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Prematurity: can music have a role in Neonatal Intensive Care Unit?

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PREMATURITY: CAN MUSIC HAVE A ROLE IN NEONATAL INTENSIVE CARE UNIT?

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List of Abbreviations

AS – Active sleep

GA – Gestational age

HR – Heart rate

INFANIB - Infant Neurological International Battery

MT – Music therapy

MS – Musical stimulation

NICU – Neonatal Intensive Care Unit

SpO2– Peripheral oxygen saturation

PAL – Pacifier Activated Lullaby

PTI – Preterm infants

QS – Quiet sleep

RBL – First Sounds Rhythm-Breath-Lullaby

RR – Respiratory rate

TIMP – Test of Infant Motor Performance

1. Abstract

Prematurity is a challenge for preterm infants (PTI) and their parents. Due to their overall immaturity, PTI have inadequate responses towards stress and an increased risk for impaired neurodevelopment. The unfriendly acoustic environment at Neonatal Intensive Care Unit (NICU) causes physiological instability, disrupts sleep cycles, and hampers important auditory experiences. The use of music as therapy in this population has been under research for decades with promising results so far. This narrative review aimed to summarize the effects of music on PTI and their parents at NICU, analyzing studies that were further classified as using music therapy (MT) or musical stimulation (MS), according to the intervention described. This review emphasizes the potential benefits of music as a complementary therapy at NICU, with positive impact on many clinical aspects, such as vital signs, sleep quality, neurodevelopment and growth, and an important influence on parent-infant bonding. Moreover, this review highlights MT for the consistency of positive results and the importance of an individualized approach. Future studies should investigate the effects of MT and MS interventions on NICU PTI based on their characteristics, trying to understand what fits best each situation, and aiming to stablish some formal recommendations.

Keywords: music; music therapy; premature infants; neonatal intensive care unit; newborn

2. Resumo

A prematuridade constitui um desafio para os recém-nascidos prematuros e para os pais. Devido à sua imaturidade, estes recém-nascidos apresentam respostas inadequadas ao stress e um maior risco de patologias do neurodesenvolvimento. O ambiente acústico hostil na Unidade de Cuidados Intensivos Neonatais provoca instabilidade fisiológica, perturba os ciclos de sono e impede experiências auditivas importantes. O uso da música como terapia nesta população tem sido estudado há décadas e com resultados promissores até ao momento. Esta revisão narrativa teve como objetivo sumariar os efeitos da música em recém-nascidos prematuros e nos pais durante a permanência na Unidade de Cuidados Intensivos Neonatais, analisando estudos cuja abordagem foi, posteriormente, classificada como musicoterapia ou estimulação musical, de acordo com a intervenção descrita. Esta revisão enfatiza os potenciais benefícios da música enquanto terapia complementar nestas unidades, com impacto positivo em vários parâmetros clínicos, como sinais vitais, qualidade do sono, neurodesenvolvimento e crescimento, e uma influência importante na relação entre os pais e o recém-nascido prematuro. Ademais, esta revisão sublinha a consistência dos resultados positivos em relação à musicoterapia e a importância de uma abordagem individualizada. Investigações futuras devem avaliar os efeitos da musicoterapia e da estimulação musical nos recém-nascidos prematuros durante o internamento na Unidade de Cuidados Intensivos Neonatais com base nas suas características, tentando compreender o que melhor se aplica em cada caso, e com o objetivo de estabelecer algumas recomendações formais.

