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ORIGINAL ARTICLE

Effects of standardized acoustic stimulation in premature infants: a randomized controlled trial

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OBJECTIVE: The objective of this study was to investigate the effects of recorded lullabies and taped maternal voice in premature infants.
STUDY DESIGN: Sixty-two preterm infants in a stable condition with $30<37$ weeks of gestation and <10 days of postnatal age were randomly assigned to hear (A) recorded lullabies or (B) taped maternal voice for 30 min each evening during 14 consecutive days or (C) receive no standardized acoustic stimulation (control group). Heart rate and respiratory rate were recorded daily before, during and after the intervention (A and B) or a comparable period with no intervention (C), whereas activity was measured on days 1, 7 and 14 of the intervention using accelerometers.
RESULTS: Both interventions led to a significant decrease in heart rate and respiratory rate during and after the stimulation when compared with the control group. The changes were more pronounced in infants with higher gestational ages ($P=0.001$). Lower activity was measured during the intervention when compared with the control group ($P<0.01$).
CONCLUSIONS: Standardized acoustic stimulation with recorded lullabies and taped maternal voice led to a decrease in heart rate and respiratory rate, and was associated with lower activity. Whether this indicates a reduced stress reaction needs to be investigated in further studies.

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INTRODUCTION

New insights into the physiology of the preterm infant and technological advances have remarkably improved survival of preterm infants during the last decades. However, the current technical environment of neonatal intensive care units (NICUs) not only provides a high standard of care but also exposes the immature infants to a wide range of adverse stimuli such as continuous illumination and noise. In contrast to the intrauterine environment, where permanent and rhythmic stimulation is provided by maternal body sounds such as heart beat and bowel peristalsis, preterm infants are exposed to an overwhelming environment with loud, sharp and unpredictable noises up to over 100 dB(A).[1–4]

On the other hand, incubators can provide isolation and may lead to a deprivation of positive sensoric stimulation (for example, auditory or tactile),[5] which is known to be necessary for a normal development.[6,7] Especially between 25 and 40 weeks of postconceptional age, when preterm infants are likely to be at the NICU, major developmental steps, in particular of the nervous system, occur. Therefore, the use of adequate stimulation at the NICU has been encouraged to provide a supportive atmosphere to the premature infant and to allow neurological maturation processes to continue in an organized manner.[8,9] However, owing to the lack of exact definitions and clear evidence, consistent recommendations concerning systematic stimulation as a supportive therapy in preterm infants do not yet exist.

Recent studies have shown that acoustic stimulation with recorded lullabies, live singing, maternal voice or recorded heart beats provides potentially positive short- and long-term effects in premature infants with respect to heart rate, oxygen saturation, behavioral measures, feeding behavior and length of hospitalization.[10–15] However, controlled randomized trials, using recommended sound levels for stimulation are still rare. Moreover, some studies showed contradictory findings concerning the effects of acoustic stimulation on physiological parameters in preterm infants such as heart rate.[10,12,13,16] Investigations, which also focus on the activity of preterm infants during acoustic stimulation, are lacking. As in most studies acoustic stimulation was performed only for a couple of consecutive days, data considering potential habituation effects are still missing.[10,15]

The aim of this randomized controlled trial was to investigate the influence of two different kinds of standardized acoustic stimulation in premature infants on heart rate, respiratory rate and activity. We hypothesized that both recorded lullabies and taped maternal voice lead to a decrease in heart rate and respiratory rate, as well as activity in premature infants, and that no habituation occurs over a period of 2 weeks.

METHODS

Study design and patients

This randomized, controlled non-blinded trial was done at a German Level III Perinatal Center during a 12-month period. The study was approved by the local ethical committee. Written informed consent of the parents was obtained for each participating infant before randomization.

Premature infants in a stable condition with a gestational age of 30 to 36 completed weeks and a postnatal age of <10 days were eligible for randomization. Exclusion criteria were as follows: (a) lack of parental consent, (b) expected hospitalization of <14 further days, (c) artificial ventilation, but not nasal continuous positive airway pressure, (d) treatment with catecholamines or β-antagonists, (e) cardiac anomalies or diseases, (f) congenital malformations and (g) hearing loss, confirmed by auditory brainstem-evoked potentials.

