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The neurochemistry of music

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The neurochemistry of music

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Music is used to regulate mood and arousal in everyday life and to promote physical and psychological health and well-being in clinical settings. However, scientific inquiry into the neurochemical effects of music is still in its infancy. In this review, we evaluate the evidence that music improves health and well-being through the engagement of neurochemical systems for (i) reward, motivation, and pleasure; (ii) stress and arousal; (iii) immunity; and (iv) social affiliation. We discuss the limitations of these studies and outline novel approaches for integration of conceptual and technological advances from the fields of music cognition and social neuroscience into studies of the neurochemistry of music.

Introduction

Music is one of a small set of human cultural universals [1], evoking a wide range of emotions, from exhilaration to relaxation, joy to sadness, fear to comfort, and even combinations of these [2–4]. Many people use music to regulate mood and arousal, much as they use caffeine or alcohol [5–7]. Neurosurgeons use it to enhance concentration [8], armies to coordinate movements and increase cooperation [9], workers to improve attention and vigilance [10], and athletes to increase stamina and motivation [11].

The notion that 'music is medicine' has roots that extend deep into human history through healing rituals practiced in pre-industrial, tribal-based societies [12]. In contemporary society, music continues to be used to promote health and well-being in clinical settings, such as for pain management, relaxation, psychotherapy, and personal growth. Although much of this clinical use of music is based on *ad hoc* or unproven methods, an emerging body of literature addresses evidence-based music interventions through peer-reviewed scientific experiments. In this review, we examine the scientific evidence supporting claims that music influences health through neurochemical changes in the following four domains:

(i) reward, motivation and pleasure;
(ii) stress and arousal;
(iii) immunity; and
(iv) social affiliation.

These domains parallel, respectively, the known neurochemical systems of

(i) dopamine and opioids;
(ii) cortisol, corticotrophin-releasing hormone (CRH – see Glossary), adrenocorticotropic hormone (ACTH);
(iii) serotonin and the peptide derivatives of proopiomelanocortin (POMC), including alpha-melanocyte stimulating hormone and beta-endorphin; and
(iv) oxytocin.

Although the evidence is often weak or indirect and all studies suffer from important limitations (Box 1), the reviewed evidence does provide preliminary support for

Glossary

Adrenocorticotropic hormone (ACTH): a hormone synthesized by the anterior pituitary, which, in turn, stimulates the adrenal cortex to release corticosteroid hormones, including cortisol.
Anterior cingulate cortex (ACC): the frontal part of the cingulate cortex; regulates autonomic functions (blood pressure and heart rate), as well as attention, reward anticipation, decision-making, empathy, and emotion.
ß-endorphin: an endogenous opioid peptide neurotransmitter found in the central and peripheral nervous system; binds to the mu-opioid receptor.
Blood volume pulse (BVP): a measure of heart rate and relative blood flow collected using a photoplethysmograph sensor.
CD4+ T cells: T cell with CD4 receptor that recognizes antigens on the surface of a virus-infected cell.
Corticotrophin-releasing hormone (CRH): a peptide hormone and neurotransmitter involved in the stress response; stimulates the pituitary for ACTH synthesis.
Growth hormone releasing-factor (GHRF): a hormone expressed in neurosecretory cells of the hypothalamus and in lymphocytes (white blood cells).
Galvanic skin response (GSR): electrical conductance of the skin; varies with activity of the sweat glands; indexes physiological and psychological arousal.
Guided Imagery and Music (GIM): a therapeutic process using music and a trained facilitator to create an environment in which one may experience personal insights and solutions to problems.
Interleukin-6 (IL-6): a cytokine (small cell-signaling molecule) with both pro- and anti-inflammatory properties.
Interferon-γ: a cytokine critical for both innate and adaptive immunity.
Natural killer (NK) cells: a type of lymphocyte critical to the innate immune system.
Proopiomelanocortin (POMC): a polypeptide hormone precursor which gives rise to a variety of peptide hormones involved in pain, energy homeostasis, and immune modulation, including ß-endorphin.
Salivary immunoglobulin A (s-IgA): a principal immunoglobulin secreted externally in body fluids including saliva and mucus of the bronchial, genitourinary, and digestive tracts. Salivary IgA is a first line of defense against bacterial and viral infections, and a reliable marker of the functional status of the entire mucosal immune system.
Mesocorticolimbic pathway: a dopaminergic pathway in the brain consisting of the mesolimbic and mesocortical pathways. The mesolimbic dopaminergic pathway originates in the ventral tegmental area (VTA) of the midbrain and connects to the limbic system via the nucleus accumbens (NAc), amygdala, the hippocampus, and medial prefrontal cortex; it plays a critical role in reward-related behaviors and reinforcement learning. The closely related mesocortical dopaminergic pathway connects the VTA to the frontal lobes.
Nucleus accumbens (NAc): a large portion of the ventral striatum; plays a critical role in pleasure and reward-related cognition and behavior.
Orbitofrontal cortex (OFC): portion of the frontal lobes involved in expectation, reward and punishment, and decision-making.
Ventral tegmental area (VTA): the neural region containing dopaminergic cell bodies of the mesocorticolimbic system, located near the midline, on the floor of the midbrain.

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Box 1. Methodological limitations across studies

There are several important limitations of the current literature on the neurochemistry of music:

(i) the heterogeneity of methods employed across studies;
(ii) the lack of a standardized means of selecting musical stimuli;
(iii) the lack of adequate nonmusical control conditions to tease apart the effects of attentional engagement, mood state modification, and arousal.

In general, music interventions were found to vary with respect to the following factors:

(i) type of intervention (passive listening vs active performance);
(ii) type of music (usually only two broad types, stimulating vs relaxing);
(iii) locus of control (experimenter-selected vs participant-selected music); and
(iv) social context (e.g., individual activity, recreational group activity, or dyadic therapist-guided intervention).

The lack of standardized methods for musical stimulus selection is a common drawback in the studies we reviewed [124] and a likely contributor to inconsistencies across studies. Music is multidimensional and researchers have categorized it by its arousal properties (relaxing/calming vs stimulating), emotional quality (happy, sad, peaceful) and structural features (e.g., tempo, tonality, pitch range, timbre, rhythmic structure). The vast majority of studies use music selected by individual experimenters based on subjective criteria, such as 'relaxing', 'stimulating', or 'pleasant/unpleasant', and methodological details are rarely provided regarding how such a determination was made. Furthermore, there is often a failure to establish whether the experimenters' own subjective judgment of these musical stimuli are in accord with participants' judgments.

We also note that the studies reviewed here nearly always lack a suitable control for the music condition to match levels of arousal, attentional engagement, mood state modification, or emotional qualities. In other words, a parsimonious null hypothesis would be that any observed effects are not unique to music, but would be obtained with any number of stimuli that provide stimulation along these axes. Indeed, this was found to be the case with the so-called Mozart effect, which purported to show that intelligence increases after listening to music. The 'control' condition in the original study was for subjects to do absolutely nothing. The Mozart effect disappears, however, when control participants are given something to do, virtually anything at all [125–127].

Box 2. The neurobiology of reward

Motivation researchers distinguish behaviors and emotional states related to reward-seeking from those states experienced after a reward is successfully obtained. Reward seeking corresponds to the 'appetitive' phase of reward, which involves anticipation, learning and goal-directed behavior. A reward successfully obtained corresponds to the 'consummatory' phase, associated in part with the hedonic and reinforcing feelings of having obtained the rewarding stimulus [128]. Dopaminergic transmission underlies both the appetitive and consummatory phases of reward [129]. However, the hedonic properties or subjective pleasure associated with having obtained a reward are primarily mediated by endogenous opioids [38,43,128,129].

