Music, selves and societies: the roles of music in effecting change – Article

Neuroscientific Insights for Improved Outcomes in Music-based Interventions

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Abstract

Music therapy is an evidence-based practice, but the needs and constraints of various stakeholders pose challenges towards providing the highest standards of evidence for each clinical application. First, what is the best path from clinical need to multi-site, widely adopted intervention for a given disease or disorder? Secondly, how can we inform policy makers that what we do matters for public health—what evidence do we have, and what evidence do we need? This article will review the multiple forms of evidence for music-based interventions in the context of neurological disorders, from large-scale randomized controlled trials (RCT) to smaller-scale experimental studies, and make the case that evidence at multiple levels continues to be necessary for informing the selection of active ingredients of interest in effective musical interventions. The current article reviews some of the existing literature on music-based interventions for neurodegenerative disorders, with particular focus on neural structures and networks that are targeted by specific therapies for disorders including Alzheimer's Disease, Parkinson's Disease, and aphasia. This is followed by a focused discussion of principles that are gleaned from studies in cognitive and clinical neuroscience, which may inform the active ingredients of music-based interventions. Therapies that are driven by a deeper understanding of the musical elements that target specific disease mechanisms are more likely to succeed, and to increase the chances of widespread adoption. The article closes with some recommendations for future research.

Music-based Interventions as Complex Interventions

Many complex interventions have been developed in recent years for neurological and psychiatric diseases and disorders. Complex interventions are programs for people with specific diseases and/or disorders that have multiple interacting components, or those that have to be implemented on a variable target population. In designing and implementing complex interventions to improve health, the Medical Research Council (MRC) of UK recommends four key elements of the development and evaluation process: Feasibility (piloting), Development, Implementation, and Evaluation (Campbell et al., 2000). Relatedly, the United States Food and Drug Administration (FDA) established the following four-phase framework for clinical trials (2018). Phase I is the modeling phase, in which the possible active ingredients of a potential intervention are delineated. Phase II is the exploratory trial, in which the active ingredients

identified from Phase I are experimentally manipulated and evaluated until an intervention is distilled. Phase III is the definitive randomized controlled trial (RCT), in which researchers conduct a formal comparison between the targeted intervention with a control intervention based on best practices at the time. Finally, Phase IV is a long-term, multi-site implementation, in which the real-life applicability and long-term effectiveness of an intervention is determined.

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Music-based interventions are prototypical complex interventions, as the target populations are intrinsically variable, and elements of the musical intervention (such as rhythm, melody, motor movement, and social interaction, among many others) may have different effects on different individuals even within a given target population. In adapting the above four-phase frameworks to music-based interventions, at each point in the pathway towards widespread adoption, therapists should be aware of the active ingredients within the intervention and how they exert their effect, and the therapy should be assessed for its scientific reliability as well as its practical effectiveness.

The central point of this article is that interventions that target the underlying neurobiology of the disease state are more likely to be successful and will increase chances for wider adoption. Dealing with the intrinsic variability of target populations requires specific knowledge on the underlying active ingredients of an intervention. Thus, while well-powered Phase III and IV RCTs are the ultimate aim, Phase I and II studies on the mechanisms underlying music-based interventions remain crucial for the design of better interventions. While this need has been discussed previously in the context of stroke recovery (Chen, 2018), the current article generalizes the reviewed literature to neurodegenerative diseases, including Alzheimer's Disease and Parkinson's Disease. From there, a few possible underlying mechanisms are described through which music can target specific brain networks. This includes networks for spontaneous cognition, motor function, and prediction and reward, as well as networks that are normally redundant but may gain crucial function during disease recovery. Finally, this article raises a few examples in which knowledge of these mechanisms may inform specific decisions regarding the pathway to recovery. Throughout the article we use the term "music-based interventions" as a generic term, and reserve the term "music therapy" for when referencing an intervention conducted by trained music therapists specifically.

