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Music Therapy for Preterm Infants and Their Parents: A Cluster-Randomized Controlled Trial Protocol

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Music therapy (MT) interventions and skin-to-skin care (SSC) both aim to address the varied needs of preterm infants, including sensory regulation and stress reduction, inclusion of parents in their infant's care, support of parents' emotional state, and enhancing the parent–infant attachment process. Few studies have investigated the combination of both modalities through randomized controlled trials. Evidence of longer-term effects is missing. This article presents a study protocol that will investigate the effects of combined family-centered MT intervention and SSC on preterm-infants' autonomic nervous system (ANS) stability, parental

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anxiety levels, and parent–infant attachment quality. 12 clusters with a total of 72 preterm infants, with their parents, will be randomized to one of two conditions: MT combined with SSC or SSC alone. Each parent–infant dyad will participate in 3 sessions (2 in the hospital and a 3-month follow-up). The primary outcome of preterm infants' ANS stability will be measured by the high frequency power of their heart rate variability. Secondary outcomes will be physiological measures and behavioral states in infants and anxiety and attachment levels of parents. This trial will provide important, evidence-based knowledge on the use of the "First Sounds: Rhythm, Breath, and Lullaby" model of MT in neonatal care, through an intervention that is in line with the Newborn Individualized Developmental Care and Assessment Program model for supportive developmental care of preterm infants and their parents. Ethical approval (no. 0283-15) was granted from the local Institutional Review Board in April 2017. This trial is registered in ClinicalTrials.gov, NCT03023267.

Keywords: *heart rate variability; music therapy; neonatal intensive care unit; skin-to-skin care; parental anxiety*

Preterm infants face high risks of mortality, morbidity, and neurodevelopmental and psycho-emotional disabilities (WHO, 2016). The environment of the neonatal intensive care unit (NICU) is characterized by overstimulation and distress due to repeated sensorial stressors such as bright lights, noise, pain from medical procedures, and separation of infants from their parents (Haslbeck, 2012). In recent years, environmental concerns in the NICU have been addressed by designing small, private rooms for parents and their infant to further reduce sensorial stressors and to increase the frequency of infant–parent visits. However, an integrative review by Pineda et al. (2017) showed that among infants born <30 weeks' gestation, those who were in private rooms had less brain maturation at term, and at 2-years-of-age had lower language scores than did infants cared for in an open ward. This information validates the need for adapted stimulation during care and parental involvement in their child's care.

Parents of preterm infants face an existential risk of their infants' life or health and have limited ability to assist in primary caregiving tasks. Therefore, they may experience various emotional reactions related to fear, guilt, or loss, and may question their parenting abilities. Consequently, high stress levels and difficulties with

interaction, intimacy, and attachment may develop (Jotzo & Poets, 2005; O'Gorman, 2006).

Several neonatal treatment modalities aim to address the needs of preterm infants and their parents and to prevent the preterm birth from becoming a major traumatic event (Als, 2009; Haslbeck, 2012). The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is a leading methodological approach that was initiated in the 1980s (Als, 1982; Als & Duffy, 1983; Als et al., 1986). The NIDCAP model presents a set of practices to assess preterm infants' developmental status and ability to withstand stress in the NICU before, during, and after caregiving procedures. Based on this assessment, an individualized care plan is proposed, that typically limits untimely stimuli, protects sleep, and fosters developmentally appropriate, family-centered interactions. NIDCAP is supported by research evidence, is applicable to all infants, and is especially successful with very- and extremely low birth weight preterm infants (Als, 2009; Als & Gilkerson, 1997; Lawhon et al., 2013).

Skin-to-Skin Care

Skin-to-Skin Care (SSC), also known as Kangaroo Care, another well-established treatment modality of developmental care, is a natural intervention during which the parent holds the infant upright, chest-to-chest, and skin-to-skin. Parents thereby serve as "live incubators" as their body temperature helps the infants maintain and regulate their own body temperature (Ludington-Hoe, 2010). The benefits of SSC include enhancing autonomic nervous system (ANS) development, maintaining infants' physiological stability, increasing immunity, optimizing breastfeeding, and facilitating parent–infant bonding (Feldman & Eidelman, 2003; WHO, 1997, 2003). A Cochrane review of SSC for low birth-weight infants, which included 21 randomized controlled trials (RCTs) with a total of 3,042 infants, found consistent beneficial effects across a variety of neonatal outcomes (Conde-Agudelo & Diaz-Rossello, 2016). Compared to conventional care, infants who experienced SSC were found to have fewer common morbidities at discharge and lower mortality. SSC contributed to increased weight, length, and head circumference, and improved breastfeeding at discharge, at 40 to

41 weeks postmenstrual age, and at one-to-three-month follow-up visits (Conde-Agudelo & Diaz-Rossello, 2016).