Thus, the emerging picture is that dopamine does not function as a 'pleasure' neurochemical *per se*, but rather, regulates motivation and goal-directed behaviors, playing a critical role in prediction and learning related to future rewarding events [38,43,130,131]. Dopamine replacement therapy in Parkinson's patients can induce 'compulsive singing' [132], which suggests a connection between dopamine and musical reward. Further studies are needed to determine whether musical reward can be parsed into distinct neurochemical mechanisms that relate to learning processes, motivational states (i.e., anticipation), and pleasure, and to clarify the role of dopaminergic and opioid neurotransmission in these sub-processes.

The subjective feelings of reward are mediated by the mesocorticolimbic system, the core of which consists of the ventral tegmental area (VTA), the ventral striatum, including the nucleus accumbens (NAc), the ventral pallidum, and prefrontal cortical areas that include the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) [38,47,133]. Reward entails the release of both dopamine and endogenous opioids within midbrain structures [38,47,130], as well as a complex network of other regions. There is an emerging consensus that learning and goal-directed actions are mediated by dopaminergic neurons in the VTA and their projections to the NAc and prefrontal cortex. Subjective feelings of pleasure, in turn, rely on the release of endogenous opioid peptides within the NAc [38,43,130].

It appears then that it is not just the specific neurochemicals (e.g., dopamine, opioids, norepinephrine) that lead to feelings of pleasure, but their interactions with receptors in specific sites of action within the brain. Thus, dopamine in one region may affect attentional control, in another region learning, and in yet another motivation.

the claim that neurochemical changes mediate the influence of music on health. Please note that in this article, we differentiate 'Music Therapy', a professional discipline and associated practice, from general music interventions.

Reward, motivation, and pleasure

All organisms engage in motivated behaviors geared towards survival [13]. This can be for individual survival, such as seeking out and ingesting food, or survival of the species, such as sexual activity. Reward is a complex construct involving motivational states (e.g., craving or wanting), prediction, goal-directed behavior, reinforcement learning, and hedonic states (Box 2). Is music the same or different than other rewards, including food, sex, and drugs of abuse? Does music have the earmarks of a rewarding stimulus, including the ability to motivate an individual to learn and engage in goal-directed behavior in order to obtain a pleasurable feeling? Does music achieve this effect via a similar neural network as other rewarding stimuli?

Musical reward

Music can evoke a wide variety of strong emotions, including joy, sadness, fear, and peacefulness or tranquility [2–4,14], and people cite emotional impact and regulation as two of the main reasons why they listen to music [3,7]. Music can produce feelings of intense pleasure or euphoria in the listener [15,16], sometimes experienced as 'thrills' or 'chills-down-the spine' [15–17]. Musical pleasure is closely related to the intensity of emotional arousal [18,19]. Even opposite emotional valences (e.g., 'happy' or 'sad') can be experienced as pleasurable [20] and listeners often report that the most moving music evokes two or more emotions at once.

Music does not have the clear survival benefit associated with food or sex, nor does it display the addictive properties associated with drugs of abuse. Nonetheless, the average person spends a considerable amount of time listening to music, regarding it as one of life's most enjoyable activities [21]. Many believe that music has special, mystical properties and that its effects are not readily reducible to a neuronal or neurochemical state [22,23]. Advances in cognitive neuroscience have challenged this view, with evidence that music affects the same neurochemical systems of reward as other reinforcing stimuli.

Functional neuroanatomy and neurochemistry of musical reward

Human functional imaging studies have demonstrated that cocaine craving or cocaine-rush [24], palatable food

Table 1. Evidence for the contribution of dopamine and opioids to musical pleasure

Study	Outcome measures	Conditions	Participants	Main findings
[17]	Self-reported thrills and chills	Self-selected music; naloxone vs placebo	Musicians and non-musicians (n=249)	Thrills ↓ by the mu-opioid-antagonist, naloxone
[28]	rCBF using PET; self-reported chills	self-selected music, neutral music, noise, and rest	Music students (n=10)	Chills ↑ rCBF in ventral striatum and midbrain
[29]	rCBF using PET; self-reported musical pleasure	Experimenter-selected music vs rest	Non-musicians (n=10)	Music ↑ rCBF in NAc, insula, hippocampus
[31]	rCBF using fMRI, network connectivity; self-reported pleasantness	Experimenter-selected music vs scrambled versions of same	Non-musicians (n=13)	Music ↑ rCBF in NAc, VTA and insula; strong connectivity of NAc, VTA, hypothalamus and insula.
[32]	rCBF using fMRI; self-reported pleasantness	Experimenter-selected music, pleasant vs unpleasant	Non-musicians (n=11)	Pleasant music ↑ rCBF in ventral striatum; ↓ rCBF in amygdala, hippocampus, parahippocampal gyrus and temporal poles
[33]	D_2 binding using ligand-based PET; self-reported chills	Self-selected vs neutral music	Unselected for musical ability (n = 10)	Chills ↑ D_2 binding in NAc; Anticipation ↑ D_2 binding in caudate
[35]	rCBF using fMRI; self-reported affective valence, arousal, familiarity, autobiographical association; directed attention	Experimenter-selected music	Unselected for musical ability (n=13)	Pleasant familiar music ↑ rCBF in insula, ventral striatum (caudate nucleus), mPFC

Note: Arrows indicate significant increases or decreases relative to baseline and/or control conditions. Abbreviations: D_2, dopamine D2 receptor; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PET, positron emission tomography; rCBF, regional cerebral blood flow; VTA, ventral tegmental area.

[25], and humor [26] yield activation within mesocorticolimbic structures similar to those shown to mediate reward in animal models (e.g., [27]). Does music activate the same neuroanatomical and neurochemical systems? Neuroimaging technology has been used to probe the functional activation [28–32], network connectivity [31], and central dopamine release [33] during perception of pleasurable music (see Table 1 for a summary and [34] for a review of the neuroanatomical basis for musical emotion).

Three studies used positron emission tomography (PET) to investigate regional cerebral blood flow (rCBF) during experienced musical pleasure [28–30]. In one study, self-selected, pleasurable music known to reliably induce 'chills-down-the-spine' was compared to neutrally-rated music [28]. Compared to neutral music, chill-inducing music was associated with a significant increase in rCBF within structures that comprise the mesocorticolimbic system and are critical to reward and reinforcement, such as the ventral striatum [including the nucleus accumbens (NAc)] and midbrain, as well as the thalamus, cerebellum, insula, anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). NAc activation was also reported during listening to unfamiliar pleasant music compared to rest [29] and during singing compared to speech [30]. These studies suggest that musical reward involves activation of the NAc, as well as opioid-rich midbrain nuclei known to regulate morphine analgesia and descending inhibition of pain [30]. Due to the relatively low spatial resolution of PET, however, it was not possible to precisely localize activity within these regions.

