## Title

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**Symposium**

# Music and Brain Circuitry: Strategies for Strengthening Evidence-Based Research for Music-Based Interventions

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**The neuroscience of music and music-based interventions (MBIs) is a fascinating but challenging research field. While music is a ubiquitous component of every human society, MBIs may encompass listening to music, performing music, music-based movement, undergoing music education and training, or receiving treatment from music therapists. Unraveling the brain circuits activated and influenced by MBIs may help us gain better understanding of the therapeutic and educational values of MBIs by gathering strong research evidence. However, the complexity and variety of MBIs impose unique research challenges. This article reviews the recent endeavor led by the National Institutes of Health to support evidence-based research of MBIs and their impact on health and diseases. It also highlights fundamental challenges and strategies of MBI research with emphases on the utilization of animal models, human brain imaging and stimulation technologies, behavior and motion capturing tools, and computational approaches. It concludes with suggestions of basic requirements when studying MBIs and promising future directions to further strengthen evidence-based research on MBIs in connections with brain circuitry.**

*Key words:* **musical components; music-based interventions; brain circuits; technologies; therapeutic effects**

## Significance Statement

**Music and music-based interventions (MBI) engage a wide range of brain circuits and hold promising therapeutic potentials for a variety of health conditions. Comparative studies using animal models have helped in uncovering brain circuit activities involved in rhythm perception, while human imaging, brain stimulation, and motion capture technologies have enabled neural circuit analysis underlying the effects of MBIs on motor, affective/reward, and cognitive function. Combining computational analysis, such as prediction method, with mechanistic studies in animal models and humans may unravel the complexity of MBIs and their effects on health and disease.**

## Introduction

Music is an integral part of every human society. Music can bring pleasure, calm anxiety, soothe sorrow, inspire and/or stimulate movement, and promote social connections. Musical experiences may also have the remarkable ability to enhance brain and cognitive development, improve function and well-being, optimize the quality of life, and possibly ameliorate the symptoms of a broad range of diseases and disorders.

Recognizing the untapped therapeutic potentials of music-based interventions (MBIs), the National Institutes of Health (NIH), John F. Kennedy Center for the Performing Arts, and National Endowment for the Arts formed a collaborative partnership, Sound Health, in 2016. The journey started with a jointly organized workshop, Music and the Brain: Research Across the Lifespan, which was held in January 2017, to evaluate the state of basic and applied music research. In this meeting, a diverse panel of experts discussed the impact of music on the brain across the lifespan (childhood, adulthood, and aging) and made recommendations for enhancing research in each of these domains (Cheever et al., 2018). In the 2018 *Dialogues Between Neuroscience and Society* lecture, musician Pat Metheny discussed with a panel of Society of Neuroscience members the impact of music on the brain and the role of music in healing. Soon after, NIH issued a series of special funding opportunities to promote basic, mechanistic, and clinical research on MBI (Chen et al., 2018, 2020; Riddle et al., 2018a,b, 2020a,b). In 2021, NIH organized three workshops focusing on Laying the Foundation: Defining

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the Building Blocks of Music-Based Interventions, Assessing and Measuring Target Engagement—Mechanistic and Clinical Outcome Measures for Brain Disorders of Aging, and Relating Target Engagement to Clinical Benefit—Biomarkers for Brain Disorders of Aging, respectively. Discussions at these workshops resulted in the development of the NIH Music-Based Interventions Toolkit (Edwards et al., 2022). NIH also intends to support the development of research networks on MBIs with a particular emphasis on developing compelling research frameworks; identifying consistent terminology and taxonomy to guide future clinical research; supporting interdisciplinary collaborations and pilot studies to test novel mechanistic hypotheses; and developing strong mechanistic measures, outcomes, and biomarkers, with a special emphasis on several brain diseases and disorders, such as pain, Alzheimer's disease, Parkinson's disease (PD), stroke, and/or aging.

A central thesis involved in all these endeavors is the question of how MBIs achieve their therapeutic potentials. The power of music to influence movement, emotion, learning, and behavior is enormous. One hypothesis is that music's impact is linked to its ability to engage multiple neural systems of the brain. But what is the support for such a conclusion? If we are ever to harness music's multitude of influences, we need a solid understanding of the neural circuitry involved and rigorous evidence about how it is engaged by music. From a brain circuitry perspective, the idea may seem straightforward: as musical sounds are first processed by auditory mechanisms in our CNS, therapeutic effects derived from MBIs would most likely require the engagement of brain circuits and other physiological systems that are directly or indirectly connected to the auditory neural circuitry involved in perceiving and processing elements of music.