Music Therapy Interventions in the Neonatal Intensive Care Unit

Music therapy (MT) for preterm infants is an evidence-based, professional adaptation of planned music activities, such as singing, playing, and listening to music. It is intended to address the various sensorial, physical, and emotional needs of preterm infants and parents, and to support their bonding process. Neonatal MT services are increasingly being studied and used in neonatal intensive care units (NICUs) (Arnon, 2011; Arnon et al., 2006, 2014; Bieleninik, Ghetti, & Gold, 2016; Hartling et al., 2009; Haslbeck, 2012; Loewy, Stewart, Dassler, Telsey, & Homel, 2013; Standley, 2012). Only a few methodological approaches that involve a music therapist specifically trained to work with preterm infants and their parents have been developed. These include the NICU-MT (Standley, 2002, 2012), the Creative Music Therapy (CMT) model (Haselbeck, 2012), and the First Sounds: Rhythm, Breath and Lullaby model (RBL) (Loewy, 2000; Loewy et al., 2013). The RBL model is a research-based, training model that has been instituted in 15 countries worldwide. It is based on music psychotherapy and includes the environment, parents, and infants. The model incorporates specific sounds of the intrauterine environment and encapsulates the culture and familiar voices of parents by having them sing lullabies of their choosing. The RBL interventions of live rhythm and breathing entrainment were tested in 11 hospitals among 272 premature infants who demonstrated improved vital signs, feeding, and sleep patterns (Loewy et al., 2013).

A recent systematic review, restricted to RCTs and to interventions involving a music therapist, included 16 studies with a total of 1,071 infants and 286 parents (Bieleninik et al., 2016). The participants, outcomes, and interventions in these studies were very heterogeneous. Most of the trials compared MT combined with standard NICU care to standard care alone. The main results of the systematic review demonstrated favorable effects of MT on infants' respiratory rate (mean difference −3.91/min, 95% CI [−7.8, −0.03], $p = .048$) and on decreased maternal anxiety ($d = -1.82$, 95% CI [−2.42, −1.22], $p < .001$).

Family-Centered MT Interventions in the NICU

Only a few studies have integrated MT into a family-centered care approach such as NIDCAP. As a starting point, Abromeit (2003) published guiding principles for applying neonatal MT interventions that are in accordance with the NIDCAP model. These include use of recorded music, selection of appropriate music stimuli, live infant-directed singing or humming, and inclusion of parents, combined with constant observation of the preterm infant's reactions. In the review by Bieleninik et al. (2016), only six studies included parents and none gave specific attention to fathers. Arnon et al. (2014) investigated combined maternal singing and SSC compared to SSC alone. The authors demonstrated beneficial effects of maternal singing during SSC on maternal anxiety levels and on infants' ANS stability, as compared to SSC alone. Schlez et al. (2011) investigated the effect of harp-playing during SSC compared to SSC alone on 52 mother–infant dyads. They also found beneficial effects on maternal anxiety during live music as compared to SSC alone. A recent study from Colombia (Ettenberger et al., 2014) compared combined MT and SSC, individual MT, and standard care. Favorable effects of both types of MT versus standard care on infants' weight gain, maternal anxiety, and rehospitalization were found. In another investigation of the RBL model, use of the parents' preferred lullabies, created individually according to their musical preferences (i.e. "song of kin"), was shown to be more effective than no lullaby or a default lullaby (Loewy, 2015).

Research Rationale

The rationale for combining MT and SSC is that SSC is the main form of interaction and physical bonding between preterm infants hospitalized in the NICU and their parents (WHO, 2003). Accordingly, the direct chest-to-chest contact in SSC is a recommended way to transmit the parental voice (Arnon et al., 2014). A trained neonatal music therapist can support parents while singing or listening to live music with their infants during SSC, by helping them interpret their baby's fine signals and attune to them appropriately. Therefore, MT can help them gain the confidence and sense of comfort they need to build intimacy and meaningful interactions (Arnon et al., 2014; Bargiel, 2004; Haslbeck, 2012; Nöcker-Ribaupierre, 2004; O'Gorman, 2006; Schlez et al., 2011).

A recent, narrative literature review (Palazzi, Nunes, & Piccinini, 2018) compared music stimulation and MT interventions and included 30 empirical studies conducted from 2010 through 2015. The review concluded that interventions applied by a music therapist were more personalized and had greater positive effects on infants' physiological and behavioral outcomes, as compared to musical stimulation. Similar to the review by Bieleninik et al. (2016), only a few of the included studies (Palazzi et al., 2018) used a family-centered MT intervention.