Four studies used higher resolution functional magnetic resonance imaging (fMRI) to investigate the neural correlates of musical pleasure [31–33,35]. Listening to pleasurable music was found to be associated with NAc activation, as well as ventral tegmental area (VTA)-mediated interactions between the NAc [31] and brain structures known to regulate autonomic, emotional, and cognitive functions [36]. Dopaminergic neurons originating in the VTA with major projections to the NAc and forebrain regions [37] are necessary for the efficacy of rewarding stimuli [38]. A strong link between emotional and cognitive subsystems during musical pleasure was uncovered, linking orbitofrontal cortex [31] with the mesocorticolimbic dopaminergic circuitry (NAc and VTA). This suggests that musical reward is dependent on dopaminergic neurotransmission within a similar neural network as other reinforcing stimuli. Pleasant (consonant) and unpleasant (dissonant) music were contrasted, and the results confirmed activation of the ventral striatum during pleasurable music listening [32]. Ventral striatum activation was also found in response to music that was pleasant due to its familiarity [35]. Strong deactivations were observed in the amygdala, hippocampus, parahippocampal gyrus, and the temporal poles in response to pleasant music [32]. As the hippocampus is known to facilitate and inhibit defensive behaviors in response to stress [32], the deactivation may be related to modulation of the stress hormone cortisol in response to pleasant vs unpleasant music. Activation of the insula in response to pleasant music has also been observed [31,32,35] – a significant finding because of the insula's connectivity to the NAc and its role in the appetitive phase of reward, particularly in addictive behaviors [39].

A limitation of many imaging studies to date [29,31–33,35] has been the use of experimenter selected music (external locus of control), which – though rated as pleasurable – might not have been as pleasurable as self-selected music. An additional limitation of the aforementioned PET and fMRI studies is that they were not able to directly investigate dopamine release during the processing of musical reward, but rather, they relied on a proxy

for neuronal activation. Recently, ligand-based PET scanning has allowed the measurement of dopamine during musical pleasure [33]. In this study, dopamine release was estimated based on competition between endogenous dopamine and [^{11}C]raclopride (a radiolabelled version of *raclopride*, a D_2 receptor antagonist) at dopamine D_2 receptor sites. Participants were tested on music containing passages that reliably produced a sensation of chills. These passages were associated with dopamine release in the NAc, whereas the time period immediately prior to the onset of chills was associated with dopamine release within the caudate. Thus, musical pleasure shows evidence of an appetitive phase related to anticipation and a consummatory phase related to its hedonic and reinforcing properties, converging with animal studies that report a similar pattern of anatomically and temporally distinct dopaminergic activity in response to drugs of abuse [40].

However, the experimenters [33] made the unsupported assumption that dopamine release in the caudate 15s prior to the onset of subject-reported chills indicated anticipation. It is unknown whether this time window coincided with the timing of actual subjective anticipation of chills. Anticipation is a complex cognitive construct that can occur on a variety of timescales (seconds, minutes, days, etc.) [41], therefore, it is possible that participants began to anticipate that they would get chills based on a musical cue presented at some earlier time point in the piece or even prior to the experiment; indeed, the protocol required that participants identify musical passages that had reliably produced chills many times in the past. It is important to consider also that caudate activity may reflect other reward-related processes (e.g., reinforcement [42]).

Another important point is that the aforementioned study [33] investigated dopamine release during 'chills' rather than more typical, everyday musical pleasure. Although functional activation within the NAc was found to be associated with both, a subjective behavioral equivalence was not established. A strength of the experiment is

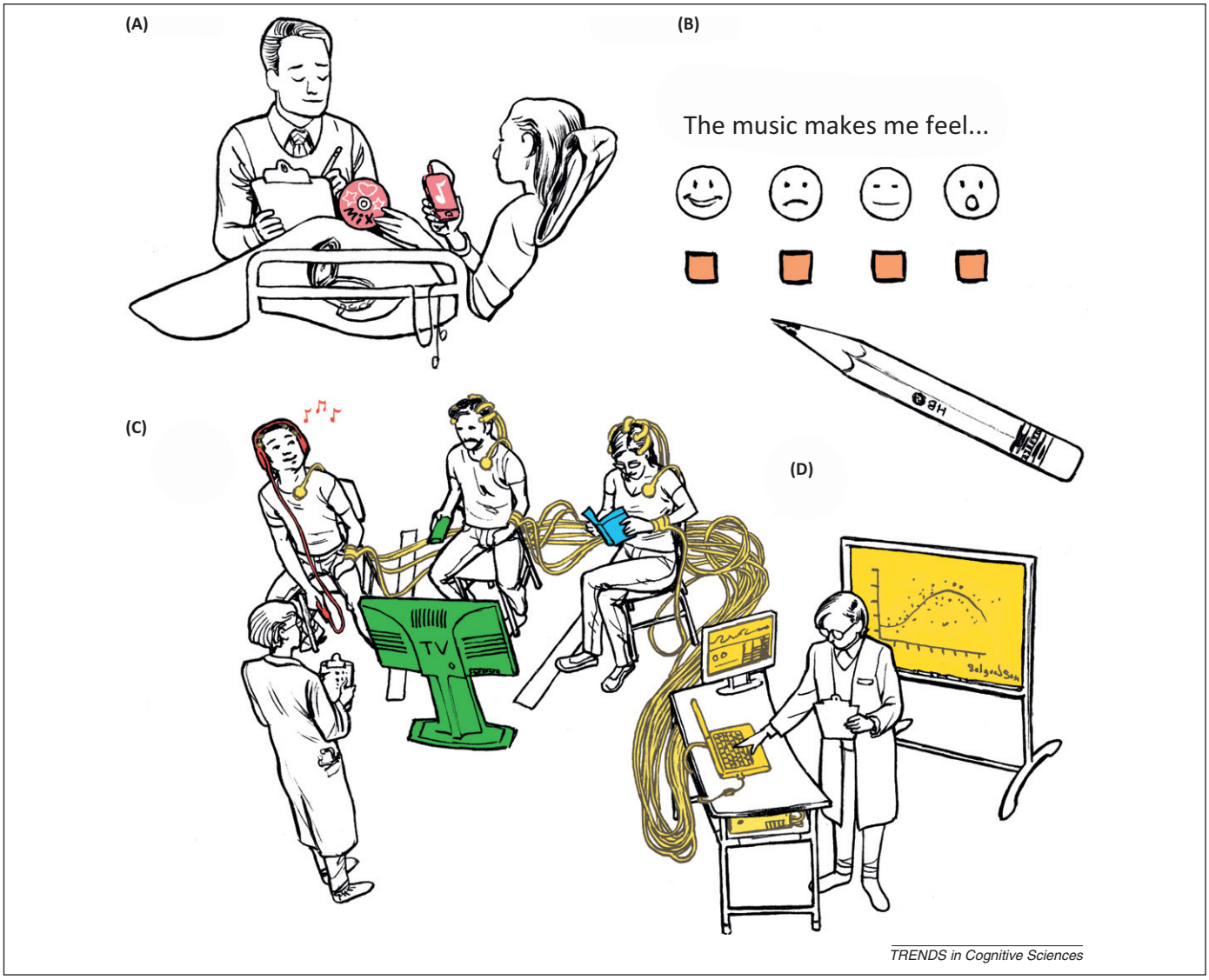

Figure 1. Summary of chief recommendations for future research. **(A)** Locus of control may mediate the effectiveness of music interventions and, therefore, it is crucial that patients be allowed to choose their own music. **(B)** Subjective ratings of musical features (such as 'happy, sad, peaceful and scary') should be recorded, instead of relying solely on the experimenter's judgment. **(C)** It is important to include parallel non-music experimental conditions in order to control for mood induction, attentional capture, intensity, and valence. In this particular case, music is compared with a television program and a book. **(D)** Physiological measures provide an essential objective counterpart to the subjective measures in (B). Figure drawn by Salgood Sam.

that the use of chills helps to separate signal from noise in the response; however, 'chills' are a relatively rare response to music that may reflect general arousal mechanisms rather than musical pleasure *per se* [15], and the relatively small subpopulation of individuals who routinely experience them may not be representative of the general population.