To test this idea scientifically, we first need to have clear definitions or characterizations of what music and MBIs are. Basic constituents of music include melody, harmony, and rhythm (Vuust et al., 2022). Each of these three elements has countless sequences, tempos, and dynamics or loudness of sound, and they can be combined in numerous ways. This enormous heterogeneity in musical contents is then implemented on a variable target population of MBIs (Loui, 2020) (Fig. 1*A*). The mode of MBI delivery also varies (Fig. 1*B*). The content of music may be heard in a receptive mode (Hanser, 2016), or it may be performed or presented by an individual in an active engagement mode often requiring some degree of motor activities, such as singing, playing an instrument, dancing, or even composing. In addition, MBIs may have a social interaction component if they are delivered in a group setting, such as listening in a concert hall with an audience, performing music as a group, or interactions between the performers and the listeners; or delivered by a music therapist to a patient or a group of patients, for instance. In MBI research, clearly describing the intervention itself, including music content and mode of delivery, in addition to other common intervention parameters, such as duration and frequency, may be the first important step. Music and MBIs have been associated with a variety of brain functions and disorders. Therefore identifying and testing the neural network connections between the auditory neural pathways where the sounds of music are first processed and other brain networks, such as motor, affective/reward, cognitive, as well as other sensory circuits, including pain, vision, and interoception, which impacts other physiological systems (Chen et al., 2021), will be critical to help us understand how MBIs may exert their therapeutic effects (Loui, 2020) (Fig. 1*C*).

This review article highlights research findings presented at the 2022 Society of Neuroscience Symposium *Music and Brain Circuitry: Strategies for Strengthening Evidence-Based Research*. Specifically, we will begin with the complexity of MBIs and the importance of neuroscience approaches to help address fundamentals of interventions, such as dosages. Comparative studies across multiple species, including birds, rodents, nonhuman primates, and humans (Fig. 1*D*), also offer significant insights into neural circuits involved in MBIs with a high level of rigor, especially regarding perception of music rhythm and the auditory and motor neural systems involved. Multiple brain imaging tools, including EEG and MRI, brain stimulation approaches, such as transcranial magnetic stimulation (TMS), as well as innovative behavioral analysis using technologies, such as motion capture and prediction analysis methods (Fig. 1*E*), further allowed investigators to probe the neural mechanisms and explore the neural network connections underlying the effects of music and MBIs on a variety of brain function and behavioral disorders.

## Fundamentals of music-based interventions

The myriad musical contents conferred by countless combinations of its constituents pose a major challenge for MBIs, especially in defining the intervention and maintaining consistency. In basic and mechanistic research, it may be possible to study musical constituents in a reductionist way by focusing on one or a few specific combinations or forms of constituents. In contrast, more holistic approaches by the music therapy community, for example, seem to share the general consensus that there is no one-size-fits-all program: while self-selected music confers the most therapeutic benefit for a variety of clinical applications, the music therapist consults with clients and caregivers to come up with the best available course of therapy with regard to content (musical components), mode of engagement (active or passive protocols), and duration and intensity (dosage) of the intervention (Wheeler, 2015).

Dosage is a fundamentally important aspect to consider when studying MBIs. Regarding the question of dosage, consider the analogous case of physical activity: the American Academy of Pediatrics recommends 60 min of activity per day in school-aged children (www.healthychildren.org), and the Global Council of Brain Health recommends to "strive for at least 150 min of weekly, moderate-intensity aerobic activity" for adults over age 50 to manage heart and brain health. Is there an equivalent "recommended dosage" for music-based interventions? The answer to this question is complex, as the experience of music itself is complex. Although every society has music, the musical cultures that societies around the world have evolved are diverse and variable (Savage et al., 2015). Even the same piece of music may elicit varying responses among individuals within the same culture, or for the same individual with repeated listening over time (Margulis, 2014). As such, music that has therapeutic benefits for one individual may not necessarily translate to another.

In this regard, neuroscience can inform the question of dosage in MBIs by quantifying the effects of receptive music (perception) and active music (production) interventions on the CNS. For instance, fMRI studies have shown that listening to self-selected music engages the auditory and reward systems more than music selected by the researcher (Pereira et al., 2011; Quinci et al., 2022), converging with the intuitions from music therapy. Longitudinal fMRI results in healthy older adults show that an 8 week receptive MBI increased functional connectivity from the auditory cortex to the reward system, specifically to the mPFC (Quinci et al., 2022). While these results remain to be further validated with control interventions that isolate the active ingredient of music listening, the idea that systematic engagement with music can change the connectivity of the auditory and reward systems is appealing because it offers a tractable method by which to quantify the impact of MBI dosage. While specific parameters of the dose–response relationship between music and health are too complex to be knowable at this time, the responsivity, sensitivity, and connectivity of the engaged brain circuits may serve as potentially viable quantitative measures for the dose–response relationship, thus offering a window of opportunity to dissect the complexity of MBIs and their impacts on brain and health in general.

### Comparative studies of musical rhythm perception

Among musical constituents, rhythm and temporal periodicity (sonic patterns which repeat regularly in time) are widely seen across species and have been richly studied. In humans, musical rhythm perception involves detecting such periodicities and generating precise temporal predictions about upcoming events (Merchant et al., 2015). This ability to detect and predict auditory rhythms is central to music's positive effect on a variety of neurologic disorders involving motor functions, including normalizing gait in PD (Benoit et al., 2014; Ghai et al., 2018; Krotinger and Loui, 2021), enhancing language recovery after stroke (Schlaug et al., 2009; Zumbansen et al., 2014), and improving phonological processing in dyslexia (Flaugnacco et al., 2015). While much remains to be understood about the neural mechanisms of rhythm perception, progress on this front has been facilitated by cross-species studies of perception along with incorporation of quantitative assessment and manipulation of neural activity.