As described in a study by Arnon et al. (2014), combined maternal singing and SSC resulted in increased ANS stability for preterm infants and reduced maternal anxiety, as compared to SSC alone. Accordingly, we hypothesized that involvement of a trained music therapist who would support the parent–infant musical interactions during SSC would result in even greater effects than those found by Arnon et al. (2014).

A study, currently being conducted, is investigating short- and long-term effects of family-centered MT (Haslbeck, Bucher, Bassler, & Hagmann, 2017). The study proposed here, using a rigorous, cluster-RCT design including fathers and mothers, will be the first to investigate the effects of combined family-centered MT and SSC, and to include long-term follow-up.

Study Objectives

The goal of the current study is to evaluate the effects of combined family-centered MT, provided by a trained neonatal music therapist, and SSC compared to SSC alone, on preterm infants' ANS and physiological stability, and on parental anxiety levels. Additionally, infants' behavioral changes during sessions, parental attachment levels, and their continued use of music in everyday life will be examined. The current paper describes the study protocol. The results will be published when the study is completed.

Methods

Design

The study is designed as a single-center, time-cluster-RCT with two parallel arms. It will be conducted in an open-space NICU. To prevent treatment contamination between groups, which would

be likely to occur in this setting, a cluster-randomized design was chosen. The clusters will be two-month period. Each time cluster will be randomized to receive either combined MT and SSC or SSC alone. Parents of eligible infants will be approached during the first month of each time cluster. All parent–infant dyads (i.e., mother and infant and father and infant, separately) will participate in two sessions of the assigned intervention during the first two weeks following enrollment, and in a three-month follow-up session at home. Accordingly, each parent–infant dyad will be analyzed separately.

Setting

The study will be conducted in a 24-bed, level III, tertiary NICU, certified in providing care according to the NIDCAP model. The unit is constructed of three, open-space rooms. Each infant has his/her own facilities with a space for parents, as well as for caregivers. A decorative curtain can be placed around the space for privacy. The first and second sessions (i.e., during hospitalization) will occur in the open-space NICU. The three-month follow-up session will usually take place in the family's home, but may be held at the hospital, outside of the NICU, according to the parent's choice.

Participants

A total of 72 preterm infants admitted to the NICU and their parents (mothers and fathers) will be enrolled. Eligibility criteria for infants are: born before 36 completed weeks of gestation, any post-natal age, clinically stable (no respiratory support and no acute illness, as determined by the neonatologist in charge), both genders, any ethnicity, from single or multiple pregnancies, with hearing confirmed by Otoacoustic Emissions Test performed at study entry, and consent to participate in the study signed by the parents. Eligibility criteria for parents are one parent willing to participate, two parents or a single parent family including legal guardians, and parents living within "reasonable" commuting distance from the treating NICU.

Exclusion criteria for infants are current treatment with medications acting on the central nervous system (such as phenobarbital, an anti-epileptic drug) or oxygen, intraventricular hemorrhage stage ≥ 3, and periventricular leukomalacia, or an estimated

hospitalization of less than 10 days from the study recruitment. Exclusion criteria for parents are insufficient understanding of the study language to answer the questionnaires and participate in MT, a documented mental illness or cognitive impairment that prevents them from being able to complete the study intervention or outcome assessments.

Baseline Data Collection and Introductory Conversation With Parents

Demographic and neonatal data will be recorded from medical charts and will include ethnic origin, gender, gestational age, and birth weight, postnatal age at each session, weight at each session, and morbidities (including apnea of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage stage 1 and 2, respiratory distress syndrome, retinopathy of prematurity, and/or sepsis). Infants' medical status will be monitored and documented during the intervention period as part of routine medical care. If it becomes necessary for medical reasons to stop an infant's participation in the study, it will recommence when the criteria for clinical stability are again met.

In an introductory conversation between the parent(s) and the music therapist, the implications of participating in the study and expectations of and attitudes toward SSC and MT intervention will be discussed. Parents' demographic data, including age, number of children, ethnic origin, socioeconomic status, and years of education, will be collected.

Interventions

Each intervention session (combined MT and SSC or SSC alone) will have a duration of 30–45 min. A total of three sessions will be offered to each dyad (mother–infant; father–infant) so that each infant can receive up to six sessions. The first session of each dyad will be offered in the first week of study participation, the second session in the following week (5–8 days after the first), and the third session three months later (Table 1). All visits will be coordinated with the medical personnel to avoid interfering with other necessary procedures or services for the infant.