Palavras-passe: música; musicoterapia; prematuros; unidade de cuidados intensivos neonatais; recém-nascido

3. Introduction

Over the last decades, advances in obstetric and neonatal care led to an increase of overall survival of PTI. However, these improvements brought other challenges. The population of ex-preterms increased and pediatricians are facing more often with problems related to prematurity, such as neurodevelopmental morbidities.[1] Thereby, interest concerning neurodevelopment long-term impairment in PTI has been growing and, consequently, related neurodevelopment follow-up and early intervention are important points of concern.[2]

Prematurity – or preterm birth - is defined as the birth of an infant born alive before 37 weeks of pregnancy completed and is divided into extremely preterm (<28 weeks of gestation), very preterm (28-32 weeks of gestation) and moderate to late preterm (32-37 weeks of gestation).[3] PTI have an increased risk for neurological deficits, conditioned by the functional and structural modifications their brains go through between 24-40 weeks of gestation, a highly important period for neurodevelopment, that is disrupted by premature birth.[4,5] The risk of major disability increases with decreasing gestational age (GA), being the group of extremely and very preterm infants at higher risk compared to moderate to late preterm.[6] Besides GA, birth weight, male gender and structural changes of the brain are other predictors of poor neurological outcome.[7]

Concerning hearing, PTI miss out on an important opportunity for auditory experiences in the uterus.[8] The intrauterine ambient is characterized by the presence of constant, periodic sounds as the mother's voice and her heartbeats.[9] Suddenly, these familiar pleasant sounds are replaced by unpredictable loud noises and alarms of medical equipment in the NICU environment.[10] There is great evidence that this has a negative effect on auditory development and language development on the long term.[11,12]

Other than prenatal and natal risk factors, PTI sometimes face other challenges during NICU hospitalization such as mechanical ventilation, bronchopulmonary dysplasia, brain injury, infection and treatments, such as postnatal corticosteroids and inotropes, that had been related to poor neurodevelopment outcomes (Fig. 1).[13-22] Besides that, noise and bright lights exposure, frequent manipulation to evaluate clinical status or to perform routine care and painful invasive life-saving procedures causes overstimulation of PTI.[10,23,24] This can be perceived as an aggression and lead to physiologic responses – apnea, bradycardia, decreased peripheral oxygen saturation (SpO2) and rising of stress hormones.[13] The normal architecture of sleep can be disrupted, with shorter REM periods. This influences various systems – metabolic, immune, and cardiovascular – and compromises weight gain. In this

period of life, assuring quality of sleep is also crucial for neural plasticity and brain development.[25]

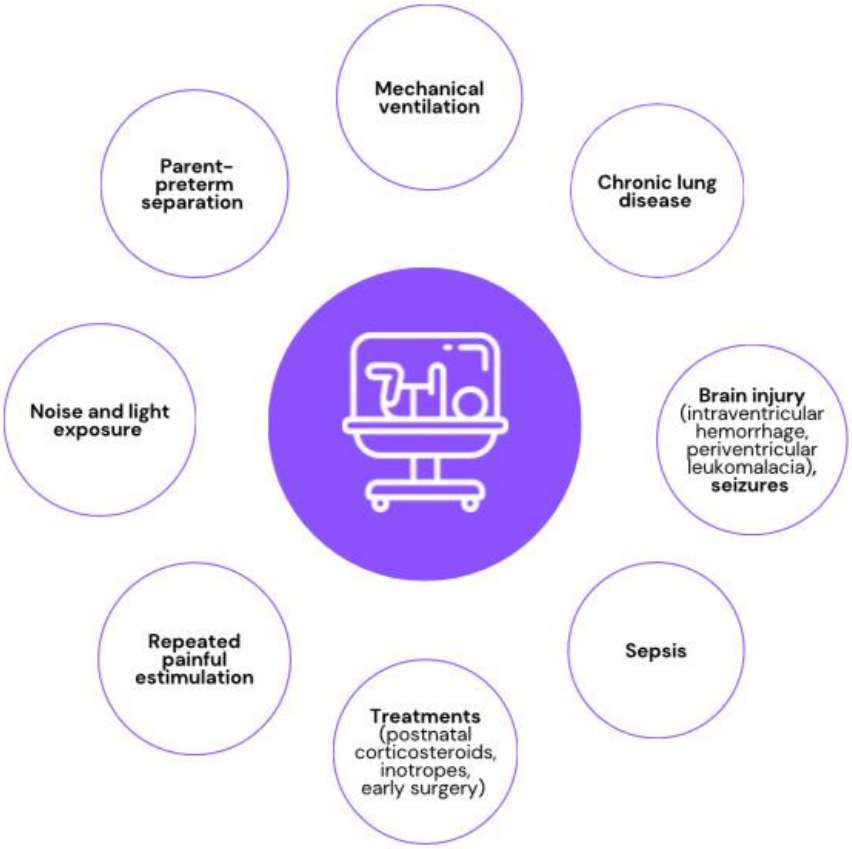

Figure 1. Risk factors for neurodevelopmental poor outcomes in premature infants.