The function of NAc dopamine release during musical reward remains unclear. One possibility it that is leads to 'wanting without liking', as has been observed in other hedonic domains, such as appetite and reward [43]. Dopamine may be associated with expectation and predictions of cues that lead to future musical reward (e.g., chills) and new theories suggest that it may also play a role in encoding the experience of chills after the fact [43].

Current evidence suggests that endogenous opioid peptides are essential for both 'wanting' and the hedonic perception or 'liking' of a rewarding stimulus [38,44]. Although this has not been tested in music, it is plausible that the positive affect or euphoria that accompanies musical activity is critically dependent on opioid mechanisms (perhaps acting synergistically with dopamine; separating these systems presents a challenge).

Music listening reportedly lowers requirements for opiate drugs in postoperative pain [45], which suggests that music may stimulate the release of endogenous opioid peptides within the brain. A frequently cited older study found that self-reported thrills and chills during music listening could be blocked by the opioid antagonist naloxone, which provided tentative evidence of a causal link between musical reward and the central release of endogenous opioids [17]. This study has several limitations, however (e.g., no non-music control condition; statistical analyses were limited to only three participants, etc.) and follow up studies are necessary.

To clarify the role of central opioids in musical pleasure and chills, we recommend: (i) the use of opioid antagonists to block the action of opioid peptides during music listening; one candidate is naltrexone, available in pill form; (ii) the use of a double-blind placebo-controlled crossover design; (iii) control conditions that consist of emotionally neutral music and a pleasurable non-music control stimulus (i.e. desirable food, television shows, books); (iv) computer-based real-time ratings of subjective pleasure states; (v) the measurement of heart rate, blood volume pulse (BVP), respiration rate, body temperature, and galvanic skin response (GSR), in order to identify the physiological correlates of self-reported musical pleasure and chills; and (vi) neuroimaging of central opioid receptors. Figure 1 illustrates these and other suggestions for future experiments.

Ligand-based PET is currently used to investigate regional opioid neurotransmission in substance abuse disorders, various chronic pain conditions, epilepsy, and in response to opioid agonists and antagonist drugs [46]. Imaging of central opioid receptors (using opioid receptor ligands) would clarify the role of these endogenous peptides in musical reward – specifically within regions previously implicated in opioid-mediated reward, including the VTA, NAc, amygdala and dorsomedial midbrain [47].

Box 3. The neurobiology of stress and arousal

The biological stress response is an elegant choreography of neuroendocrine, autonomic, metabolic, and immune system activity that involves multiple feedback loops at the level of the central and peripheral nervous systems [118]. Together these systems trigger short-term adaptive behaviors, including arousal, vigilance, and focused attention, and temporarily inhibit functions that are nonessential during a crisis, such as eating, digestion, growth, and sex drive. In tandem, cardiovascular changes, such as elevated heart rate and rapid breathing, serve to increase oxygenation and glucose supply to the brain and skeletal muscles, thereby facilitating the 'fight-or-flight' response. Music has been shown to modify heart rate, respiration rate, perspiration, and other autonomic systems [134], corroborating anecdotal reports that many people use music to achieve physical and psychological balance, grounding, or 'centeredness'.

Several key neurochemicals mediate the stress response (see [135], for a review). These include the glucocorticoids (e.g., cortisol), a product of the HPA stress axis, which regulate metabolism and immune function. Cardiovascular changes are induced by the catecholamines, norepinephrine and epinephrine, which are, in turn, regulated by the brainstem locus ceruleus and central and peripheral autonomic nervous system. Other important mediators of the stress response include the hypothalamic hormones AVR, corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), serotonin, and the peptide derivatives of proopiomelanocortin (POMC), including α-melanocyte stimulating hormone and β-endorphin. It is important to note that these stress mediators act not only in peripheral tissue, but act on target receptors within brain regions mediating cognitive function, emotion, reward and the sleep-wake centers of the brain [136]. Here, they initiate higher-order cognitive and behavioral responses to stress, and – under non-pathological conditions – act to suppress them once the stressor has subsided [136]. The amygdala, for example, is rich in cortisol receptors and interacts with norepinephrine input and hippocampal connections [137].

The biological stress response is highly adaptive in the short-term; however, prolonged activation of these systems has detrimental consequences for health. Stressful events that are either severe, prolonged, or of uncertain duration may result in chronic activation of systems. Prolonged, elevated circulating levels of glucocorticoids (e.g., cortisol) act as neurotoxins, weakening the ability of neurons and other cells to resist injury and making them more vulnerable to the effects of toxins and the normal attrition process [135]. Finally, although glucocorticoids act as an immunosuppressant under conditions of acute stress, they may promote a state of chronic low-grade inflammation in the long term [138].

These neurotoxic and pro-inflammatory effects of chronic stress have been linked to a host of negative health outcomes, including impairments in normal cognitive functioning, increased susceptibility to infectious disease, anxiety and depression, cardiovascular disease, dementia and Alzheimer's disease [135,136].

Stress and arousal

All organisms seek to maintain homeostasis. Stress can be defined as a neurochemical response to the loss of homeostatic equilibrium, motivating the organism to engage in activities that will restore it (Box 3). Lifestyle choices that reduce stress are thought to be highly protective against diseases [48] and music may be among these [49–51].

The effects of music on stress and arousal

Relaxing music The potential therapeutic effects of music listening have been largely attributed to its ability to reduce stress and modulate arousal levels. Listening to 'relaxing music' (generally considered to have slow tempo, low pitch, and no lyrics) has been shown to reduce stress and anxiety in healthy subjects [49,52], patients

Table 2. The effects of music on biomarkers for stress and immunity

Study	Population	OT	CORT	ACTH	E	NE	β-end	GH	NK	Il-6	IgA
Experimenter-selected relaxing music											
[69]	Surgery patients		↓								
[70]	Surgery patients		↓								–
[120]	Surgery patients	↑									
[99]	Surgery patients				↓			↑		↓	
[139]	Surgery patients		↓								
[52]	Healthy		–								↑
[59]	Healthy		↓								
[60]	Healthy						↓				
[61]	Healthy		↓								
[62]	Healthy		–	–	–	–	–	–			
[100]	Healthy		–							↓	
[104][a]	Healthy		–								↑
[105][b]	Healthy										↑
[140][c]	Healthy										↑
[141]	Healthy[d]		↓								
[142]	Healthy		↓	–	–	↓					
Experimenter-selected stimulating music											
[62]	Healthy		↑	↑	–	↑	↑	↑			↑
[63]	Healthy		↑								
[143][e]	Healthy		↑								
[144][f]	Lung infection patients		↓								
[145][g]	Dancers		↓								
Participant-selected music (various styles)											
[84]	Surgery patients		↓						↓		
[85]	Surgery patients		–		–	–					
[86]	Surgery patients		–		–	–					
[87]	Surgery patients		↓		–	–					
Group drumming											
[94]	Healthy								–	↑	
[97]	Healthy								↑↓		
[98]	Healthy		↓						↑		
Singing											
[57]	Singers	↑	↑↓[h]								
[58]	Singers		↓								↑
[106]	Singers		↑↓[i]								↑
[108]	Non-musicians										↑

Note: Arrows (↑ or ↓) indicate significantly higher or lower levels relative to baseline and/or control conditions; arrows pointing in both directions (↑↓) indicate bidirectional changes; dashes (–) indicate no significant change. Blank fields indicate that the particular neurochemical marker was not investigated. Unless otherwise specified, subjects were unselected for musical ability. Abbreviations: OT, Oxytocin; CORT, Cortisol; ACTH, Adrenocorticotropic Hormone; E, Epinephrine; NE, Norepinephrine; β-end, β-endorphin; GH, Growth hormone; NK, Natural killer cell count or activity; IL-6, Interleukin 6; IgA, immunoglobulin A.