Challenges of Music-based Interventions

Systematic reviews of music-based interventions have demonstrated some benefits in multiple neurological and psychiatric disorders including depression (Maratos et al., 2008), dementia (McDermott et al., 2013; van der Steen et al., 2018; Vink et al., 2003), autism (Gold et al., 2006), aphasia (Schlaug et al., 2010), and acquired brain injury (Magee et al., 2017). However, the quality of much of the evidence is mixed (Magee et al., 2017; Vink et al., 2003). As Phase III RCTs are regarded as a high level of evidence (Wright et al., 2003), it is worth pursuing RCTs with careful attention to experimental design and a well-matched control intervention, an important topic that is reviewed elsewhere (Bradt, 2012). Nevertheless, in music as in many complex behavioral interventions, the RCT may be impossible or impractical due to its requirements for double-blinding. While examining other options to the RCT below, more work is still needed in Phases I and II of the complex intervention cycle, in which the theoretically important active ingredients of interventions are defined and distilled into a high-quality RCT, with an appropriate control intervention that engenders similar expectancy effects to the experimental treatment.

One difficulty of RCTs is that many of the blinding requirements are not always available when offering music-based interventions. This leaves us with several alternatives. One option is an open-label trial (NCI, 2020), in which both the participants and the researchers know which intervention is being administered (but it should be designated as such), or to have multiple music-based designs in which specific elements are varied without the participants being aware. Another important aspect to consider for the RCTs is that the necessary sample size of the trials scales with the complexity of the design, and can require up to hundreds of participants. This often leads to inclusion considerations that do not take into account the immense range of individual differences relating to music processing, such as the effects of musical training and experiences (Trainor & Corrigall, 2010). Therefore, the risk of a type 2 error (false negative) is increased by having too inclusive a patient group (Savovic et al., 2012). This might mean that for music interventions, there is a need to continue searching for alternative ways of producing high-level evidence.

Meta-analyses of RCTs for music interventions provide helpful information about the potential effect sizes as well as the quality of evidence favoring music therapy over treatment-as-usual, or over other control interventions. As an example, a systematic review and meta-analysis of nine RCT and other clinical controlled studies in major depression (total $n = 411$) shows that compared to treatment-as-usual, there is moderate quality evidence (i.e., the true effect is likely to be close to the estimate of the effect (Aalbers et al., 2017)) that the addition of music therapy reduces clinician-rated depressive symptoms and patient-reported depressive symptoms (Aalbers et al., 2017). However, little is known about how music therapy compares against other psychological interventions such as cognitive behavioral or psychosocial interventions (Aalbers et al., 2017). Evaluations of music therapy in depression suggest that a meaningful and important component of the therapy is active engagement, wherein the patient engages in the production of sounds along with the therapist (Maratos et al., 2011). The benefits of active sound production for people with depression are thought to be tied to aesthetic, physical (motor or agentic), and relational (interpersonal) gains (Maratos et al., 2011). These three types of gains are maximized in interventions that feature improvising music together with a therapist who acts as a supervisor and partner, such as in the Nordoff-Robbins technique (Nordoff & Robbins, 1977). Understanding the neural networks that underlie this co-improvisatory experience may inform

neurorehabilitation therapy protocols in which the networks that are disrupted in the typical course of the disease are specifically identified and targeted in the intervention.

While meta-analysis found moderate quality of evidence for the efficacy of music therapy in depression, the picture is more complex for several other disorders. For autism spectrum disorders (ASD), a meta-analysis of RCTs to date (10 studies; 165 participants) showed that music therapy helps children with ASD improve verbal communication and social skills (Geretsegger et al., 2014; Gold et al., 2006). However, the methodological strength of these findings is limited by small sample sizes and differences between outcome measures. In addition, more experimental work is needed to examine whether the effects of music therapy endure past the duration of the intervention.

For acquired brain injury including stroke and tumors, a meta-analysis of 29 trials including 775 participants showed that music intervention, including active and receptive music therapy, improves gait and motor function of the upper extremities via rhythmic auditory stimulation (Magee et al., 2017). Music interventions were also found to be beneficial for communication outcomes following aphasia, with moderate effect sizes of up to .75 standard deviations improvement in the intervention group (Magee et al., 2017). However, the studies reviewed were found to present a high risk of bias, undermining the quality of the evidence (Magee et al., 2017).