Infants were randomly assigned to one of two intervention groups or a control group by opening consecutive sealed envelopes.

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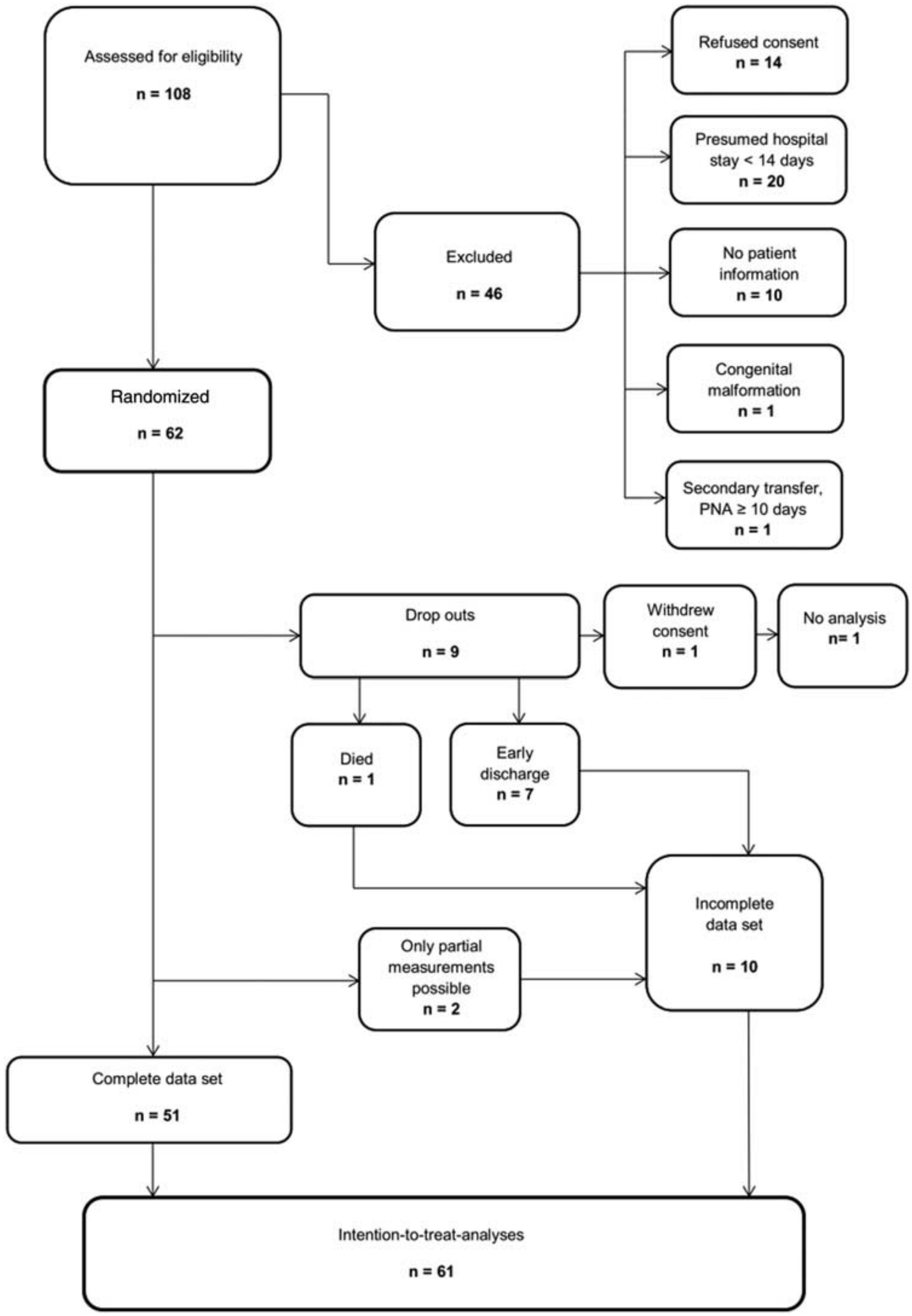

Figure 1. Flow chart of the study population, indicating the number of infants screened, excluded, enrolled and analyzed.