Recent work has begun to elucidate the neural circuits for recognizing rhythmic communication signals based on tempo. For example, female field crickets are attracted to male calling songs within a narrow range of pulse rates, and this selectivity is mediated by

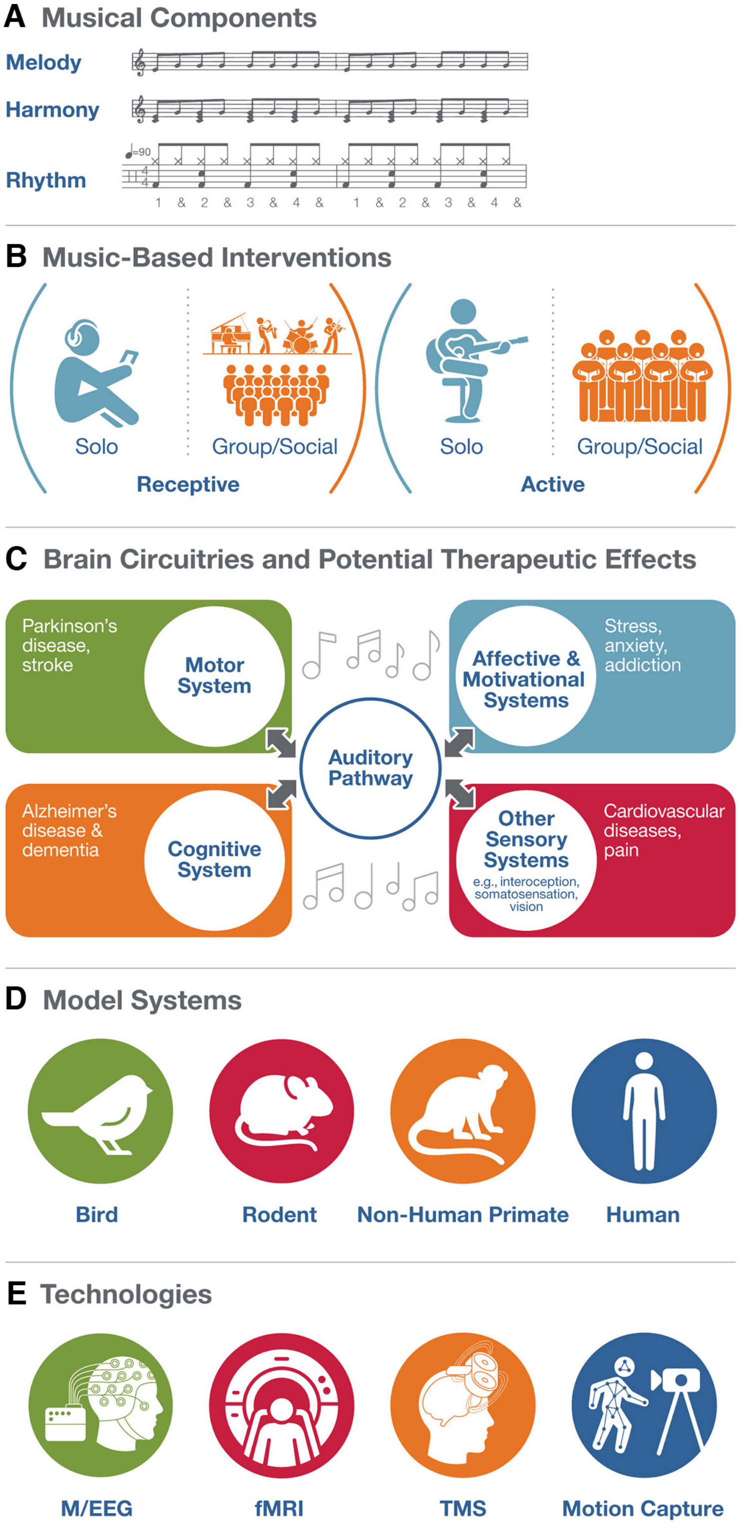

**Figure 1.** Evidence-based research on MBIs. ***A***, Illustrative examples of components of music, including melody, harmony, and rhythm. ***B***, Examples of the modes of delivery of MBIs. Receptive modes: when a subject passively listens to musical components. Active modes: when a subject actively performs musical components. Solo modes: when a subject is passively listening to (receptively) or actively performing musical components. Group/Social modes: when a subject is receiving or performing music in a group setting, or when a subject is, or subjects are, interacting with a music therapist or therapists. ***C***, Brain circuits engaged in potential therapeutic effects by MBIs. Musical components are first processed through the auditory pathway. Evidence has emerged to support neural network connections between auditory and motor or affective/motivational systems, which may underlie MBI's therapeutic effects on related diseases, such as PD, stroke, stress, anxiety, and addition. The neural network connections between the auditory pathway and cognitive or other sensory systems, such as interoception, somatosensation, nociception, and vision, remain to be explored for implications on diseases, such as Alzheimer's disease, dementia, cardiovascular diseases, and pain. ***D***, Examples of biological/model systems studied in MBI research include birds, rodents, nonhuman primates, and humans. ***E***, Examples of technologies used to study MBIs. Examples of brain imaging technologies include MEG, EEG, and fMRI. An example of brain stimulation technology is TMS. An example of behavior capturing technology is a motion-capture and tracking system.