The postnatal period of a PTI can also be a stressful and difficult challenge for their parents. The premature birth of a child, the unreadiness, the feeling that they are not able to attend to their child's needs without help of a primary care professional can be rather traumatizing. Parents often handle their worries about their children's health condition, while facing these feelings of insecurity, fear, guilt, and stress on their own.[26-29] Mothers of PTI have higher risk of developing anxiety disorders and post-partum depression, and some studies point out that 20% of parents still show signs of stress one year after their stay at the NICU.[30,31] On the other hand, mother's privation can also be stressful for the infant.[32,33] Prematurity and the prolonged stay at NICU act as barriers to the natural process of mother-child bonding.[34] These biological and other socio-economic aspects, that are present from prenatal period and through life, are also known to have an impact in brain development and should not be neglected.[32-34]

In a time when there is an extended knowledge on this subject and in advanced medical care, allowing PTI with lower GA to survive and thrive, the role of complementary therapies, able to improve clinical outcomes and decrease risk of developing deficits or health issues, is increasingly important.

MT is an emerging intervention that has been studied for decades. MT, in general, is defined by the World Federation of Music Therapy as the "professional use of music and its elements as an intervention in medical, educational, and everyday environments with individuals, groups, families, or communities who seek to optimize their quality of life and improve their physical, social, communicative, emotional, intellectual, and spiritual health and wellbeing".[35] There are a few reasons that make music an intuitive therapy to implement in this period. First, auditory development begins quite early, during the third trimester of pregnancy.[36] Infants' hearing structures and neural pathways are in place and completely functional at 28 weeks of gestation.[37] Also, research shows that as early as 32 weeks of gestation, there is already an ability to understand and remember auditory stimuli, such as the mother's voice.[38] Secondly, the communication between the infant and the mother has, on its own, an intrinsic "musicality" - prosody -, a spontaneous characteristic of speech.[39] Finally, music can neutralize the overstimulation of the NICU, creating a soothing environment that benefits the infants and nurtures the parent-infant relationship.[40]

However, this definition narrows the spectrum of interventions that can fit into the concept of MT, since many of the already described on the literature are not conducted by a qualified therapist. The presence of a trained professional allows the session to be carefully adapted to the infant, attending to its specific needs and providing an individualized approach.[41] There is increasing evidence recommending the use of qualified therapists. Having this in mind, for the purpose of this study, we will define MS as all interventions that are not planned or executed by a music therapist.

In this narrative review, we aim to collect and summarize evidence on the application of music on PTI and their parents in the NICU, from 2000 to 2022. We intend to explore the different approaches and highlight their advantages and disadvantages. By doing so, we hope to conclude on whether music should be a part of NICU's clinical practice.

4. Methods

This narrative review is based on a thorough literature search of the Medical Subject Headings (MeSH) terms in PubMed/Medline, on National Library of Medicine (NIH), Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Embase databases, between june 2022 and december 2022. The MeSH terms *Music* OR *Music Therapy* AND *Preterm Infants* AND *Neonatal Intensive Care Unit* were used in this research. These terms were also combined with secondary terms in order to refine the results, such as *Vital Signs* OR *Blood Pressure* OR *Heart Rate* OR *Respiratory Rate* OR *Body Temperature* OR *Sleep* OR *Growth* OR *Development* OR *Developmental Disabilities* OR *Behavior Problems* OR *Feeding Problems* OR *Pain Management* OR *Parent-child Relations* OR *Mother-child Relations* OR *Maternal-fetal Relations*. This research included publications between 2000 and 2022.