[a]The experimenters selected happy and sad music.

[b]The experimenters selected 'designer music', reported by the composer to have a 'balancing effect' on one's mental and emotional states.

[c]The experimenters selected Muzak 'environmental music'.

[d]The participants were musicians and non-musicians.

[e]The experimenters selected fast and sedative music; results are for difference between fast and sedative or no music.

[f]The experimenters selected Bach's 'Magnificat' for its major tonality and association with 'happy' emotions.

[g]The experimenters selected Tango music.

[h]Decreases in females, increases in males.

[i]Decreases during rehearsal, increases during performance of same repertoire by same participants.

undergoing invasive medical procedures (e.g., surgery, colonoscopy, dental procedures [45,50,53–55], pediatric patients undergoing medical procedures [49], and patients with coronary heart disease [56]. Music listening following painful medical procedures (e.g., surgery) has also been found to reduce sedation, as well as pain and analgesic requirements [45,50], although the effect sizes are small [45]. These effects are conventionally considered to be owing to the ability of music to distract or modulate mood.

The effects of relaxing music on stress hormones levels along the hypothalamic-pituitary-adrenal (HPA) axis have been investigated in healthy subjects at rest [57,58], in combination with imagery [59,60] and during stressful tasks [52,61]. Table 2 summarizes experimental evidence across a range of physiological markers.

A form of music therapy that combines relaxation techniques and listening to classical music called Guided Imagery and Music (GIM) was found to reduce HPA activation in healthy subjects [59,60]. Two markers of HPA-activation were found to decrease following GIM, cortisol [59] and β-endorphin [60]. Cortisol levels decreased following GIM compared to silence, but control conditions involving music listening alone and silent imagery alone were not provided [59]. β-endorphin decreased when music listening was combined with guided imagery, but not when either one was presented alone [60]. These studies reveal that GIM therapy reduces activation of the HPA stress axis, but they fail to isolate effects of music *per se*. The therapist-participant interaction is presumably a contributing factor, as well.

Three studies compared the neurochemical effects of music, based on experimenter-selected criteria, including style, rhythmic properties, and arousal/valence dimensions. In one study, experimenter-selected classical music that the experimenter deemed relaxing (60-100 beats/min; soft sounds) was compared to techno music that the experimenters deemed stimulating (130-200 beats/min; screeching sounds). Subjects in this study reported no preference or engagement with a particular musical genre. Techno music increased plasma cortisol, ACTH, prolactin, growth hormone and norepinephrine levels [62], consistent with heightened HPA axis and sympathetic nervous system activity (this finding was replicated by [63]. The relaxing classical music did not cause the expected reduction in HPA and sympathetic activation (highlighting the need for a more standardized approach to musical selection). Interestingly, the authors report that changes in norepinephrine, β-endorphin and growth hormone during techno music listening were negatively correlated with harm-avoidance and positively correlated with novelty seeking traits. These findings suggest that – in addition to musical style – underlying personality dimensions are factors that mediate physiological stress responses to music. This is consistent with an emerging literature which suggests that individual differences in personality and cognitive traits influence psychological and physiological responses to different types of music (e.g., [64,65]). Background music, for instance, causes larger interference with cognitive processes among introverts compared to extraverts (e.g., [66]).

Another study selected three pieces of music that putatively 'differed in their rhythmic characteristics', including a Strauss waltz (regular rhythm), a 'modern classic' by H.W. Henze (irregular rhythm) and a 'meditative piece' by Ravi Shankar (non-rhythmic; [67]). Neurochemical effects of music were compared to a silent baseline. The meditative piece significantly reduced plasma levels of cortisol and norepinephrine, whereas the other two pieces had no effect. A caveat concerns the informal selection criteria for the music: although the music was selected based on rhythmic properties, the authors provided no objective description of these.

A separate study collected music ratings prior to the experiment with high inter-rater reliability [68]. Music that was rated as relaxing and positive (low arousal, high valence) or arousing and negative (high arousal, low valence) was played and salivary cortisol was measured; no differences were found between the two music conditions. However, the experiment did not employ a factorial design and, therefore, the effects of arousal and valence were confounded and may have masked cortisol responses.

Relaxing music during stressful tasks Two music studies simulated everyday stress associated with performance at work or school. Khalfa et al. [61] obtained measurements across multiple time points post-stressor (every 15 min for up to 2 h), and reported a more rapid lowering of cortisol levels after listening to relaxing music compared to a silent control. Knight and Rickard [52] measured salivary cortisol 20 minutes post-stressor. Music listening had no effect on salivary cortisol levels, but did prevent stress-induced increases in heart rate and systolic blood pressure compared to silence. This discrepancy in findings may partly reflect the differences in sample collection.

The effects of passive listening to relaxing music in the absence of additional manipulations have been investigated during medical procedures, primarily surgeries (Table 2). Post-operative levels of subjective, cardiovascular, respiratory, and neuroendocrine markers of stress were measured [50]. Patients listened to music that was determined by the experimenter to be soft and relaxing (60-80 beats per minute and described as a New Age style) either pre-, peri- or post-operatively. Listening passively to experimenter-selected relaxing music during the post-operative period was most effective, resulting in a significantly greater decrease in serum cortisol compared to controls following cardiac surgery [69] and hernia repair [70]. Again, there was no effort to differentiate between the anxiolytic effects of music vs a distraction effect, which might have been obtained using other relaxing stimuli as well.

Underlying mechanisms of action

One proposed mechanism for the ability of music to regulate stress, arousal, and emotions is that it initiates reflexive brainstem responses [71]. Music modulates brainstem-mediated measures, including heart rate, pulse, blood pressure, body temperature, skin conductance, and muscle tension [72]. Stimulating music produces increases in cardiovascular measures, whereas relaxing music produces decreases [73], patterns observed even in infants [74]. These effects are largely mediated by tempo: slow music and musical pauses are associated with a decrease in heart rate, respiration and blood pressure, and faster music with increases in these parameters (e.g., [75]). This follows given that brainstem neurons tend to fire synchronously with tempo [76].

Noradrenergic (norepinephrine) neurons in the brainstem and midbrain regulate the autonomic responses of heart rate, blood pressure, and respiration [77], along with cholinergic [78] and dopaminergic neurotransmission [79]. Brainstem activation also mediates sensory and motor function through epinephrine, norepinephrine, and serotonin [79]. Simple musical properties, such as tempo, may therefore affect central neurotransmission underlying cardiovascular and respiratory control, motor function, and potentially even higher order cognitive functions, such as the setting of attentional filters.