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a network of interneurons that processes instantaneous pulse rate using a coincidence detection mechanism (Schoneich, 2020). While preference for pulse rate is hard-wired in many invertebrates, experience can shape neural responses to call rates in other species. For example, excitatory neurons in a mouse auditory cortex are innately sensitive to the most common rate of pup distress calls (~5 syll/s), but their tuning can broaden to a wider range of rates following cohousing with pups producing a range of call rates (Schiavo et al., 2020).

Moving beyond tempo, several studies have shown that auditory responses can be modulated by the presence of rhythmic patterns. For example, in gerbils, responses of neurons in the inferior colliculus are greater for noise bursts that occur on the beat of complex rhythms compared with the same bursts off the beat (Rajendran et al., 2017). In mice, excitatory neurons in the auditory cortex integrate signals over longer timescales and distinguish between rhythmically structured and irregular sequences by adjusting spike timing (Asokan et al., 2021). Moreover, in monkeys, EEG recordings have shown that deviant sounds elicit a larger auditory mismatch negativity signal when they are embedded in isochronous versus randomly timed sequences (Honing et al., 2018).

While such studies demonstrate context-dependent modulation of neural activity in auditory regions, there is growing evidence that human rhythm perception relies on interactions between auditory and motor regions, even in the absence of movement. As discussed later in this review, neuroimaging studies have shown that activity in several motor planning regions, including the premotor cortex, supplementary motor area, and basal ganglia, is greater when a stimulus has a strong periodic pulse, or beat (Grahn and Brett, 2007; Kung et al., 2013; Kasdan et al., 2022). In addition, transient disruption of auditory-motor connections using TMS can disrupt beat perception in humans without affecting perception of the timing of absolute intervals (Ross et al., 2018). Together, these results support the hypothesis that perception of temporal regularity depends on the interaction of auditory and motor regions.

Investigation of the functional contribution of motor regions to auditory rhythm perception would benefit greatly from a small animal model that (1) possesses reciprocally connected auditory-motor circuitry; and (2) can recognize rhythmic patterns. Like humans, songbirds possess specialized auditory-motor circuits for learning and producing rhythmically patterned sequences (Norton and Scharff, 2016; Roeske et al., 2020). Anatomical, physiological, and histochemical studies have found remarkable similarities in the premotor, auditory, and basal ganglia circuitry of birds and mammals, including shared cell types, patterns of connectivity, electrophysiological properties, and laminar organization (Doupe et al., 2005; Goldberg and Fee, 2010; Goldberg et al., 2010; Wang et al., 2010). A recent study found that zebra finches, the most commonly studied songbird, can detect temporal regularities in auditory sequences and predict the timing of calls of a vocal partner, allowing them to adjust the timing of their own answers to avoid overlap (Benichov et al., 2016). This ability to predictively adjust call timing was disrupted by lesions of vocal motor regions, consistent with the idea that call timing plasticity depends on the interaction of forebrain motor and auditory regions. However, it remains unclear whether zebra finches can perceive rhythms holistically or whether they learned the specific time interval between the vocal partner's calls and their own.

To examine whether songbirds can perceive rhythms holistically, as humans do, a behavioral paradigm to test whether zebra finches can learn to recognize a fundamental rhythmic pattern, equal timing between events, or "isochrony," has been developed (Rouse et al., 2021). Humans readily recognize isochrony across a wide range of rates (Espinoza-Monroy and de Lafuente, 2021), indicating a facility with perceiving the relative timing of events, not just absolute interval durations. Using a sequential training procedure, whether zebra finches could discriminate between isochronous and arrhythmic sequences of a repeated song element was probed. By varying sound element identity and tempo across stimuli, birds were incentivized to attend to the relative timing in auditory sequences, rather than to specific spectral features or interval durations (Rouse et al., 2021). Once birds reached a performance criterion for overall accuracy, they were tested for the ability to generalize the discrimination to stimuli at novel tempi. This study found that zebra finches, like humans, can robustly recognize isochrony across a broad range of rates, including rates 20% slower and 25% faster than the original training stimuli. Notably, birds that successfully discriminated isochronous from arrhythmic stimuli listened to more intervals before responding than birds that failed, suggesting that success at rhythm discrimination is related to attention to global temporal patterns. This aligns with evidence from neuropsychology studies showing that neural mechanisms underlying detection of relative timing are distinct from those involved in encoding absolute timing (Grube et al., 2010; Teki et al., 2011; Breska and Ivry, 2018).

