections 4.2.1 and 4.2.2 of this paper discussed

- The tendency among studies for music to be tested on specific individual biomarkers without a consideration of how this fits into the overall interactions between the systems.
- The limited number of papers examining in detail which pathways had caused biomarkers to be altered and how the alteration of each biomarker might have impacted on other biomarkers.

By providing a framework showing some of the broad interactions that have been discussed in the psychoneuroimmunology literature of the previous few decades, this model aims to encourage discussion in these two areas, suggest other systems and groups of biomarkers that it may be of value to researchers to test, and hopefully increase the literature in facets of music and psychoneuroimmunology that are currently understudied.

6. Conclusion

In 2002, Nunez et al. (2002, p. 1048) reported that there was 'little information on the immunological response to … music'. This paper has demonstrated a clear increase in such literature over the past decade (40 studies 2003–2013, compared to 22 between 1993 and 2003, and only 1 study prior to this). The effect of music on a number of biomarkers is now well established, and many studies on other biomarkers are demonstrating promising patterns that, it is hoped, will be clarified through further study. The important role played by stress pathways in producing an immune response to music has been highlighted by this study, and further research will hopefully give a clearer insight into which types of stress are most responsive to music and how musical variables can best be manipulated to reduce stress levels.

Three challenges facing the advancement of research into music and psychoneuroimmunology have been identified, and in light of this, a new model has been proposed to act as a framework for the design of future research and analysis of results. In line with this model, we recommend that future research should give clear descriptions of the types and length of stress experienced by study participants and the aural, physical, social and personal perception of the music involved; studies should consider groups of biomarkers in conjunction with one another in order to assess the knock-on effect that the alterations of hormones and immune cells have on each other and on the body; and studies should propose and test models of the psychological, neurological and immunological mechanisms causing these effects. This will hopefully provide a more comprehensive understanding of the influence of music.

Inevitably, there are limitations to this review. We have included all studies found to satisfy the selection criteria, regardless of whether their results were statistically significant or not, as identifying biomarkers that music cannot alter is also an important task. Nevertheless, there is a potential for publication bias towards positive results, which may mean that studies producing negative or inconclusive results have not been distributed, nor included in this review. Our findings should also be interpreted in light of the constraints we imposed on the present review. First, this review only considered new studies, so there are some articles theorizing on the mechanisms behind music's psychoneuroimmunological effects that have not been discussed. Nevertheless, it is hoped that as these theories become better known, they will be tested as part of future research projects. Secondly, every attempt was made in the keyword searches to find all studies relevant to this review. However, due to the diverse disciplines involved in psychoneuroimmunology, it is possible that studies examining some aspect of music's impact on the immune system confined themselves to a more discipline-specific vocabulary rather than including keywords associated with psychoneuroimmunology so were not brought to attention in the screening process.

Research into the psychoneuroimmunology of music has the potential to influence our holistic models of healthcare. If music is found to have a significant effect on the immune system's ability to fight disease, it will have a profound impact on its incorporation into healthcare settings including hospital waiting rooms; procedures such as surgery; and treatments such as chemotherapy and psychotherapy; as well as placing a larger significance and responsibility on our day-to-day consumption of music. This could not just affect the domain of medicine, but also the roles of musicians and the missions of arts organizations. It is hoped that by taking stock of previous research in this review, future studies will be aided and encouraged, increasing our insight into an intriguing field.

Conflict of interest statement

All authors declare that there are no conflicts of interest.

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