During all sessions, the parent–infant dyad will be in SSC position: The parent will sit on a couch, reclining at an approximately

Table 1

Schedule of Enrollment, Interventions, and Assessments

	Allocation	Enrollment	Study Period			Close-out
TIMEPOINT	Before Enrollment	0	Immediately After Enrollment	1 week (5–8 days) After Enrollment	1 month After Enrollment	3 months After Enrollment
Randomization of 12 time clusters (2 months each)	X					
Enrollment:						
Eligibility screen		X				
Introductory conversation with parents						
Informed consent (expected: about 6 per time cluster)		X				
Interventions:						
MT + KC or KC session, depending on randomization			X	X		X
Assessments:						
Demographic data		X				
Medical data		X				
HRV and other physiological measures of infant (before to after each session)			X	X		X
STAI of parents (before and after each session)			X	X		X
MPAS (parents)		X			X	X
Use of music in everyday life (parents)						X

Note. HRV = monitoring of heart rate variability and related physiological measures; KC = kangaroo care; MPAS = Maternal Postnatal Attachment Scale; MT = music therapy; STAI = State Trait Anxiety Inventory.

40-degree angle near the infant's isolate or incubator. The infant will be placed in skin-to-skin contact on the parent's chest, in an upright, prone position. The first two sessions will take place in the NICU. The third session will take place in the living room of the infant's home in quiet surroundings. Before and during each session, sound volumes will be monitored and recorded by a sound analyzer (Extech SL130, Extech Instruments, Nashua, NH, USA) placed near the infant's ear to avoid sounds higher than the recommended limit of an hourly Leq of 50 dB(A), an hourly L10 of 55 dB(A), and a 1-s L_{max} of 70 dB(A), all A-weighted, slow response scale (Graven, 2000). Normothermia will be controlled by a temperature probe for continuous monitoring.

Experimental Group: MT During SSC. The MT and SSC interventions are based on the fundamental principles of the First sounds: RBL model (Loewy, 2000, 2015; Loewy et al., 2013). It is designed to attend to the needs of the preterm infants and their parents by attuning to the infant's breath, movement, and sounds; creating parents' preferred lullabies; supporting parents' musicality; and providing the intrauterine sound environment. The MT intervention is flexible, encouraging parents to be as active as possible by singing, talking, and breathing with their baby. The music therapist's involvement (such as singing, playing, speaking with the parent) will change according to the parent's preference and/or the infant's reactions during the session. The MT intervention is designed as follows:

- Warm-up: Introduction with verbal inquiry of parent's physical and emotional state. Guided relaxation for reorganization of parent's breathing patterns may be accompanied by an ocean disc (a special disk that mimics the swooshing sounds in the womb).
- Vocal warm-up and improvisation: Humming to repeated, simple, melodic patterns modeled and supported by the music therapist; gradually developing the humming to singing "Ah" or "Oh" vowels. According to the parent's preference, this may be accompanied by guitar or ocean disc.
- Singing parent's preferred lullabies: According to the parent's choice, the music therapist will provide vocal or instrumental support for the parent to sing two or three songs of their choice, adapted to a soft, simple lullaby rhythm.

- Closure: A few moments of silence and reorganization of breathing. Verbal reflection on the session's events, inquiry regarding the parent's experience.

The music therapist will help the parent adjust and attune the live music to the infant's breathing patterns, movements, vocalizations, or other visible reactions. Parents will be guided by the music therapist to adapt their rhythm, tempo, vocals, and breathing according to the infant's reactions. They will be encouraged to share their thoughts, insights, and emotional experiences.

In case a parent does not wish to sing, instead of vocal warm-up and singing, the dyad will be provided with music, listening to the music therapist's singing or playing live music according to the parent's musical preferences, or parent will carry on with slow recitation of a story or a poem.

The protocol presented here describes a flexible intervention, because parents may need some time to "warm up" and receive some modeling before they feel comfortable enough to sing to their infant during SSC. The transition from receptive to active approaches and vice versa may occur for other reasons as well: the infant may be over-stimulated by singing; the parent may tire after a while or will simply want to talk to the baby. Accordingly, the first session may differ from the second in terms of the level of parental and music therapist's involvement, depending on the parent's and infant's needs at the moment. The main aim of the intervention, regardless of the type of approach, is to assist the dyad to become comfortable during SSC, to reorganize parents' breathing patterns, and to help them become better attuned to their infant's needs and by doing so, encourage communicative musicality between the parent and infant as a basis for their companionship and interaction (Trevarthen & Malloch, 2009).