A partial explanation is that the brainstem interprets music as signals related to survival, and then initiates corresponding physiological responses. For example, music commonly classified as 'stimulating' mimics sounds in nature, such as the alarm calls of many species, that signal potentially important events (e.g., loud sounds with sudden onset and a repeating short motif). Interestingly, positive affect and reward anticipation have also been associated with high frequency, short motif calls (e.g., [80]). This, in turn, heightens sympathetic arousal (heart rate, pulse, skin conductance, and breathing). By contrast, 'relaxing' music mimics soothing natural sounds such as maternal vocalizations, purring and cooing (soft, low-pitched sounds with a gradual amplitude envelope), which decrease sympathetic arousal.

Locus of control

Locus of control is significantly correlated with recovery, health, and well-being (e.g., [81,82]). Given that even a trivial or illusory sense of choice enhances people's motivation, patient-selected music should generally be more effective than experimenter-selected music [50,83].

Surgery patients post-operatively exposed to music of their own choosing showed decreased cortisol levels compared to controls, and self-selected music proved more effective than experimenter-selected New Age music [84]. Thus self-selected music may buffer endocrine stress responses during recovery. Because no participants chose New Age music, locus of control and musical genre were confounded in this experiment.

Spinal surgery patients listened to self-selected music from a 'large number' of available tracks on a laboratory computer [85]. These tracks were all 'soft melodies', including pop, classical, and sacred music, as well as nature sounds. Post-surgery pain, anxiety, and blood pressure were significantly lower in the music condition (cortisol remained unchanged). Participants were allowed to select music of any genre from a set provided by the experimenters. The effects of musical genre on experimental outcomes were not reported and one can assume that personal control, although unmeasured, was low.

Two studies that allowed patients to pre-select music from their own personal collections showed mixed results. One investigated the effects of music prior to surgery on physiological markers of stress (e.g., heart rate, blood pressure, and electrodermal activity; serum cortisol, epinephrine, and norepinephrine) and reported no significant changes [86]. Another investigated the effects of music on cortisol levels in awake patients during cerebral angiography – typically a stressful procedure [87]. Music prevented increases in cortisol levels compared to silence; however, patients with very high levels of self-reported anxiety did not benefit. Thus a patient's psychophysiological state prior to music listening may contribute to variability within and across studies. Contrasting findings regarding the effects of music on post-surgical stress markers may also reflect differences in the timing of music delivery (e.g. pre-, during or post-medical procedure) and the type of procedure (e.g., minor surgery, highly invasive surgery, angiography). An alternative hypothesis is that passive music listening may be less effective than active music making toward stress reduction in surgical patients.

One study compared a benzodiazepine (midazolam) to music prior to surgery using the State Trait Anxiety Inventory (STAI) as a dependent measure [88]. Relaxing music was compiled by a licensed music therapist and presented to patients randomly assigned to a music vs drug condition (both groups received the same attention and care). Baseline anxiety was reduced significantly more by the music than by the drug. Heart rate also decreased more in the music group, although systolic blood pressure decreased more in the drug group (there was no difference in diastolic BP).

Summary and future directions

Music is among those lifestyle choices that may reduce stress, protect against disease, and manage pain [51]. Two markers of the hypothalamic-pituitary-adrenal (HPA) axis, ß-endorphin and cortisol, were found to decrease with music interventions. Stimulating music increased plasma cortisol, ACTH, prolactin, growth hormone, and norepinephrine levels. Personality factors and individual differences in musical preferences mediate these effects. In real-world tasks, music prevented stress-induced increases in heart rate and systolic blood pressure compared to silence. In surgeries, music listening post-operatively was effective in decreasing serum cortisol levels. Music initiates brainstem responses that, in turn, regulate heart rate, pulse, blood pressure, body temperature, skin conductance, and muscle tension, partly via noradrenergic neurons that regulate cholinergic and dopaminergic neurotransmission.

Music perception and cognition are subjective and influenced by individual differences in traits and temporary differences in mood states. Future studies would benefit from having participants rate the arousal properties and emotional dimensions of the music, as well as how much they enjoy it. Future work would also benefit from distinguishing the effects of music itself from other possible factors, such as simple distraction; and employing manipulations to verify that attention is equally engaged during the music, non-music and silent conditions.

Immunity

Immune responses are broadly categorized as either innate or adaptive. The innate immune system represents the first line of defense against infection and includes cells and proteins that are nonspecific to particular antigens, such as natural killer (NK) cells and phagocytes. The adaptive immune system provides a secondary, antigen-specific response during which cells with a memory for specific pathogens are created (e.g., T cells; [89]).

Stress and aging have detrimental effects on both immune system responses, leading to a weakening of defenses against new pathogens and increases in systemic inflammation. Compared to the vast literature devoted to stress and aging, relatively little attention has been focused on psychosocial and lifestyle factors that may improve immune system functioning [90]. Positive emotions, such as optimism [91], and stimuli eliciting those emotions, such as humor and laughter [92,93], may mitigate the negative effects of age and stress. Given that

music enhances mood and reduces stress, it stands to reason that it may also improve immune function [51].

Group drumming circles

Recreational music-making has been proposed as a cost-effective means of improving mood and reducing stress among the elderly [94], healthcare professionals [95,96], and corporate employees [97]. Group drumming is used because it allows for creative self-expression without the need for musical expertise [98]. Participants perform rhythmic sequences of increasing complexity and gradually incorporate directed imagery into their drumming. The sessions involve social interaction among group members, instructor-participant interaction and humor – any one of which is likely to affect immune responses in participants. Further controlled experiments are necessary to tease apart these factors.

In one typical study, group drumming was compared with (i) a pre-intervention baseline, (ii) a resting condition during which participants sat in a circle while reading newspapers and magazines provided by the experimenter, and (iii) listening to recordings of previous drumming sessions. A trend toward increased NK cell activity was found in the group drumming condition, along with an increased 5-DHA-to-cortisol ratio, which suggests enhanced immune functioning and a buffering of the stress response [98] (DHA is an endogenous neurosteroid secreted by the adrenal gland and is a precursor to androgen production). In a second study, group drumming was associated with a decrease in gene expression of the stress-induced cytokine interleukin-10 (IL-10), and interferon-γ [97] and bi-directional changes in NK cell activity. NK cell activity was reduced in individuals with high pre-intervention levels, whereas the opposite was found for individuals with low pre-intervention levels.

A third study found that group drumming counteracted age-related declines in immune functioning [94]. Older adults (>60 years) displayed significant increases in total number of lymphocytes (including NK cells), T cells, CD4+ T cells, memory T cells, and production of interferon-γ and interleukin-6 (IL-6, a cytokine with both pro- and anti-inflammatory properties), relative to a pre-intervention baseline. There were no significant changes observed in younger adults.

These three studies claim that recreational music-making counteracts the patterns of immune modulation that normally occur due to stress and aging, particularly in individuals with dysregulation, including older adults. Although this is plausible, no study controlled for the effects of group interaction, instructor guidance, and humor that are experienced in group drumming. A more suitable control condition would involve a group activity session that followed the same method and sequence of events as the group drumming session protocol, except that the activity would be strictly non-musical (e.g., story-telling, skit-acting, etc.).