It should be mentioned that no articles written in Portuguese or Spanish were found; therefore, only articles written in English were retrieved in this study. Furthermore, systematic and narrative reviews, observational studies, medical books and other relevant sources were included, followed by the exclusion of incomplete papers. The abstracts of identified articles were assessed for relevance, along with screening of their references for further relevant publications. Studies regarding multimodal approaches, in which the part of music/music therapy could not be isolated from other interventions were excluded.

Finally, the included studies were further classified into the categories of MT - when containing the intervention of a music therapist and an individualized approach - or MS - when planned by other health professionals or researchers, in a standardized way.

5. Discussion

5.1. Physiological parameters

The acoustic environment at NICU triggers negative physiological responses on PTI that can result in adverse clinical status, such as apnea, bradycardia and decreased SpO2.[13,23,42,43] In these stress-related states, there is a relative dominance of the sympathetic over parasympathetic nervous system.[44] Music antagonizes this dominance by restoring sympathetic-parasympathetic balance.[44-46]

There are conflicting results on the effect of music on physiological parameters. Dora *et al* found positive effects on heart rate (HR), respiratory rate (RR) and SpO2, while comparing white noise and lullabies groups to control.[47] As for Namjoo *et al*, none of these registered a significant difference, despite the use of live and recorded music. This may be due to the heterogeneity within these studies.[48] They address different approaches (MT *versus* MS), diverge on the number, frequency and duration of music sessions, and vary on participants' inclusion criteria (GA, birthweight, clinical status, etc.).[49-51]

However, considering the studies included, MT was more consistent on positive results regarding physiological outcomes. Lowey *et al* investigated the effect of Gato-box and Ocean Disc on vital signs, under the principles of the First Sounds Rhythm-Breath-Lullaby (RBL) model.[52] The RBL model is based in the notion of entrainment – an habituation response to external stimuli that allows infants to synchronize their physiological rhythms – and focuses on entraining PTI's vital rhythms through music, allowing them to self-regulate.[52] Gato-box and Ocean Disc are two instruments designed to take part on music therapy sessions. Ocean Disc is a metallic instrument that simulates maternal heartbeats – the "whoosh"-like sound of the placenta – and is played to mirror the infants' breathing patterns. Gato-box, on the other hand, is a wooden box played to entrain the infant's heartbeat.[52,53] The music therapist plays these instruments in conformity with the PTI's vitals and infants respond back by adapting to the stimulus. When subjected to this therapy, PTI showed stabled HR and increased SpO2, making it clear that the approach reached its purpose of enhancing infants' self-regulation and physiological stability.[52] Later, Lowey corroborated these same results by using "Twinkle" or the "song of kin" lullabies.[53] The "song of kin" consists of the use of lullabies selected by parents, reflecting their familiar and cultural heritage into more personalized interventions.[53] Varisco *et al* reported less HR variability in PTI that were sung to by parents, which is a sign of stability and illustrates a parasympathetic-sympathetic balance.[54] These findings were confirmed by systematic reviews that emphasized the importance of having a music therapist

involved.[49,51] Costa *et al* underlined that it could also be interesting to evaluate long-term physiological effects in future studies.[49]

Negative results were more often found in MS studies and studies involving infants suffering from clinical conditions that affect their stability, such as brain injury.[55-57]

5.2. Pain management

PTI hospitalized at NICU are frequently submitted to painful procedures that can influence their physiological parameters and behavioral states. Their neurological immaturity makes them susceptible for long-term effects of pain, which highlights the importance of pain management in this period.[58]

Mozart's music has shown to be safe and effective in controlling pain during heel-lance procedures.[58] Bergomi *et al* theorized that this effect is maybe due to the repetition of melodic lines exclusively found in Mozart's music when compared to other compositors. The periodicity on the melody mimics physiological body function and is, therefore, enjoyed by the brain.[58] Similar results were found in later publications, which attested a positive effect of music on pain management.[59] Music and white noise groups scored significantly less on pain scales when compared to control groups. It is thought that this analgesic effect results from the release of endorphins, which antagonizes sympathetic system responses during pain.[59]