Meta-analytic evidence from music-based interventions for people with dementia also shows variations in the quality of evidence, with small samples and high risk of performance bias and detection bias resulting from unblinded studies (van der Steen et al., 2018). A recent RCT for Alzheimer's Disease (Lyu et al., 2018) compared performance on neuropsychological tests on a total of 298 AD patients who were randomly assigned to three months of singing intervention, lyric reading intervention, and no-intervention control. Results showed that singing improved verbal fluency and alleviated psychiatric symptoms and caregiver distress compared to lyric reading. Specifically, music therapy was more effective for cognitive measures in mild cases of AD but more effective for emotional and social measures in moderate to severe cases.

Taken together, although a large number of studies have been published evaluating musical interventions in a variety of diseases and disorders, the evidence is mixed and is plagued by limitations in sample sizes, risks of bias, and differences in outcome measures across studies, as well as by the intrinsic variability between different cases and levels of severity even of the same apparent disorder. These limitations highlight the need for a deeper understanding of the mechanisms underlying different pathologies, and the ways in which music might support privileged access towards these underlying mechanisms, thus offering tangible routes towards rehabilitation and recovery.

Targeting Specific Brain Networks

Having outlined some of the challenges from existing interventions as indicated by meta-analyses of music-based interventions on a variety of disorders, I now turn to specific findings from clinical and cognitive neuroscience that may inform future interventions. As health interventions have different therapeutic goals depending on the disease, they should also target different systems and networks within the brain. In this section I review a few possible networks that could be targeted by specific music-based interventions, especially for neurodegenerative diseases and disorders.

Networks for Familiar Music

One possible route through which effective interventions may function is by activating areas and networks that are spared in brain degeneration or injury. In Alzheimer's Disease (AD) as an example, the ventral premotor area and anterior cingulate cortex, which are selectively activated in healthy young adults while listening to familiar music that has long been stored in memory, is also relatively spared in the atrophy, hypometabolism, and beta-amyloid burden that is characteristic of AD (Jacobsen et al., 2015). In other words, musical memory may be spared in patients with AD because brain areas that encode familiar music are different from brain areas for other, more impaired brain functions and regions, such as spatial memory in the hippocampus (Erickson et al., 2011). This idea of direct access to familiar music during neurodegeneration is an intriguing one, as it may be linked to recent anecdotal reports such as in the movie *Alive Inside*, where participants with AD were immediately transformed to states of improved mood and cognitive ability upon listening to familiar music from their youth (Rossato-Bennett, 2014). Nevertheless, more validation is still needed for the idea of spared access to musical memory in AD, especially since Jacobsen et al. (2015) did not directly test individuals with AD for musical memory; rather they tested young adults in musical memory and extrapolated the results to non-task-related imaging for biomarkers of AD. Understanding the mechanisms for musical memory in AD specifically in individuals affected by AD would be extremely helpful for identifying strategies for targeted music-based interventions.

The areas found by Jacobsen et al. (2015), to be more active during familiar music, namely ventral premotor and anterior cingulate cortices, are also involved in multiple musical functions, ranging from the generation of musical ideas during improvisation (Limb & Braun, 2008; Pinho et al., 2014) to the control of vocal pitch during singing (Zarate et al., 2010). Another line of work shows that the anterior cingulate is also involved in reward-based decision making (Bush et al., 2002). Specifically, evidence from animal recordings and human functional magnetic resonance imaging (fMRI) consistently show that activity in

the anterior cingulate reflects the size of reward signals from the dopaminergic system, as well as the degree of surprise when the reward deviates from one's predictions (Hauser et al., 2014; Hayden et al., 2011). Even when one is predicting a reward by imagining it (without actually receiving reward), the anterior cingulate cortex is sensitive to the size of the predicted reward (Hayden et al., 2009). Thus, areas of the brain that code for prediction and reward are active during some aspects of music production and music perception, especially during the perception of familiar and self-generated music (Freitas et al., 2018). These findings have implications for music-based interventions: it suggests that familiar and self-generated music may be most motivating for patients. Furthermore, the fact that these same regions are spared in early-stage AD (Jacobsen et al., 2015) provides additional support for early-stage AD, such as mild cognitive impairment (MCI), as a point during which music-based interventions may be most effective (Wang et al., 2020).