Passive listening to experimenter-selected relaxing music

Passive listening to relaxing music has been associated with decreases in IL-6 in critically-ill patients [99] and healthy participants [100]. This is consistent with a beneficial effect of musical intervention on stress-related cytokine production [101]. Increases in levels of growth hormone were also reported in critically-ill patients during music-induced relaxation [99] and a similar response to music listening has been reported in healthy participants [62]. Growth hormone releasing-factor (GHRF) is expressed in neurosecretory cells of the hypothalamus and lymphocytes [102], which suggests a modulatory role for music in immune regulation; there is further evidence of an interaction between GHRF and IL-6 in human lymphocytes [99].

Several studies have investigated the effects of music on salivary immunoglobulin A (s-IgA), a principal immunoglobulin secreted externally in body fluids, including saliva and mucus of the bronchial, genitourinary and digestive tracts [103]. Salivary IgA is a first line of defense against bacterial and viral infections [103], and a reliable marker of the functional status of the entire mucosal immune system [104].

Increased s-IgA concentrations from baseline have been reported following experimenter-chosen music that was relaxing [52,105]. Both studies, however, used only silence as a control, thus the effects could be due to attentional engagement or mood modulation rather than music *per se*. A third study [104] used appropriate control conditions and also accounted for salivary flow rate (which has been shown to modulate s-IgA concentrations [106]). In this study, the authors investigated the effects of emotional valence (e.g., happy vs sad) on s-IgA levels using experimenter-selected music vs visualization (a control for mood). Music was associated with increased s-IgA levels compared to resting levels and the visualization condition, regardless of the emotional valence of the music. This suggests that mood manipulation through music has beneficial effects on immunity beyond other mood-induction methods. Further research is needed to confirm this.

Blood plasma levels of IgA (as opposed to s-IgA) were measured in surgery patients who listened to experimenter-selected 'calming music' vs silence [64]. There was no significant difference in blood plasma IgA levels among patients in the music condition compared to the control condition, even though the stress marker cortisol was significantly decreased with music. An important consideration in this study – and others involving surgery patients – is that the effects of local anesthetic infiltration may interfere with the effects of musical intervention on biological measures [107].

Group singing

Three studies found that group singing elicits a greater increase in s-IgA concentrations than passive listening [58,106,108]. Saliva samples were taken from members of a professional chorale during rehearsals and performance of a classical music piece [106]. After controlling for salivary flow rate, s-IgA concentrations increased 150% during rehearsals and 240% during the performance. Self-reported positive affect and relaxation among professional singers showed a significant positive correlation with s-IgA levels during performance, but not rehearsal. In a multiple regression model, self-reported stress did not show a

significant correlation with s-IgA, although this factor still contributed to a proportion of the variance in s-IgA. Thus, active performance may have a particularly strong impact on mucosal immunity, and this effect is related to the mood-enhancing effects of the musical activity.

Summary and future directions

A small number of studies found that music boosts the innate or non-specific immune system, indicated by increased NK cell activity and mucosal immunity; music has anti-inflammatory properties, indicated by positive changes in cytokine profile. These results, though promising, are still preliminary and warrant more careful follow-up studies that control for effects of extraneous variables. Experiments involving group drumming and group singing have ecological validity, in that they represent an organic process that has existed since prehistoric times and may have advantages over solitary musical activity.

Inadequate control methods make it difficult to draw any firm conclusions regarding the contribution of music itself to these beneficial effects. Social support is known to mitigate the damaging effects of psychological stress and aging on health and to improve immune system functioning. Studies that show a beneficial effect of group drumming and singing on immunity suggest that the social aspects of music, and their neurochemical underpinnings, are potentially relevant to health and well-being, although the relative contributions of social support and musical activity are confounded in group drumming.

Social affiliation

An emerging body of evidence indicates that social factors play an important role in human health outcomes [109]. Synchronized activities, such as music, dance, and marching, have long been known to foster feelings of social connection, specifically interpersonal trust and bonding [9,110,111] (see also [112], for a review of dance as therapy for Parkinson's patients). Many human and animal activities are rhythmic, including walking, talking, clapping our hands, dancing, sexual activity, and rocking a baby. When rhythmic activities are performed by groups of people they tend to become synchronized, reflecting social coordination [9,113].

Oxytocin and vasopressin – two neuropeptides known to regulate social behavior (Box 4) – are possible candidates that mediate the social effects of music [114]. However, only the role of oxytocin has been investigated in the context of music – the role of vasopressin and the interaction between the two chemicals remain unexplored.

Music, social affiliation, and neurochemistry

Two species of 'singing mice', which display an unusually complex vocal repertoire, exhibit high oxytocin receptor binding within brain regions related to social memory, including the hippocampus and medial amygdala [115]. Injection of oxytocin into female hamsters increases ultrasonic vocalizations aimed at the establishment and maintenance of pair bonds for mating purposes [116]. Conversely, oxytocin receptor infant knockout mice engage in fewer vocalizations and show marked social deficits and higher stress levels [115,117]. These findings establish the biological basis for a social component in music and support the notion that music plays an important role in creating social bonds.

Box 4. The neurochemistry of social affiliation

Oxytocin, a neuropeptide released by the posterior pituitary gland, mediates social bonding and affiliation [114] and has been proposed to underlie the protective effects of social support on health [109]. However, growing evidence suggests that oxytocin is not simply a 'love hormone'. Oxytocin organizes social behavior in a manner highly dependent on the context and the traits of the individual [146]. Oxytocin is not prosocial *per se*, but rather, regulates stress and anxiety, affective motivational states, and/or perceptual selectivity related to social information [146].

Paradoxically, endogenous levels of oxytocin also increase during 'gaps' in social support or poor social functioning in healthy [147], anxious [148], and depressed [149] individuals (demonstrating that absence makes the heart grow fonder – or at least more attached). Oxytocin may thus act as a distress signal prompting the individual to seek out social contact [147]. To reconcile this paradox, it has been proposed that oxytocin regulates the salience of social information and is capable of eliciting positive and negative social emotions, depending on the situation and individual [146]. Promising preliminary evidence suggests that oxytocin pharmacotherapy can help to promote trust and reduce social anxiety in patient populations, including those with social phobia and borderline personality disorder [146]. Non-drug therapies, such as music, may exert similar therapeutic effects via oxytocinergic regulation. It remains unknown whether music causes release of oxytocin at levels commensurate with other activities or with the effective dosages of exogenous oxytocin used experimentally.

Vasopressin – a neuropeptide closely related to oxytocin and known to regulate social behavior – is another possible candidate mediating the social effects of music [114]. For instance, vasopressin mediates the perception of emotion in faces with gender-specific effects [150].

The *AVPR1a* (vasopressin) gene has been shown to mediate affiliative, social, and courtship behaviors [150], and is associated with music listening and audio structuring ability [151]. Oxytocin is known to be associated with the *AVPR1a* gene, which suggests a role for vasopressin-oxytocin interactions in moderating the effects of music on social bonding and affiliation.

Another important theory proposes that opioids are the 'glue' that binds individuals together [152]. The brain opioid theory of attachment proposes that, during mammalian evolution, this system became co-opted for the reinforcement of more sophisticated survival mechanisms, namely social affiliation among groups, mating dyads, and between mother and offspring [153]. Endogenous opioids – particularly β-endorphin – may play a dual role as a pain signal in response to social isolation and a 'satiety' signal during social contact. Consistent with this, studies in a variety of nonhuman species demonstrate that low levels of endogenous opioids or delivery of opioid antagonist drugs trigger separation distress behaviors and lead animals to seek out contact (i.e., the appetitive behaviors), whereas increases in opioid levels – either due to positive social contact or agonist drugs – reduce these behaviors (i.e., the consummatory phase of social interaction [152]). Many individuals report listening to music when they are lonely. If music can increase opioid production, this would provide a plausible connection between music and comfort.