As for studies involving the influence of MT interventions on pain, Costa *et al* identified positive effects on PTI undergoing retinopathy examinations.[49] Only one study failed to identify positive effects on pain scores.[51]

5.3. Growth, feeding and hospitalization time

Weight gain is a positive sign of growth, especially on PTI, and is usually associated with a decreased length of hospitalization. The healthy term infant is able to do coordinated suck-swallow-breath movements that make oral feeding viable with minimal repercussions on HR or respiration outcomes. Also, due to their organized behavioral states, feeding-related signs are more easily read by caregivers.[60] When it comes to PTI, neurological immaturity produces uncoordinated sucking movements and altered behavioral states, which results in cardiorespiratory impairment. Energy spent on nutritive sucking decreases SpO2 and consumes calories, which results in weight loss.[60]

Non-nutritive sucking is used to promote sucking behaviors and has substantial effects on encouraging full oral feeding, reducing the length of hospital stay.[61] Based on these principles, Standley *et al* developed the Pacifier Activated Lullaby (PAL), an equipment that stimulates continuous sucking behaviors by activating a set of selected lullabies, making the presentation of music contingent to the sucking behavior.[60,62,63] They verified that PAL reduced the length of gavage feeding, especially in infants >34 weeks of gestation, when they are thought to be neurologically ready for nipple feeding.[60] This is, however, contradicted by following studies suggesting that the most benefit is found on infants prior to 30 weeks of gestation.[64] PAL also improved the subsequent rate of nipple feeding on PTI – and the more they practiced, the more they seemed to get it.[62] The sucking rate was two times higher in the group using PAL, which not only confirms the hypothesis of discrimination between on/off condition, but also shows that infants seek this stimuli.[63] Therefore, music acts as a powerful reinforcement to non-nutritive sucking behaviors.

A pilot study attested that Mozart's music had a meaningful reduction on resting energy expenditure.[65] Although the mechanisms involved are not entirely clear yet and resting energy expenditure is only a component of all energy expenditure, these findings might suggest that music can increase metabolic efficiency and improve weight gain.[65]

Although most studies included in this category involved MS approaches, MT seems to be equally effective: maternal lullaby singing increased weight gain and reduced length of stay by ten days when compared to control group.[55] Positive results were also achieved with Gato-box therapy, which stimulated sucking behaviors as well.[52] This is in line with the analysis of systematic reviews and proposes that music can be a powerful tool to improve sucking ability and to stimulate nipple feeding, increasing weight gain and, consequently, reducing the length of NICU stay.[51,66]

5.4. Neurodevelopment and behavioral state

PTI have an increased risk for developing structural and functional network alterations, which translates into deficits in neurological outcomes.[2]

Lordier *et al* used resting state functional magnetic resonance imaging to investigate the influence of Mozart's music on a previously defined neuronal pathway of interest, thought to be affected by premature birth.[2] This circuitry of interest included the salience network, that takes part on complex brain functions such as communication and integration of sensory, emotional, and cognitive information.[67] Compared to the control group, the music group

displayed significantly higher functional connectivity in connections involving auditory, sensorimotor and medial superior frontal networks. This means that listening to music during NICU stay enhances sensory perception and improves the capacity to detect and respond to salient stimuli. They also found that there was an increased activity involving the primary auditory cortex in infants who were listening to previously heard music, which corroborates the development of familiarity processing and suggests that they are already able to identify and remember auditory stimuli.[2]