The finding that zebra finches, like humans, can categorize rhythms based on global temporal patterns contrasts with prior work in vocal nonlearners. For example, rats can be trained to discriminate isochronous from arrhythmic rhythms but show weak generalization when tested with stimuli at novel tempi, suggesting a strong reliance on absolute timing for rhythm perception (Celma-Miralles and Toro, 2020). Thus, the combination of a well-defined auditory-motor circuit and the ability to recognize relative timing make songbirds a tractable small animal model to investigate the contributions of motor regions to detecting temporal periodicity and predicting the timing of upcoming events, two hallmarks of rhythm perception in humans. Future experiments manipulating neural activity can test for a causal role of forebrain motor regions in the perception of rhythmic patterns independent of rate, and neural recordings will help to reveal whether predictive activity emerges in motor regions as birds learn to discriminate isochronous from arrhythmic stimuli. More generally, such mechanistic studies of auditory-motor interactions during rhythm perception should help to inform music-based interventions for enhancing function in normal and disease states.

## Music and motor circuits

Similar to the animal species discussed earlier, humans have a special way of perceptually and motorically interacting with rhythmic stimuli. Repeating patterns of beats, or meter, establish a temporal scaffolding that shapes future expectations, shapes the perceptual meaning of individual events, and enables behavioral synchronization among groups of people.

One of the more intriguing ideas emerging from the field is that the motor system may be important for the ordered perception of musical structure, even in the absence of overt movement (Repp, 2005; Schubotz, 2007; Zatorre et al., 2007; Arnal, 2012; Patel and Iversen, 2014; Ross et al., 2016; Rimmele et al., 2018).

Many accounts, such as the Action Simulation for Auditory Perception (ASAP), emphasize the role of the motor system as a source for generating temporal expectations about upcoming events, a critical biological function, specifically hypothesizing motor to auditory connectivity (Patel and Iversen, 2014; Cannon and Patel, 2021). Recent work has specifically examined the motor system's involvement in shaping the perception and imagery of auditory rhythm in the absence of movement, directly testing the predictions of the ASAP and other motor hypotheses and providing insight into temporal perception using advanced EEG and Mobile Brain/Body Imaging (MoBI) methods. MoBI is a new imaging approach using mobile brain imaging methods, including the EEG and/or near infrared spectroscopy synchronized to body motion capture and other behavioral and psychophysiological data streams to investigate brain activity supporting participants actively interacting with their environment and/or with others (Makeig et al., 2009; Gramann et al., 2011, 2014).

EEG measures voltages present at the scalp as a result of dynamic electrical activity in the brain, but any single electrode measures the sum of activity from many regions of the cortex. One solution is independent component analysis (Makeig et al., 1996), a method to optimally unmix the scalp signals and identify putative cortical sources. A recent study used auditory and motor localizer trials and independent component analysis to identify the most unimodal auditory and motor independent components in human participants and then examined auditory-motor interactions during a meter imagery task (Cheng et al., 2022). Participants first heard an unaccented control series of drum strokes, followed by accented strokes that established a duple (1-2) or triple (1-2-3) meter, followed again by unaccented strokes with the instruction to continue imagining the previously established meter. To verify the imagery task, participants finally tapped the meter they had imagined. By comparing brain activity during the unaccented control and the meter imagery conditions, two predictions of ASAP were confirmed: (1) representation of meter was present in brain signals during meter imagery in both auditory and motor regions; and (2) robust, bidirectional motor to auditory connectivity (assessed using a directional measure of "causal" influence) (Korzeniewska et al., 2008) was present during imagery. A problematic potential confound for any work on imagery is the presence of possibly unintentional, subtle movements, which can be ruled out by using MoBI methods, including motion capture and the measurement of muscle potentials. The use of neurostimulation to causally manipulate brain activity makes it possible to directly test the importance of the motor system for auditory perception. ASAP proposes a specific pathway to mediate auditory/motor reciprocal interactions, the dorsal auditory stream linking auditory cortex to premotor cortex via parietal cortex (Rauschecker, 2011). One can predict that interruption of this pathway would disrupt beat perception. TMS is one method by which activity on localized cortical regions can be temporarily suppressed (e.g., using continuous theta-burst stimulation) (Huang et al., 2005). Continuous theta-burst stimulation over parietal cortex has been shown to impact aspects of beat perception but spare other forms of temporal processing, providing causal evidence in favor of ASAP (Ross et al., 2018).