Networks for Music and Reward

Improvisation is a form of music making that requires active engagement and real-time selection of musical materials (Loui, 2018), and has been used as a form of music therapy (Trondalen, 2017). Specifically, the classic modes of "cold" cognition (Lepper, 1994), including language, attention, executive function, and working memory, although intimately involved in the music making process (Janata et al., 2002), are not the only routes through which music affects the patient. In contrast, social and emotional modes of relating to others can also be powerful and important ingredients of successful therapy. As humans are a social species, music is also inherently social (Savage et al., 2020). Music making is an activity that can promote social bonding across many cultures and ages (Freeman, 1998; Savage et al., 2020). The experience of intensely pleasurable music can cause dopamine release in the meso-limbic reward system (Salimpoor et al., 2011), a system that also mediates social bonding as shown from combined positron emission tomography (PET) and fMRI recordings from mothers' brains as they watch their infants at play (Atzil et al., 2017). The dopaminergic reward-related regions, particularly ventral striatum and ventromedial prefrontal cortex, are also important for prosocial decision making (Zaki & Mitchell, 2011) and disclosing information about oneself (Tamir & Mitchell, 2012). These same areas can be engaged in the experience of pleasurable music: enhanced functional connectivity between them has been observed during the experience of music that one judges to be desirable (Salimpoor et al., 2013). Furthermore, people who experience strong reward responses to music are found to have larger volume in white matter connectivity in the brain between auditory areas (superior temporal gyrus) and areas important for emotional processing (insula) and

social and reward processing (nucleus accumbens, medial prefrontal cortex) (Sachs et al., 2016).

On the other hand, there may be some individuals who are less responsive to music-based interventions: musical anhedonia is a recently-identified condition of indifference towards music (Belfi & Loui, 2020). People with musical anhedonia not only report not enjoying music, they also have reduced physiological arousal and reduced activity in their reward system when listening to music that their peers report to enjoy (Loui et al., 2017; Martinez-Molina et al., 2016). Since this small but significant part of the population shows reduced reward sensitivity to music, they may be poor candidates for music therapy that targets the reward system.

Thus, musical interventions may affect clinical outcomes through neural pathways for emotion, empathy, and social reward, which are very directly related to the brain's dopaminergic system which rewards successful predictions and learns from unsuccessful ones (Gold et al., 2019). Understanding these intrinsic differences in auditory access to the reward system may help identify individuals who are most responsive to music therapy, and tailor the amount and type of music therapy needed to best engage the brain for supporting individuals with neurodegenerative diseases and disorders.

Spontaneous Activity in Brain Networks

In addition to brain networks activated by music perception and production, the effects of music listening on spontaneous activity across the brain are also of interest here, especially due to the changes in spontaneous brain activity over the course of neurodegeneration as one enters dementia. The concept of a true resting state of the brain has gradually been refuted over the past 20 years of studies in cognitive neuroscience. When the brain is not undergoing any specific task conditions, the "resting" condition resulted in spontaneous activity in a set of regions together known as the default mode network (DMN). These regions include ventromedial prefrontal cortex, posterior cingulate cortex, and left and right inferior parietal lobules, as well as the hippocampal formation and parahippocampal cortex (Christoff et al., 2016). The disruption in the spontaneous activity of the DMN is linked to multiple psychiatric and neurodegenerative disorders, including autism, schizophrenia, and AD (Buckner et al., 2008). In the case of AD, the DMN's continuous activity is thought to be linked to energy metabolism such that its disruption leads to the insidious formation of AD pathology (Buckner et al., 2008). This same set of regions is deactivated during most cognitive tasks but is more active during mind-wandering, prospection, self-referential thought, creative thought, and autobiographical memory—mental states that fall under the general category of spontaneous cognition (Buckner et al., 2008; Christoff et al., 2016). Importantly, many musical experiences engage these DMN-dependent modes of

spontaneous cognition: for example, musicians who are trained to improvise show more spontaneous activity in the DMN (Belden et al., 2020), and listening to emotional music restores the spontaneous activity of the DMN (Taruffi et al., 2017). These findings relate DMN to the spontaneous cognitive processes that occur during music listening and music production, and suggest that music may facilitate restoring reduced or disrupted brain activity during neurodegenerative disease. Specifically, by targeting spontaneous cognitive processes, music-based interventions may aim to restore DMN activity, thus slowing the trajectory of AD pathology.