Recent publications are in line with these findings. Ren *et al* demonstrated that PTI are not only capable of processing different musical features - such as timbre, tone, and rhythm – but also that each feature stimulates different functional areas.[68] Timbre and tone activate the prefrontal cortex, involved in high-order cognitive functions such as working memory and planning. Rhythm, on the other hand, is associated with improved function of the auditory cortex, Broca's area and premotor cortex, important areas for future processing of language and cognition. Finally, timbre alone was proven to stimulate the primary somatosensitive cortex, the superior frontal gyrus and the postcentral gyrus, suggesting that music can encourage motor behaviors. Although these changes were observed, long-term musical interventions are recommended to achieve permanent effects on cerebral functional connectivity.[68]

Another study stated that after three weeks of MS, participants exhibited a marked improvement on their activity, displaying more limb movements.[69] To assess infants motor performance, the Test of Infant Motor Performance (TIMP) and Infant Neurological International Battery (INFANIB) scales were used.[69] TIMP is a standardized test, developed to identify neuromotor disturbances and to assess the efficacy of physical and occupational therapies. Among other parameters, it evaluates the motor response during different movements and postures, as well as the infant's attention to visual and auditory stimuli. INFANIB is another tool used for the assessment of neuromotor development. It assesses posture, extremity and axial tone, primitive reflexes, and postural reaction.[69] Their higher scores and the fact that these infants turned their heads towards the source of music during the intervention suggest that music exposure may improve their state of alertness and create a habituation response to this kind of stimulation, inducing them to explore their surroundings.[69]

These results on neurodevelopment seem to be achieved through music independently of the type of intervention. A recent pilot study assessing the impact of MT on this topic showed great results as well, with 9 in 10 infants showing improved general movement scores while being sung to by parents or being played MT instruments – Ocean Disc and Gato box – under the RBL principles.[70]

Although there is a lot of evidence supporting the use of music for achieving neurodevelopmental outcomes, it becomes a less obvious choice when it comes to improve the infant's behavioral status. In most studies, the infant's behavioral state is assessed through the application of several scales, the most common being a 6-point behavioral scale, that distinguishes between "quiet sleep" (state 1), "active sleep" (state 2), "drowsy" (state 3), "quiet awake" (state 4), "active awake" (state 5) and "crying" (state 6). Two meta-analyses concluded that there were no immediate or short-term positive effects on behavioral outcomes, which was confirmed by a subsequent clinical trial.[50,51,71] We should, however, point out that most negative results came from studies where the intervention consisted of MS. As for MT, it showed to be beneficial even if applied for a short period of time (~30 minutes).[46] The infants' clinical status seems to be determinant on how the therapy is received as well, since PTI with severe brain injuries didn't benefit with MT.[57]

MS had great impact on infants displaying inconsolable crying – a crying period that lasts longer than five minutes and continues despite nursing interventions – which was less frequent and five times less durable in the intervention group.[72]

5.5. Sleep

Sleep plays an important role on development, especially during the first year of life. A good nighttime sleep diminishes the number of awakenings and, thus, the disturbances they cause.[48] A significant organization of sleep occurs during the last trimester of pregnancy, in which occurs the differentiation of two distinct sleep states – active (AS) and quiet sleep (QS). PTI's sleep states are characterized by increased "indeterminate sleep" and "transitional sleep". These segments are sleeping periods in which behavioral and electroencephalogram features do not match entirely the definition of AS or QS, revealing immaturity.[73]

Recorded music has demonstrated its positive effects on sleep, increasing the mean duration of nighttime sleep, when compared to live intervention and control groups.[48] Although it hasn't reached statistical significancy, a trend to more mature sleep-wake cycles was reported with MS interventions, suggesting that there might be a small effect of music on QS.[74] Mature sleep-wake cycles are a sign of neurological integrity, they are present in healthy term infants and, therefore, considered a good prognostic sign.[73,75]