Opioid peptides alone are unlikely sufficient for the regulation of social 'reward'. In nonhuman species, opioid and dopaminergic systems interact with oxytocin and vasopressin within mesocorticolimbic brain regions to regulate the motivational and reinforcing properties of social contact [114] and reduce physiological stress responses [154]. Emerging evidence suggests that oxytocin, vasopressin, and dopamine are necessary for the establishment of social bonds, whereas endogenous opioids contribute to feelings of 'dependence' that are necessary for humans to maintain long-lasting social relationships [152].

Music is widely regarded, among other things, as a system for emotional communication [110,111]. To the extent that speech communication modulates oxytocin levels, one might hypothesize that musical activities increase oxytocin levels. Oxytocin levels within the brain cannot be measured directly and it is not known whether peripheral oxytocin levels are a reasonable proxy for central release [118]; at present, researchers rely on serum levels as a presumed proxy. In one study, maternal speech ('motherese', a music-like signal) was found to cause peripheral oxytocin release in children who had been exposed to a social stressor [119]; indeed, the mother's voice alone was as effective as full maternal contact for oxytocin production. A single 30-minute singing lesson was associated with an increase in serum oxytocin levels relative to a pre-lesson baseline in both professional and amateur singers, with no reported differences between groups [57]. Open-heart surgery patients who listened passively to experimenter-selected 'soothing' music (i.e., soft, relaxing, of 60 to 80 beats per minute, with a volume of 50–60 dB) for 30 minutes one day after surgery had higher levels of serum oxytocin compared to bed-rest alone [120].

Confounding factors exist in the experiments reviewed here. In [57], musical activity was confounded with a social/group participation context and no nonmusic control condition was included. In [120], music listening was confounded with the patient's personal contact with healthcare providers administering the music.

It will be important for future studies to include nonmusical control activities that are well matched for social context (alone, in groups, with a teacher, etc.), medium of expression (i.e., vocal or verbal activities), type of intervention (active or passive), and mood. For example, a control condition for a private singing lesson could be a lesson in vocal technique for public speaking; listening to audiobooks could serve as a control for passive music listening. Using the participants' depression and anxiety scores as covariates to determine whether these factors contribute to the effects of musical manipulations on subjective relaxation and levels of oxytocin and physiological stress markers will also be valuable. Finally, it will be crucial to investigate directly the hypotheses that (i) musical activity – particularly when performed in groups – increases trust, social bonding and positive affect, and (ii) these beneficial social effects are mediated by oxytocin. Table 2 summarizes the findings by major psychobiological marker, participant population, and experiment.

Concluding remarks

Claims about the healing power of music are found in many pre-industrial societies and in ancient Greece. Over the past three decades, modern experimental methods have been brought to bear on the question of whether the effects are genuine and whether they are attributable to music *per se* as opposed to ancillary or confounding factors. A great deal has been discovered about the neuroanatomical basis for music [121], whereas not much is known about its neurochemical basis. Studies of the neurochemistry of music may be the next great frontier, particularly as researchers try to investigate claims about the effects of music on health outcomes (i.e., incidence of disease, severity of symptoms, quality of life, etc.) and clinical outcomes (i.e., efficacy of therapeutic interventions), which are more likely in neurochemical studies than in neuroanatomical ones.

If the notion of music as medicine is to be taken literally, it is crucial to employ as rigorous designs for its investigation as for testing traditional forms of medication. It may turn out that the mechanism of action for music is not due to the music itself, but to embedded or ancillary factors, such as distraction, mood induction, locus of control, and perceptual-cognitive stimulation. If this is the case, music may be effective, but not uniquely so – other interventions (crossword puzzles, films, plays) may show equivalent effects if matched for embedded factors.

The promise of music-based treatments is that they are noninvasive, have minimal or no side effects, are inexpensive, convenient, and completely 'natural'.

Consider, for example, the standard medication used for pre-surgical anxiety reduction, benzodiazepines. They are effective, but have a high incidence of unwanted side effects, including amnesia, as well as paradoxical agitation and hyperactivity. The amnesia, in addition to being stressful, can cause patients to forget physician instructions [88].

The evidence for the beneficial effects of music on reward, motivation, pleasure, stress, arousal, immunity, and social affiliation is mounting (excellent reviews can also be found in [53,122]). We consider the evidence to be promising, yet preliminary, due to numerous confounds and limitations of many studies performed to date. We note that – in most studies – the methods used did not qualify as Music Therapy, in that music intervention was not administered to participants by a licensed therapist. Instead, music intervention was administered to the participants by the experimenter or another type of health care professional (e.g., nurse). It remains to be investigated whether music administered in the context of a music therapy session is more effective than music interventions administered by other types of healthcare practitioners or by the

Box 5. Questions for future research

- Are the beneficial effects of music due to distraction, mood induction, feelings of social bonding/support, or other factors?
- Does musical pleasure arise primarily from anticipatory processes, consummatory processes, or both? Experimental administration of mu-opioid antagonists may be helpful in elucidating this question.
- What are the differential effects, if any, of playing vs listening to music?
- Are some people more likely to experience positive effects of music than others? If so, what individual differences (e.g., personality traits, genetic, or biological factors) modulate the effectiveness of music interventions?
- What comparison stimuli can be used to match music along dimensions of arousal, valence, attentional engagement, and mood induction?
- What is the role of endogenous oxytocin in mediating musical experience? This question could possibly be operationalized by administering tests that index level of social attachment, generosity, or altruism, such as the 'trust game' [155].
- What are the neurochemical and neuroanatomical homologues for music experience in non-human animals?
- What is the optimal role for skilled music therapists in the administration of musical interventions for health outcomes?

patients themselves. Future studies would benefit from the inclusion of music therapists as consultants or active members of research teams, because their perspective on the application of music in clinical settings may be informative.

We believe that three areas of research could have great impact on the field in the near future (Box 5):

(i) True experiments in which patients are randomly assigned to musical intervention or a rigorously matched control condition in post-operative or chronic pain trials. Here, it will be important for control tasks to include an equal amount of experimenter–participant interactions, as well as a stimulus that is well-controlled for similar arousal properties and emotional qualities. One control for music employed in the past is recorded speeches matched to music along several dimensions [123]; other suitable controls might include films, TV, comedy recordings, or audio books.

(ii) Experiments that aim to uncover the neurochemical basis of musical pleasure and reward, such as through the use of the mu-opioid antagonist naloxone in order to discover whether musical pleasure is subserved by the same chemical system (endogenous opioids) as other forms of pleasure. Suitable pleasurable conditions would need to be administered as comparisons, for example, food pleasure.

(iii) Experiments that aim to uncover the connection between oxytocin, group affiliation, and music, perhaps by administering oxytocin in a double-blind placebo protocol, to determine if oxytocin can induce or replicate many of the socially-mediated feelings attributed to music, such as social bonding and social comfort.

Other exciting avenues for future research include investigations into the contribution of stress hormones, vasopressin, dopamine, and opioids using biological assays (e.g., blood serum, saliva, urine), and pharmacological interventions with neuroimaging techniques. Although the controlled experimental approach of investigating one chemical system at a time while holding other factors constant is invaluable, there are undoubtedly neurochemical interactions that create emergent phenomena – these must ultimately be understood and addressed in multifactorial designs.

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