While it is common to think of music as an auditory phenomenon, something we can thoroughly enjoy through headphones, music and movement are inseparable in several ways. Until the advent of recorded music, all music was created by movement. Many types of music strongly compel movement and dance, an aspect that has been used profitably in therapies for movement disorders. One example may be active MBIs that take advantage of musical groove, which is the pleasurable urge to move to music, possibly through connections to broader neural circuits, including the motor systems. The experience of groove is strongest for slight violations to rhythmic structure (Janata et al., 2012; Witek et al., 2014), and is causally linked to sensorimotor coupling as demonstrated by TMS studies (Stupacher et al., 2013). As such, the use of groovy music to motivate dance may be an important ingredient in active MBIs for movement disorders, such as PD, which is associated with a loss of internal cues for timing and movement, as evidenced by impaired rhythm discrimination in PD patients (Grahn and Brett, 2009). As music and dance engage sensorimotor coupling through rhythm and groove, this has inspired interventions, such as Dance for PD, which is a program that uses dance as an intervention for individuals with PD and their caregivers. Standardized neurologic pre-post testing showed a reduction of Parkinsonian symptoms following 4 months of Dance for PD, with better improvement observed for those who were more accurate at finger-tapping in rhythm to music, suggesting more accurate sensorimotor coupling (Krotinger and Loui, 2021). The presence of lifelong dance experience was also associated with greater reductions of both motor and nonmotor symptoms after dance intervention, suggesting that long-term training engages the predictive processes that may underlie more efficient sensorimotor coupling, which may have synergistic benefits for active MBIs.

In the past 15 years, the field of MoBI has emphasized the study of brain activity underlying active and naturalistic interactions with the environment and with others, using mobile neuroimaging methods, such as EEG, to measure brain dynamics synchronized to full-body motion capture and other behavioral and psychophysiological data streams (Makeig et al., 2009). The approach is particularly attractive in therapeutic and at-home contexts because of the emerging availability of low-cost and portable EEG systems, simple camera-based motion capture, and low-cost wrist-worn physiological sensors. The study of music is a natural fit to MoBI, which has been successfully applied to studies of individual and group musical behavior (Maidhof et al., 2014) toward understanding of interpersonal interactions among performers (Chang et al., 2018; Varlet et al., 2020), between performer and audience (Swarbrick et al., 2018), and among audience listeners and dancers. Cooperative musical and dance interactions involve developing trust (Stupacher et al., 2013; Trainor and Cirelli, 2015), are positively related to interpersonal empathy (Novembre et al., 2019), and can be effective for the communication of intentions and emotion through movement (Leslie et al., 2014). A recent study showed that cooperative musical interactions led to long-lasting changes in interbrain phase coherence (Khalil et al., 2022), perhaps indicative of a lasting cooperative set. These relationships underlie aesthetic interactions but also therapeutic ones; thus, this line of work may have broader implications for the understanding of how to create and evaluate effective therapeutic interactions in general (Foubert et al., 2021). By enabling low-cost and portable assessment of brain and body states, MoBI methods will improve understanding of the mechanisms by which ecologically complex MBIs achieve therapeutic goals. These methods will also open the way for exciting new modalities of real time brain/body feedback for rehabilitative and augmentative training (Blanco and Ramirez, 2019; Turner et al., 2021).

## Music and reward circuits

The reward system consists of various neural structures, including the midbrain tegmentum, the striatum in the basal forebrain, the ventromedial and orbitofrontal cortex, and various other regions all interconnected in complex ways (Haber, 2017). It plays a role in many basic biological functions and is thought to underlie our experience of hedonic pleasure (Berridge and Kringelbach, 2015). Yet, until about two decades ago, it was not even known whether the pleasure generated by music was mediated by this same system; indeed, some philosophical traditions argued strongly against it (Skov and Nadal, 2020).

A series of neuroimaging studies has shown that the striatum and related structures become activated when people experience pleasure from music, and that these responses scale with the degree of musical pleasure experienced (Blood and Zatorre, 2001; Koelsch et al., 2006; Montag et al., 2011; Salimpoor et al., 2013; Matthews et al., 2020), as summarized in a recent a meta-analysis (Mas-Herrero et al., 2021b). Furthermore, psychophysiological indices of autonomic system engagement (heart rate, skin conductance, respiration, etc.) also increase with subjective reports of musical pleasure (Grewe et al., 2007; Salimpoor et al., 2009). In addition, the laboratory of R.J.Z. showed that the striatal response is dopaminergic in nature (Salimpoor et al., 2011; Ferreri et al., 2019), and that it is related to reward prediction mechanisms (Gold et al., 2019), thus linking musical engagement of the reward system to the extensive animal literature on dopaminergic mediation of reward prediction error (Schultz, 2016).

These findings were critical in setting the stage for a scientific understanding of music's effects but do not on their own provide a functional model of how music activates the reward system. Furthermore, imaging studies are necessarily correlational in nature, so causal evidence was required to really prove the point. Recent advances have addressed both these issues.

Several studies have shown that, as the subjective liking of music increases, the functional connectivity between auditory cortical systems and reward structures also increases (Salimpoor et al., 2013; Shany et al., 2019; Quinci et al., 2022). This idea is very important as it suggests that patterns of sound processed in the auditory system are assigned value within the reward system. More specifically, sensory prediction errors computed in auditory cortical networks are believed to be propagated to the reward system where they are assigned value according to a reward prediction mechanism (Zatorre, 2023). Thus, according to this model, musical pleasure would arise from the crosstalk between these two systems.