Regarding MT interventions, there were positive effects as well. In a study comparing the effects of a default lullaby – "Twinkle" – with the "song of kin" and control groups, there was a rise in the percentage of sleep time after two weeks of therapy in the lullaby group.[53] On the other hand, the "song of kin" revealed an important effect on sleep patterns on infants

diagnosed with sepsis.[53] Another study, using the RBL principles, found a statistically significant increase on overall sleep quality over two weeks using the Ocean Disc. The group using Ocean Disc got 95.7% AS time, comparing to the 71.1% AS time on control group.[52] This is extremely relevant since REM periods generate spontaneous activity, which is vital for organization of central nervous system circuits and somatotopic maps.[76] Animal experiments have shown that lack of REM sleep during early stages of development can lead to behavioral problems.[77] Given its importance on neuronal restitution, body temperature regulation and energy saving, sleep is the most important behavioral state for newborns, especially PTI, so it's essential to assure a good quality sleep in this population.[78-81]

5.6. Parent-infant bonding and maternal anxiety

The premature birth of a child can be a stressful and disturbing moment for parents.[82] The reality of an early birth, the NICU environment and the perception that they cannot properly care for their child make parents develop feelings of helplessness and guilt.[26,83] Reports show that mothers of PTI are more likely to develop post-partum depression and anxiety for months or years after being discharged from NICU.[28,30] These disorders make them less sensitive to their child's interaction signals, compromising the infants' nutrition, growth and neurodevelopment, and also hampering their connection.[84-86] Besides that, early separation from the mother affects oxytocin system, impacting long-term infants' prosocial behaviors.[87]

Literature is very consensual about the use of music to prevent maternal anxiety and depression and promote parent-infant bonding. Watching their babies display positive reactions - such as smiling and eye opening - while listening to music, made parents feel like they could relax as well.[88,89] When compared to control groups, mothers on the MT group had less incidence of post-partum depression and anxiety.[55,56,90,91] Parents' well-being automatically made them more available to sense and entrain the infants' breathing rhythm, while experiencing the positive effects of music themselves, creating moments of true connection and intimacy.[87,92]

By allowing mothers to relax, music increased breast milk secretion, the best nutrition for newborns.[93,94] Beyond its antioxidant properties, breast milk is rich in cholesterol, crucial for myelination. Breast fed PTI have 20% less risk of dying when compared to those not breast fed.[95] The act of breast feeding itself is also a propitious moment for mother-infant interaction – improving its efficiency is enhancing mother-infant bonding.[93,94]

Although there are positive effects with both MS and MT, there seems to be a huge advantage on MT, related to the intervention of a music therapist. Their guidance through all sessions gave parents a better understanding of their child and how to properly interact with him.[89] Beyond that, it provided empathetic listening to mothers and created a safe space for parents to express themselves, while developing intrinsic parental skills and sharing a special moment with their child. Haslbeck *et al* stated that most parents strongly recommended music as a complementary therapy in the NICU, without having to be directly questioned about it.[92] For its ability on creating a peaceful atmosphere, many parents reported that music continued to accompany them on their everyday lives, helping them to soothe their baby through the hardest times.[89]

There's no such clear benefit on infants with severe brain injury. Studies involving this population have not reached statistical significance for improving maternal anxiety and promoting bonding.[57] This might be related with these infant's inherent physiological and behavioral instability and the negative impact this has on parents. Their anxiety about their children's condition makes it difficult to freely sing and adapt to their child and to the therapy.[57] MT interventions should be studied and modified to meet these infants' characteristics and needs.

Longer intervention periods are also recommended to assure a positive effect.[96]

5.7. Music therapy *versus* musical stimulation

Music has a positive impact on all aspects of PTIs development, with decades of literature supporting its implementation as a complementary therapy at NICU (Table 1). Although both MT and MS have shown their strengths through the many branches of development, MT was more consistent on positive results and had a clear vantage on physiological parameters and parent-infant bonding. MT constitutes an individualized approach, tailored to meet each infant´s characteristics and needs. This makes all sense in an era when we are starting to understand that Medicine is not "one size fits all". The presence of the music therapist is a key feature.[49,51,89] Their function is to plan and guide MT sessions, adapting musical stimuli to the infants' reactions and vitals. They allow parents to better understand their child's needs and how to interact properly.[89] MT teaches parents how to entrain the infant's physiological rhythms, allowing infants to connect with their surroundings and to self-regulate. More than a therapy for PTI, it certainly addresses parent's needs as well, providing empathetic support and allowing them to ease their minds through a hard time. It is, therefore, a family-centered therapy.