Rhythmic Stimulation of Motor Networks

Another route through which a music intervention may promote recovery from a disease or disorder is by engaging brain networks that are shared between music making and other activities that are hyper- or hypo-active in the normal state of the disease. One such example comes from the use of rhythmic auditory stimulation (RAS) for Parkinson's Disease (PD). PD results from deficient activity levels in the nigrostriatal pathways within the dopaminergic system (Purves et al., 2008). Replacing the depleted activity of the dopaminergic system, such as by administering dopamine agonists (such as L-DOPA) (Purves et al., 2008), may aid in reducing Parkinsonian symptoms, thus slowing the progress of Parkinson's Disease. Music and movement provides a promising route to therapeutic outcomes in movement and gait because music engages the dopaminergic system, with movement and gait specifically involving the nigrostriatal pathway (Ashoori et al., 2015). Experimental evidence has been found for the effective use of RAS and dance as therapy for PD patients (Ashoori et al., 2015). Specifically, rhythmic auditory stimulation appears to improve the synchrony of activity in the motor system of the brain. Hackney and Earhart (2009) conducted an RCT with 58 PD patients comparing before and after 13 weeks (20 hours of classes altogether) of either tango, waltz/foxtrot, and a no-treatment control. Results showed that both dance groups improved significantly in balance and walking distance. These gains from dance training may be related to the rhythmic content of music and dance, as rhythmic auditory stimulation is shown to improve gait patterns and reduce falls in patients with PD (McIntosh et al., 1997; Thaut et al., 2018). Part of the success of rhythm and dance training may be attributable to the role of rhythm in directing attention to repeated stimuli. The role of rhythms in auditory stimuli in entraining brain activity in the auditory and motor systems is well documented, both in theoretical models (Large & Jones, 1999) and in empirical data from magnetoencephalography studies (Fujioka et al., 2015; Morillon & Baillet, 2017; Morillon et al., 2014). Dance music may provide an especially useful set of stimuli for PD patients as they tend to contain clear rhythmic content, thus optimally entraining the auditory-motor systems.

Despite these gains, though, results have yet to be shown to generalize to gold-standard neuropsychological scales, such as the Unified Parkinson's Disease Rating Scale (UPDRS) which is frequently used to assess PD severity in the clinic (Goetz et al., 2008). While the two treatment groups discussed above (Hackney & Earhart, 2009) did not improve on the UPDRS, the control group performed worse at post-test than a pre-test, after the period of no-treatment. One possible explanation for why dancing was beneficial for PD is that the treatment increased physical fitness, which is correlated with symptom reduction in PD as assessed using the UPDRS (Zhu et al., 2019). To tease apart the different mechanisms by which dance could affect PD, more evidence is needed to link music and rhythmic stimulation specifically to gains in the disease severity of PD, and methodologically these findings underline the utility of standardized pre- and post-intervention measures on all treatment and control arms of the intervention.

Redundant Pathways Offer Approaches to Recovery

While the results discussed above can be used to inform the design of future, longer-term treatments, an ongoing challenge is to continue refining music interventions as our knowledge of the central nervous system expands. The human central nervous system has long been conceptualized as a collection of interacting networked areas and pathways, each with its own set of characteristic structures and functions (Purves et al., 2008). Considering just the white matter of the brain, the brain consists of major white matter pathways as well as u-fibers (byways) between major highways (Loui, 2015). These networks can offer multiple pathways towards normal music making, and the apparent redundancy among these pathways may also be important for recovery (Loui, 2015).

One classic example of multiple redundant pathways is the homology between left and right hemispheres of the brain. In cases where one hemisphere is damaged, such as in stroke, tumor, or traumatic brain injury, the other hemisphere can affect recovery in interesting ways. This has been shown in melodic intonation therapy, a musically intoned speech therapy, for patients with severe non-fluent aphasia. After 15 weeks of melodic intonation therapy, 11 patients recovering from Broca's aphasia, which is usually caused by stroke in the left-hemisphere, showed microstructural white matter changes in contralateral language homologs (inferior frontal gyrus, posterior superior temporal gyrus) in the right hemisphere (Wan et al., 2014). The locations of these clusters correspond with areas in and around the arcuate fasciculus. In contrast, a matched group of patients who did not receive melodic intonation therapy showed no such change in brain structure. This pattern of results suggests that the musical intervention exerts its effects by acting on contralateral homologs of the affected areas (Wan et al., 2014).