If this idea is correct, it leads to the prediction that people with little or no hedonic response to music should exhibit reduced interactions between the two systems. This is precisely what was observed in a series of experiments exploring specific musical anhedonia, defined as a condition in which individuals experience very little pleasure to music, yet have no perceptual deficit, nor any generalized depression or anhedonia (Mas-Herrero et al., 2014). When tested with functional imaging, people with musical anhedonia showed reduced functional connectivity between auditory and striatal areas compared with average listeners and also compared with "hyperhedonic" music lovers, who showed the greatest degree of functional interaction (Martinez-Molina et al., 2016). Furthermore, structural imaging of musically anhedonic people showed evidence of reduced anatomic connectivity in auditory-orbitofrontal white-matter tracts (Martinez-Molina et al., 2019).

These findings strongly support the auditory-reward interaction model of musical pleasure. But more direct causal evidence was still lacking. If musical pleasure arises from these interactions, modulations of this auditory-reward circuit ought to lead to modifications of the experience of pleasure. To do so requires a method that allows for stimulation of deep structures. TMS is typically used to modulate cortical structures but can also be used to influence the striatum via targeting of dorsolateral frontal areas that are connected to it (Strafella et al., 2001). Importantly, depending on the parameters of stimulation, it is possible both to upregulate dopamine activity in the striatum or downregulate it (Pogarell et al., 2007; Ko et al., 2008).

A recent study combined these brain stimulation methods with the music-induced pleasure measures (behavioral and psychophysiological) already validated in the neuroimaging studies described above (Mas-Herrero et al., 2018). The results clearly showed that, after receiving excitatory TMS (compared with sham) targeting dorsolateral frontal cortex, listeners reported higher subjective rankings of music-induced pleasure, as well as higher objective psychophysiological responses; conversely, after inhibitory TMS, both types of dependent variables were reduced. The finding that the degree of pleasure we feel can be modulated in either direction by transiently changing the excitability of certain brain structures fits the predictions of the model very well. But the final step in the logical chain would require that a direct link be shown between modulation of auditory-reward connectivity and modulation of music-induced pleasure.

To achieve this goal, Mas-Herrero et al. (2021a) repeated the TMS experiment with a new sample of volunteers and different musical excerpts, but this time fMRI was acquired immediately after the TMS session, to document the neural changes associated with the stimulation. The behavioral findings from this study mirrored those from the previous one, showing that the stimulation effects are robust and replicable. The most important finding from the fMRI data were that the functional connectivity between the right auditory cortex and the right ventral striatum was modulated in direct relationship with the degree to which the stimulation changed pleasure ratings. Thus, enhancement or decrement in pleasure following stimulation was related to upregulation or downregulation of the auditory-reward circuitry. This outcome thus provides definitive, causal evidence in favor of the hypothesis that these interactions underlie the experience of musical pleasure.

Although much remains to be discovered, these experimental findings, together, provide a mechanistic understanding of the neural basis of music-induced pleasure. Such basic-science knowledge is essential to move forward with potential applications of music to various disorders. Indeed, we know that affective states can be manipulated via music (including mood induction or emotion regulation, for example). It is likely that the reward system plays a key role in these functions, which is consistent with the view of music as a transformative technology of the mind (Patel, 2008, 2018; Loughridge, 2021) in the sense that music both emerges as a creative product of the mind and can shape the mind by affecting its function. This underlying mechanism may therefore explain why music can be used to improve mood, reduce anxiety, and enhance well-being in many different clinical groups, including psychiatric disorders (Gebhardt et al., 2014), depression (Maratos et al., 2011), stroke (Särkämö et al., 2008), heart disease (Bradt et al., 2013), and dementia (Guétin et al., 2011; for systematic reviews and meta-analysis, see Sihvonen et al., 2017; de Witte et al., 2020).

## Music and cognitive and sensory circuits

The relationships between music and cognitive or sensory functions have been explored largely in human subjects.

Longitudinal studies have shown that multiple years of music education or training are associated with enhanced executive functions, including inhibition, planning, and verbal intelligence in school-aged children (Jaschke et al., 2018; Hennessy et al., 2019). Similarly in older adults, musical practice has also been shown to benefit cognitive function (Roman-Caballero et al., 2018); while various forms of MBIs seem to benefit cognitive functions, including short-term and working memories, digit span, orientation, fluency, abstraction, and psychomotor speed, as well as reduce pain in people with dementia (Hofbauer et al., 2022). A substantial amount of literature can also be found to support music as an adjuvant pain treatment (Lunde et al., 2019). In contrast, relatively few studies focus on the brain mechanisms by which MBIs deliver their cognitive and sensory effects in humans (Chaddock-Heyman et al., 2021) or in an animal model (Zhou et al., 2022).