Each infant's behavior will be assessed every 5 min by another music therapist, trained to identify preterm infants' behavioral cues and states. In case of crying, signs of hunger or persistent signs of stress, the intervention will be paused until regulation is achieved.

A female music therapist trained in neonatal MT according to the RBL model will conduct the intervention. The music therapist (first author) is trained in the RBL model and in training other music therapists, as well. She has seven years of clinical experience

working with families and has worked in neonatal care for four years.

Control Group: SSC Alone. Standard SSC treatment as described above is recommended to all families admitted to the NICU. During SSC sessions, the investigator (assessor) will sit near the parent and record the infant's physiological and behavioral data using verbal communication, if needed. No therapeutic conversation, music playing, or singing will be used. Prior to the control sessions, parents will be informed that they are being assessed during SSC time without any intervention. They will be requested to act naturally, as they usually would during SSC time, with the limitation of not singing to the baby or speaking with the assessor. The assessor will explain that they will sit quietly behind them, and monitor them every 5 min. The assessor will turn to the dyad in case they need any help related to placing the infant or attention to physiological needs (signs of stress, hunger or anxiety).

Outcomes

The primary outcome will be ANS stability in preterm infants of the study group (MT + SSC) compared to the control group (SSC alone), measured by the high frequency (HF) of infants' heart rate variability (HRV). Secondary outcomes will be stability and stress in the infants in the study and control groups, (measured by low frequency (LF) and LF/HF ratio of HRV, physiological changes in heart rate, respiratory rate, oxygen saturation, and behavioral state changes). The secondary outcome of parents' anxiety and attachment levels will be measured by anxiety and attachment questionnaires. At the 3-month follow-up visit, parents will be asked to report about the use of music in their everyday lives.

Preterm infants' secondary outcomes of stability and stress (including HRV indicators, heart rate (HR), respiratory rate (RR), oxygen saturation, and body temperature) and behavioral states will be measured and recorded every 5 min in all sessions, from 10 min before until 10 min after the sessions end. Anxiety levels in parents will be measured before and after each session. Parental attachment level will be measured at the beginning of the first session, a month afterward, and at the beginning of the follow-up session. Parents' use of music in their everyday lives will be assessed at the beginning of the follow-up session. All measurements will be

the same for the experimental and control arms except only the MT+SSC group will receive MT. Each parent's outcomes will be analyzed separately, not pooled or averaged between parents. No specific analysis of fathers will be conducted.

The description of outcome measures is provided in the next section.

Description of Outcome Measures

Preterm Infants Autonomic Nervous System (ANS) Stability. The primary outcome is the parasympathetic response of the ANS in preterm infants, as indicated by the difference in HF power of the infants' HRV between the first and last 15 min of the second intervention session. HF power is regarded as an indicator of the parasympathetic system, an indicator of stability and stress. High values represent a positive outcome. It will be measured continuously and documented every 5 min during each intervention session, beginning 10 min prior to the intervention until 10 min after it ends. The first session is considered more preparatory; therefore, data from the second session will be used as the primary outcome because by then, the parents will be familiar with the procedure.

Secondary measures for infants' ANS stability will be the LF and LF/HF ratio of HRV. The interpretation of LF and LF/HF ratio is less clear (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, p. 366). In this study, LF will be considered an indicator of the sympathetic system and LF/HF ratio as the relationship between relaxation and stress. Low values of LF, high HF, and low LF/HF ratio are thought to indicate signs of ANS stability and low stress (Arnon et al., 2014). The data analysis will compare the change from the first to the last 15 min of the second intervention session.

Monitor Systems

HRV parameters will be calculated using electrocardiogram (ECG) signals. The analog ECG signals are derived from a cardiorespiratory monitor (Philips, Agilent monitors, Irvine, CA, USA; www.usocmedical.com) with leads attached to the infant's chest, left leg, and palm, as part of their routine medical care. The monitor tracks and records vital signs of heart rate, respiratory rate, and oxygen saturation. The analog ECG signals of the heart rate are

then uploaded to an HRV computer software (ANSR1000 System Ansar, Inc., Philadelphia, PA, USA), and converted to digital values to reflect cyclical changes in the beat-to-beat intervals. An algorithm included in the software automatically removes artifacts. A peak detection algorithm is used to detect the R-wave peaks in the ECG recordings and calculate the R-R intervals (time intervals between successive normal heartbeats). These data are transformed into a waveform across a spectrum of frequencies. According to common standards, LF is defined as 0.04–0.15 Hz and HF as 0.15–0.4 Hz. The frequency components will be measured in normalized units (ms^2/Hz) and also presented as absolute values (ms^2; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HF power will also be measured by the Newborn Infant Parasympathetic Evaluation monitor (MDoloris Medical Systems, Lille, France). This monitor is connected to the ECG monitor and enables real-time analysis of the HF power for preterm infants. It was primarily built to measure ANS reactions not only to pain but also to noise and odor. Typical values are in the range of 40–60 units. Higher values represent better ANS stability (Butruille et al., 2015).