These therapy-induced changes in brain structure are encouraging, as they provide more direct neuroanatomical evidence for effectiveness of the intervention. Meanwhile, it is noteworthy that even regardless of intervention, individual differences in brain structure can still affect recovery. A cross-sectional study examined structural magnetic resonance imaging (specifically diffusion tensor imaging) data from 33 patients recovering from aphasia, and showed that recovery is most successful for patients with large volume and high white matter integrity in frontotemporal pathways in the right hemisphere (Pani et al., 2016). Importantly, only right-hemisphere regions that were contralateral homologs to critical language-processing regions in the left hemisphere were found to predict recovery; in other words, the structure and function of the pre-morbid brain is an important predictor in how well a patient may recover from intervention. These findings are particularly important in relating the extent and specificity of a patient's brain damage to functional outcomes, and suggest that the structural connectivity of the right hemisphere supports aphasia rehabilitation (Barrett & Hamilton, 2016).

Arising Recommendations for Music Interventions

The studies reviewed above have identified a set of brain networks implicated in musical functions. A few guiding principles are that auditory-motor and reward networks are more active when listening to familiar music, they rely on rhythmic stimulation, and that there are redundant pathways including those that are engaged in ongoing, spontaneous activity. Based on these principles, future music-based interventions may capitalize on redundant brain networks for perception and production of music, speech, and motor movement to increase the chance of recovery. For example, if a patient lacks the motor control to engage in creative music making, they might nevertheless benefit from listening to familiar music, since such listening engages the same neural regions that are activated for prediction and reward. Another example is that music that engages mind-wandering and autobiographical memory, such as improvisatory music, may be useful for engaging spontaneous cognitive processes, which engages the default mode network which has disrupted metabolism in AD. A third example is that a prescreening of reward sensitivity to music (such as using the Barcelona Music Reward Questionnaire (Mas-Herrero et al., 2013)) may be beneficial prior to deploying resources for music-based intervention, since musical anhedonics are unlikely to be highly responsive to music-based interventions that target the reward system. In summary, music-based interventions need to be tailored according to knowledge of how specific aspects of music (such as rhythm, social interaction, and emotion induction) affect the mechanisms underlying the clinical problem. In planning and administering such various music-based interventions, the patient should be kept informed of the neural mechanisms behind chosen interventions. This includes the targeted neural mechanisms for a given intervention, as well as any downstream effects that the intervention may have due to possible interactions between targeted neural mechanisms and other related systems in the central nervous system. For example, a receptive music-based intervention for Alzheimer's Disease, which affects mood via its engagement of the prediction and reward system, may affect cognition even though cognitive mechanisms are not specifically targeted, due to the intricate links between emotion and cognition as identified above. Finally, large-scale studies are still desperately needed for increasing confidence in the mechanisms underlying each music-based intervention, and beneficial collaborations may arise between those who design interventions and those who conduct mechanistic research.

Conclusions

Taken together, evidence suggests that while music interventions may offer a pathway towards better outcomes for various disorders including but not limited to AD, PD, and aphasia, in many cases the quality and quantity of the evidence is mixed. Here I have reviewed selected research from the cognitive neuroscience of music, especially those that relate brain networks to musical functions. A few guiding principles are that auditory-motor and reward networks are involved during music listening, and are more active when listening to familiar music. Rhythmic music predictably stimulates activity in auditory-motor brain networks. Rhythmic patterns of brain activity are not only driven by musical stimuli, but are also part of ongoing, spontaneous activity patterns that characterize the brain, such as in the default mode network. Finally, there are multiple, redundant pathways that enable the musical experience, which may offer possibilities for recovery from brain injury or disorders. In forging a future of music intervention practice that withstands the challenges arising from the intrinsic variability of complex interventions, and merits enthusiastic support from multiple stakeholders, findings from cognitive neuroscience may offer some possibilities towards better outcomes in a variety of diseases and disorders.

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