Interventions

The 'Lullabies group' was exposed to recorded lullabies in a standardized manner using a commercially available CD with classical melodies sung by females ('Wiegenlieder Vol. 1', Carus-Verlag, Stuttgart 2009).

For infants in the 'maternal voice group,' mothers were asked to tape the reading of a chapter from the German book 'Der kleine Prinz' (English: 'The Litte Prince') by Antoine de Saint-Exupéry (Karl Rauch Verlag, Düsseldorf 1950 and 1998). After reviewing the quality of the recording, the reading was transcribed to a CD.

Infants randomized to one of the intervention groups received their specific stimulation on 14 consecutive days for 30 min between 2000 and 2100 h, about 30 to 60 min after feeding and in the absence of their parents. Infants in the 'control group' received no standardized acoustic stimulation.

For the intervention, a small passive speaker was placed inside the incubator or the cot, respectively, at a distance of ~ 20 cm from the infants' ears. The acoustic stimulation was presented with a volume of 55 to 65 dB (A), which was checked before each stimulation using a sound level meter McCheck MS-67 pro (ETT GmbH, Braunschweig, Germany).

Setting

According to their condition, the infants were cared and studied at the NICU or the newborn special care unit. The NICU included three rooms of ~ 25 m^2 each and with four incubators per room. Visiting hours for the parents were 0900 to 1200 h and 1430 to 2000 h. The special care unit included 15 cots in 6 rooms with different sizes, varying from 1 to 6 cots

Table 1. Baseline characteristics

	Lullabies (n = 20)	*Maternal voice (n = 20)*	*Control (n = 21)*	*P-value*
Gestational age at birth (weeks)				0.21
Median	33,3	32,0	33,4	
Range	30.0–36.3	30.0–35.0	31.3–35.0	
Age at start of study (days)				0.03
Median	5	6	4	
Range	2–9	2–9	1–9	
Birth weight (g)				0.21
Median	1732	1685	1990	
Range	870–3050	740–2895	995–2495	
Apgar score (5 min)				0.25
Median	8	8	8	
Range	3–10	5–10	5–10	
Male (%)	12 (60)	12 (60)	9 (57)	0.71
SGA (%)	4 (20)	6 (30)	4 (19)	0.65
Prenatal steroids (%)	9 (45)	12 (60)	10 (48)	0.85
Associated disorder[a] (%)	2 (10)	3 (15)	0 (0)	0.19
Continuous positive airway pressure (%)	3 (15)	3 (15)	3 (14)	0.98

[a]Necrotizing enterocolitis, intracranial hemorrhage and sepsis.

per room. At this unit, parents were allowed to visit their infants whenever and as long as they want.

Before, during and after each intervention, the acoustic background level was measured by placing a sound level meter in the middle of the room. The surrounding sound level was also measured for the control group at comparable time periods. The average acoustic background level during the intervention periods was 48.82 dB(A) in the NICU and 54.92 dB (A) in the special care unit.

In addition, the light intensity was measured throughout a representative 24-h period (Luxmeter Mavolux 5032 C, Gossen GmbH (Nuernberg, Germany)). The mean light exposure was 756 ± 601 lx (in the NICU) and 380 ± 26 lx (in the special care unit) during daytime and 5 ± 13 lx (in the NICU) and 7 ± 12 lx (in the special care unit) during night.

Measurments and outcomes

Recording of heart and respiratory rates. All infants were routinely and continuously monitored using Solar 8000i monitors (GE Medical Systems Deutschland GmbH & Co. KG, Solingen, Germany). For this study, heart rate and respiratory rate were collected each minute during three periods as follows: 15 min before, 30 min during and 15 min after intervention. Means were calculated for each of these periods. In the control group, data collection was done during comparable time intervals each evening.