Table1. Summary of the reported main benefits of music on PTI and parents during NICU stay.

Clinical variables	Reported effects
Physiological parameters	Stabilizes HR, RR and SpO2
Pain management	Reduces pain during painful procedures, such as heel-lance procedures and retinopathy examinations Improves overall pain control
Growth, feeding and hospitalization time	Reduces the length of gavage feeding Stimulates sucking behaviors Improves the rate of nipple feeding Reduces resting energy expenditure Increases weight gain Reduces length of stay at NICU
Neurodevelopment and behavioral state	Enhances sensory perception Improves detection and response to salient stimuli Stimulates future cognitive functions: working memory, planning, language and cognition Encourages motor behaviors Improves state of alertness and stimulates the exploration of the surroundings Decreases both frequency and durability of inconsolable crying
Sleep	Increases duration of nighttime sleep Increases overall percentage of sleep time Improves sleep patterns on infants diagnosed with sepsis Increases overall quality of sleep (increasing AS time)
Parent-infant bonding and maternal anxiety	Decreases incidence of maternal anxiety and postpartum depression Creates moments of connection and intimacy Increases breast milk secretion Improves parental understanding about the infant's needs and stimulates parent-infant interaction Allows parents to better express themselves

AS: active sleep; HR: heart rate; NICU: neonatal intensive care unit; RR: respiratory rate; SpO2: peripheral oxygen saturation

5.8. Recommendations for future studies and clinical practice

Most studies revealed promising results regarding music interventions on NICU infants and parents, but the heterogeneity related to the quality of the studies and methodology used (sample of patients, type and time of intervention, outcome measures), makes it difficult to establish formal recommendations in this context. However, music can be considered a complementary therapy as part of a patient-centered approach, which offers the sense of

comfort and satisfaction to the PTI and parents, in addition to being low cost, non-invasive and easy to implement.

Even if none of the included studies reported signs of PTI's overstimulation during exposure to music, it's important that future studies and clinical practice follow recommendations on noise level limits. According to Sociedade Portuguesa de Neonatologia, sound levels >45 decibel should be considered harmful and transitory sounds should never exceed 65 decibel.[97] This way, NICU acoustic ambient supports physiologic stability and sleep quality, intelligible verbal communication and communication between parents and health care professionals.[97]

Future studies should address the effects of music on different GA, birthweights and underlying diseases, such as brain injury and its sequels. They should also compare both MS and MT, helping to understand which intervention suits better each situation and establish some clinical practice guidelines, if possible.

Finally, at the moment, the LongSTEP study is in course. It's an international, multicentre, assessor-blind, pragmatic randomized controlled trial designed to evaluate long-term effects of MT on PTI and their parents at NICU and/or after discharge, across a 12-month period.[98] By applying previously studied and tested models, such as RBL, LongSTEP focuses on studying the long-term effects of parental singing on parent-infant bonding, PTI's general and socioemotional development and parental symptoms of depression, anxiety and stress.[98] Furthermore, it intends to examine medical and social factors, such as socioeconomic status, that may be associated with the effects of MT. Its results will allow us to understand in which way can MT be used to promote these infants' development and improve parental psychological outcomes, not only at NICU but throughout their lives.

6. Conclusion

The NICU stay is a challenging time for PTI and their parents. Music has proven to be a powerful complementary therapy, improving physiological and developmental outcomes and nurturing parent-infant relationships. MT was consistently better on positive results when compared to MS, especially on physiological parameters and parent-infant bonding. Its key feature is the presence of a music therapist, adapting interventions to meet both the infants' and the parents' needs. Future studies should address the effects of both interventions on different GA, birthweights and underlying diseases, to understand what fits best each situation. Music is a great asset for clinical practice at NICU. If there are obstacles on prematurity, music is certainly one way to try and overcome them.

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