Infants' Physiological Stability. Physiological stability in infants will be measured by their immediate physiological markers including heart rate, oxygen saturation, and respiratory rate. It will be measured and recorded every 5 min during all sessions (for technical specifications and data collection schedule, see *HRV* section). Normal range values of heart rate (120–160 beats/min), respiratory rate (30–60 breaths/min), and oxygen saturation (≥90%) are considered indicators of better physiologic stability. Heart rate and respiratory rate are higher and oxygen saturation is lower than normal ranges when a preterm infant is faced with stressful stimuli.

Parental State Anxiety. Parental state anxiety levels will be measured by the State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). This is a validated self-report questionnaire with 20 statements describing current anxiety symptoms. For all study participants, the validated Hebrew version will be used (Netz, Zeav, Arnon, & Daniel, 2005). Each item is scored on a scale from 1 (*not at all*) to 4 (*very much*), leading to total scores ranging from 20 to 80, with higher scores indicating

more anxiety. The participating parent will be asked to complete the STAI at the beginning and end of each session.

Infants' Behavioral States. Infants' behavioral states during all sessions will be measured by the two music therapists (assessors), who have been trained to identify the various states by a certified NIDCAP trainer. Infants' behavior will be assessed every five minutes before and during each session. The Brazelton Neonatal Behavioral Assessment Scale (Brazelton & Nugent, 2011) will be used to categorize six possible behavioral states: 1. Deep sleep, 2. Light sleep, 3. Drowsy, 4. Quietly awake/alert 5. Actively awake and aroused, and 6. Highly aroused, crying.

Parental Attachment Level. Parental attachment level will be evaluated using the Maternal Postnatal Attachment Scale (MPAS) (Condon & Corkindale, 1998). The MPAS is a self-report questionnaire including 19 items investigating parents' behaviors, attitudes, and feelings toward their infant. Each item is scored on a 5-point Likert scale and then computed as a complete score (sum of all items), ranging from 19 to 95, where higher scores represent good attachment. The scale has demonstrated internal consistency reliabilities (alphas) of 0.78–0.79, test–retest reliability of 0.86, temporal stability coefficients of 0.48–0.67, and exemplary convergent validity (Condon & Corkindale, 1998). The MPAS is one of the most recommended attachment questionnaires that is specifically designed for and appropriate to the preterm birth period and to the NICU hospitalization. There are some minor differences between the Maternal and the Paternal versions of the questionnaire (two items are slightly different, and two other items were adapted for fathers). However, we chose to only use the maternal version, as we intend to compare parents in the experimental and control group, and not between genders. Also, there were no gender-specific or gender-related words in the maternal version, so it is appropriate to use for both genders. Each parent will complete the MPAS at three time points: beginning of the first session, one month afterwards, and at the three-month follow-up.

Music Use in Everyday Lives. In addition to the outcomes listed above, we intent to add another evaluation related to the process measurement, to obtain an indication of treatment adherence. Accordingly, the parents from both groups will be questioned regarding their use of music in everyday life at follow-up, to evaluate

the degree to which they have incorporated music into their life with their child following the intervention. The use of music will be evaluated through a semi-quantitative questionnaire composed especially for the current study. It includes three yes/no/other questions and a semi-quantitative question, inquiring about the parents' use of music in everyday life routines, such as, "Have you used music during your activities with your child? If yes, how many times a week, 1, 2–3, or >7?"

Power Calculation and Sample Size Justification

The minimal clinically important difference for HF power in infants is unknown. The power calculation for the primary outcome was informed by a previous study (Arnon et al., 2014), which found mean values of HF power of 16.8 (SD = 2.4) ms^2/Hz during maternal singing combined with SSC, as compared to 10.5 (SD = 5.7) ms^2/Hz during SSC alone (i.e., pooled SD = 4.37, effect size $d = 1.44$). In the present study, the effect may be more pronounced because a music therapist is involved (e.g., 20 vs. 10.5 ms^2/Hz with SD = 4.37, corresponding to a very large effect size of $d = 2.17$). The study was, therefore, powered to detect a large effect in HF power ($d = 0.80$). In an individually randomized trial, with a 2-tailed, 5% significance level, and 80% power, a sample size of 26 infants in each group would be necessary. However, this sample size needs to be adjusted for clustering (design effect) and dropout. The design effect is defined as $D_{eff} = 1 + ICC * (m - 1)$ (Eldridge & Kerry, 2012) and was calculated for a cluster size of $m = 6$ participants per cluster and intraclass coefficient (ICC) = 0.01, resulting in $D_{eff} = 1.05$ (i.e., a 5% increase in sample size). ICC of 0.01 was chosen to provide adjustment for potential clustering, although we do not expect strong cluster effects in this time-clustered design. We have no reason to expect strong fluctuations by calendar month within the same unit. Drop-out is assumed to be 20%. The resulting required sample size is 58. Therefore, we plan to recruit a total of 72 participants (12 clusters with 6 participants each). Recruitment will continue until at least 60 participants with valid, complete data for the primary outcome measure are included.