One concept for music to shape cognitive circuits lies in its ability to engender predictions (Vuust et al., 2022): as we become exposed to musical sounds throughout the lifespan, the brain continuously and automatically learns to form predictions for sounds that will likely come next, and the implicit learning of these predictions and minimization of prediction errors shapes the cognitive circuits that give rise to one's body of knowledge, including of music within the culture. As a concrete example of these cognitive circuits at work, most listeners within the Western culture show implicit knowledge of musical scale: in common-practice Western music, musical scales are based around the octave, which is a doubling of acoustic frequency. This knowledge is based on exposure to the environment through one's culture, and the ability to learn from the environment via statistical learning as a cognitive mechanism is key among the cognitive circuits that give rise to musical knowledge. To test the cognitive mechanism of statistical learning outside of Western culture, Loui and colleagues (Loui et al., 2010; Loui, 2022) used digital musical technology to create music in the Bohlen–Pierce scale, which is an alternative tuning system based on a tripling of acoustic frequency. Systematically manipulating predictions for music composed in this new scale affected liking of the new music: more frequently presented patterns were more preferred, suggesting a dose–response type relationship between familiarity and preference. The statistical learning of predictions was comparable across U.S. and Chinese populations, suggesting a relatively similar dose–response relationship across cultures. Furthermore, functional neuroimaging showed that statistical learning of predictions was tied to the activity and connectivity of the auditory and reward systems (Kathios et al., 2022). Together, these results underlie the idea that prediction and reward may be a cognitive mechanism that explains how musical sounds become rewarding. Future work is needed to relate prediction and reward learning to the transfer effects of musical experiences toward more domain-general cognitive functions, which may in turn underlie the success of MBIs for multiple clinical populations.

## Discussion

Collectively, this review aims to highlight a few approaches and examples of studies on music and a variety of brain circuits, rather than attempt to be comprehensive in the entire literature covering music and neuroscience. As we study music in the context of brain and health, thus studying music as an intervention, it is important to clearly define and describe the basic contents of an MBI, either including the chosen melody, harmony, and rhythm at the minimum, or articulating the contents of the self-selected music at the onset of a study. Whether an MBI is delivered in a receptive mode to a study subject by passively listening to the musical content or in an engaging active mode with the study subject participating in producing the musical content, or both, should also be clearly specified, in addition to whether an MBI involves a group setting, either as a group listening or performing event or as an interaction between therapists, teachers, or performers and patients, students, or audience. Clear specifications of the musical content and delivery mode can enable a better design of the control interventions as often required in rigorously designed mechanistic and clinical studies. Like all other types of intervention studies, determining the dosages, including intensity of the music contents as well as the frequency and duration of the delivery, should be a fundamental requirement for MBI studies.

In terms of comparative studies of MBIs, this review has emphasized the power of animal models in vocal learning species, such as songbirds, in elucidating auditory-motor interactions in rhythm perception, which may ultimately help us understand how and why periodic auditory rhythms can help normalize motor function in disorders, such as stroke and PD. Animal models are also critical for understanding interactions between auditory regions and other neural circuits, including the reward system and pathways for detecting and coding noxious stimuli that cause pain. For example, work in songbirds has begun to elucidate auditory-reward interactions. In male birds, dopaminergic neurons are sensitive to the quality of the bird's own vocal performance, exhibiting differential firing rates when song performance is better or worse than expected ("reward prediction error") (Gadagkar et al., 2016). Similarly, recent work in mice has begun to shed light on the neural mechanisms underlying the ability of music to attenuate pain intensity in humans (Garza-Villarreal et al., 2017). Using a mouse model for peripheral pain, Zhou et al. (2022) found that sound (and potentially music) presented at a level slightly above background noise can blunt behavioral signs of pain by modulating cortico-thalamic input from auditory regions to posterior and ventral posterior nuclei of the thalamus. This effect can last for several days after sound exposure, so it cannot be explained by sound's short-term effect on attention. Together, these studies highlight the utility of animal models for investigating the mechanistic underpinnings of both active and receptive MBIs. Future endeavors captalizing on the power of molecular genetics in combination with sophisticated behavioral assays to probe motor, affective, cognitive, and sensory systems, such as audition, pain, interoception, and vision, may facilitate the discovery of novel mechanistic insights into MBIs.

In human brain circuit studies, EEG, MEG, and fMRI have helped to elucidate neural networks involved in MBIs. Much of the brain imaging evidence has supported the engagement of auditory, motor, and reward/affective neural circuits, some of which is further enhanced evidence provided by brain stimulation studies using technologies, such as TMS and high-resolution behavioral data collected by cutting-edge motion capture technologies. The evidence for engagement of cognitive and other sensory brain circuits unique to MBIs has, however, been relatively scant. Future studies incorporating powerful brain imaging and stimulation technologies and novel behavioral assessments may be needed to ascertain whether cognitive and other sensory circuits are also engaged during MBIs in human populations.

In conclusion, the complexity of MBIs and their potential impact on multiple brain circuits may require sophisticated computational approaches to further mechanistic understandings. Predication analysis, already applied for studying the relationships between music and motor, reward, and cognitive circuits, is a well-tested example of how a computational approach may enhance mechanistic insights. Development of cutting-edge computational tools, including machine learning methods, may help inform evidence-based research of MBIs in the future.

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