Randomization of Clusters and Allocation Concealment

The clusters will be at equal intervals of two months each. This timeline was selected based on the local NICU staff's knowledge of

the average duration of hospitalization for stable preterm infants, which is about 1.5 months. The planned data collection period for this trial is 24 months, corresponding to 12 clusters. We expect that each cluster will include 6–8 infants. An external researcher with no direct contact with the participants (third author) will carry out the randomization in advance. To ensure an even distribution of the clusters along the trial period and to prevent a result in which, for example, all control clusters occur together, we decided to conduct a constrained randomization using pairwise matching clusters (Nietert, Jenkins, Nemeth, & Ornstein, 2009). Thus, six pairs of consecutive time clusters will be randomized using an electronic procedure to generate a 50% chance of being allocated to each condition (a coin flip—tossing a coin for the first cluster, then again for the third, etc.). The consecutive clusters (the second, fourth, etc.) will receive the opposite allocation from their predecessors. The randomization result will be communicated to the clinician by email at the beginning of each cluster.

Blinding. The research team and the invited participants will be aware of the treatment that is available in their cluster. Blinding of participants is not possible due to the nature of the intervention. The primary outcome is based on objective measurement and may be unlikely to be affected by subjective bias. The neonatologist interpreting the HRV data will be blinded to treatment allocation.

Recruitment. The senior neonatologist and a certified developmental nurse working at the NICU will screen patients for eligibility, recruit participants, and obtain informed consent. Participants will be enrolled individually during the first month of each cluster period only. The second month will be reserved for allowing sufficient time for families to complete the sessions and be released home before a new cluster begins.

Data Analysis Plan

The primary analysis of all outcomes will be based on the intention-to-treat principle using linear mixed effects (LME) modeling. The LME method allows for the use of all available data and assumes that missing data are missing at random. The causes for missing data are of major importance in order to understand their possible effect on the results (Gold, 2019). Random missing data may occur due to unanticipated events during NICU

hospitalization—families may be released home sooner than planned without completing all study sessions or an infant's participation may be stopped due to medical withdrawal unrelated to the study. Accordingly, each parent–infant dyad will be accounted for separately. In case both parents participate with their infant, each parent will complete all three sessions. A double dose (yes/no) score will be calculated for each infant: yes, when both parents participate in the study and no, if only one parent participates. This parameter will be analyzed as a between-subject variable.

Data will be presented as mean (SD) or median (range) as appropriate, with numbers and percentages for nominal variables. The normality of continuous data will be assessed using graphical methods (such as histograms and q-q plots). If non-normality is indicated, either transformation will be applied or appropriate generalized linear mixed models will be fit. Baseline characteristics will be compared between groups using mean (SD) and median (range) for all variables, including demographic and medical characteristics (e.g., gestational age and weight) and outcome variables, to verify the success of cluster randomization.

To analyze effects, a significance level of 5% will be used for the primary outcome and a level of 1% for secondary outcomes, to account for multiplicity. Multiplicity refers to "the statistical issues connected to performing multiple tests on the same sample; ... *p*-values have to be smaller before they can be trusted to reflect a real effect" (Gold, 2019, p. 2). Bivariate tests for continuous variables such as post-menstrual age or weight at testing (*t*-tests for normally distributed data and Mann–Whitney test for non-normally distributed variables) will be used. Chi-squared test or Fisher exact test for binary variables, such as gender or small- or appropriate size for gestational age) will be used to compare effects between groups.

In order to identify effects from the first to the last session or effects during a session, LME models will be used to model changes over time for outcome variables that are measured repeatedly, such as HRV, HR, RR, oxygen saturation, and parental anxiety. We will use a 1% significance level to account for multiplicity. The time clusters will be accounted for using a random effect in the linear mixed-effects model. Family will also be accounted for using a random effect because the unit of analysis is infant–parent dyad

and if more than one parent participates, there will be more than one observation per family. The time point (session no. 1, 2, or 3) and the type of therapy (MT+SSC or SSC alone) will be included as repeated effects in the LME models.

As an *a priori* adjustment to the analysis, we will examine all covariates together and will perform a multivariable regression analysis. The covariates that will be adjusted for *a priori* will include baseline measures of demographic and neonatal data such as: ethnic origin, infants' sex, gestational age, postnatal age at study entry, and neonatal morbidities such as apnea of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage stage 1 and 2, respiratory distress syndrome, retinopathy of prematurity, and sepsis.

All outcome variables, including mean HF power of all sessions, mean infants' heart rates, respiratory rates, oxygen saturation levels, body temperatures, infants' behavioral scores, and parents' MPAS and STAI questionnaire scores from all sessions, will be analyzed by multivariable repeated-measures Analysis of Covariance (ANCOVA) with adjustments for the above covariates. Analyses will be conducted using SPSS for Windows version 14 (SPSS Inc., Chicago. IL, USA) and R version 3.5.0 (www.r-project.org).

Ethical Considerations. The study was approved by the Institutional Review Board in April 2017 (Ethical approval no. 0283-15) and was registered in (ClinicalTrials.gov, NCT03023267). Participation will be offered to all eligible families, of any gender, race, ethnicity, or national origin, with clarification that their choice will have no impact on the routine care of their infant. Before enrollment, parents will be provided with information on the study objectives and procedures, and a written informed consent form for their infant's participation and for themselves.

Monitoring. The local research team will provide annual progress and final reports on eligibility screening, recruitment, participation completion, and adverse events to the hospital research authority and to the trial registry site. Ethics approval will be renewed annually, as well. Additionally, one coauthor (C. Gold) will receive monthly reports on updated recruitment data sets from the local team for monitoring purposes.

Confidentiality and Data Management. Demographics and data collected during sessions will be stored in a designated computer

with access limited to the local team only. Participants' identifying data will be kept separately in a paper file in a designated, locked cabinet in the hospital. Participation in the study will be reported in the medical files, without revealing group allocation. Participants will receive a study identification code. Demographics and data collected during sessions will be uploaded to the designated computer at the end of each cluster (i.e., every two months) using the study code numbers only. There will be no double data entry, but a double-check. The paper source documents: the paper forms on which data are recorded during the sessions will be entered once. The recorded data (extracted from the monitor) will be double checked by an independent person (S. Arnon, second author) to verify that the entered values are correct.

Discussion

The results of this study can add important, evidence-based knowledge regarding an MT intervention that follows the NIDCAP model approach. The proposed MT intervention will use live music only, which can be adapted in real-time to the fine changes and needs of the infants and parents. Most importantly, it will position parents as leaders of the intervention, which is very important when providing developmental care for preterm infants (Loewy et al., 2013). Parents will be taught and encouraged to continue to incorporate the technique into their everyday lives, and by doing so, use music as a meaningful health resource. The innovative aspects of the study include fathers' experiences and examining the longer-term effects regarding their experiences. None of the RCTs in the field has given special attention to these two important factors (Bieleninik et al., 2016).

We hypothesize that combining MT and SSC will benefit preterm infants' physiological and behavioral stability, and decrease parental anxiety. Potential biases may be related to the importance of parents in the process. Selection bias could result in positive effects for both groups if parents who believe in developmental care agree to participate in the study and are more cooperative than those who do not believe in developmental care. Outcome bias may occur due to the open study design, as the two study groups are not blinded to their treatment allocation. This possibility will be explored in follow-up interviews and addressed in the discussion

of the results. Additionally, there are known beneficial effects to SSC alone, which may mask beneficial outcomes of combined MT and SSC. However, considering that a previous study (Arnon et al., 2014) found beneficial effects of maternal singing over and above SSC alone, we can expect that a strong enough beneficial effect of MT will be evident. Other confounding variables could be SSC sessions in addition to those of the study (length, timing, frequency), and the exact nature of MT sessions (i.e., active vs. receptive). However, these data will not be collected due to imprecise measures of SSC outside the study protocol and our consideration that active and receptive methods of intervention are both parts of MT. Cluster randomization is used to avoid contamination between the study groups. Parents allocated to the control group will not be exposed to MT in the NICU. We hypothesize that the cluster design will be well-adapted to the NICU, parents, and infants. In the current study, we will not compare the outcome variables between fathers and mothers. However, we might conduct a *post hoc* analysis looking into differences between parent–infant dyads according to parental sex.

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Conflict of interest

None declared.

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