Measurement of activity. Measurement of activity started on day 1 of the intervention and was repeated on days 7 and 14 of the intervention. Activity was recorded during stimulation (intervention groups) or no stimulation at comparable time periods (control group) by using a GT3x+ accelerometer (ActiGraph, Pensacola, FL, USA), positioned on the infant's leg at the midpoint between the knee and ankle. The GT3x+ weighs 19 g and was set to collect raw tri-axial (axis 1 = vertical, axis 2 = horizontal and axis 3 = perpendicular) acceleration at 30 Hz. Before measurement, the position of the accelerometer was initialized on the device. The analysis of the recorded data was accomplished via Data Analysis Software ActiGraph, Version 6. Activity was analyzed using Vector Magnitude values $[\mathrm{VM} = \sqrt{(\mathrm{vertical})^2 + (\mathrm{horizontal})^2 + (\mathrm{perpendicular})^2}]$, which are the combined sampled acceleration from all three axes calculated on one minute epoch basis from the raw data.

Recording of activity started about 30 to 60 min after feeding, which means during a similar period of activity for all infants. During recording of activity infants were lying in their incubators or cots and parents were not present, and did not hold their infant.

Primary and secondary outcomes. The primary outcome was the difference in mean heart rate during the stimulation (30 min interval) compared with prior stimulation (baseline) ($HR_{dur\text{-}bef}$). Secondary outcomes included the differences between the mean heart rate after and before stimulation ($HR_{aft\text{-}bef}$), the differences between the mean respiratory rate during and before stimulation ($RR_{dur\text{-}bef}$), as well as after and before stimulation ($RR_{aft\text{-}bef}$) and the activity during stimulation with actigraph.

Statistical analysis

For this pilot study, an empirical number of 20 infants per group was assessed.

Baseline characteristics of the study population and the outcome data (heart rate and respiratory rate) are given as median (range) for continuous data or as absolute number (percent) for nominal data.

For the analysis of the primary endpoint, the mean change in heart rate was calculated for each infant from all available differences $HR_{dur\text{-}bef}$. Closed testing procedure was applied to allow for multiple comparisons, while controlling the type-I error rate for the analysis of the primary endpoint. In a first step, Kruskal–Wallis test was used to compare the mean changes between the three groups. If this test reached significance, pairwise comparisons between groups were performed with two-sided Mann–Whitney *U*-tests.

Sensitivity analyses using mixed models for repeated measurements were done, to use all available changes per infant and to additionally adjust for gestational age and postnatal age. These analyses confirm the results of the main analysis (data not shown).

Analyses of secondary outcomes such as $HR_{aft\text{-}bef}$, $RR_{dur\text{-}bef}$, $RR_{aft\text{-}bef}$, as well as changes in activity were done similar to the analysis of the primary endpoint.

For all outcomes, two-sided 95% confidence intervals (95% CIs) were calculated for pairwise comparisons when these were performed. *P*-values < 0.05 were considered statistically significant.

All analyses were performed on the intention-to-treat population. Statistical analyses were done using SPSS version 21.00 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) and R version 3.0.2 (www.r-project.org).

RESULTS

Patients

From 1 March 2012 to 31 January 2013, a total of 108 eligible premature infants with a gestational age of 30 < 37 weeks were admitted. Forty-six infants were excluded for the following reasons: (a) lack of parental consent ($n = 24$), (b) expected short hospitalization ($n = 20$), (c) admission at ⩾ 10 postnatal days ($n = 1$) and (d) congenital malformation ($n = 1$).

Of the remaining 62 preterm infants, 20 were randomly assigned to the 'Lullabies group,' 20 to the 'Maternal voice group' and 22 to the 'control group.' During the study, nine infants dropped out: in one infant of the control group parents withdrew consent, one infant died from necrotizing enterocolitis and seven infants were discharged before completion of the study period. Because of technical problems, data collection in two infants was incomplete (Figure 1).

The infants' characteristics in the three groups are shown in Table 1. The three groups did not differ significantly with respect to the infants' baseline characteristics, except postnatal age at the start of the study. Five (13%) infants had complications typical for preterm infants: in the 'Lullabies group,' one infant had an infection and one had an intraventricular hemorrhage (grade II according to Papile); in the 'Maternal voice group,' two infants had necrotizing enterocolitis (stage II according to Bell) and one infant an intraventricular hemorrhage (grade III according to Papile). However, these five infants remained in stable condition during the study period. Significant hearing loss was excluded in all participating infants using automated auditory brain stem response (MAICO MB 11 BERAphon, MAICO Diagnostic GmbH, Berlin, Germany) with a signal intensity of 35 dB.

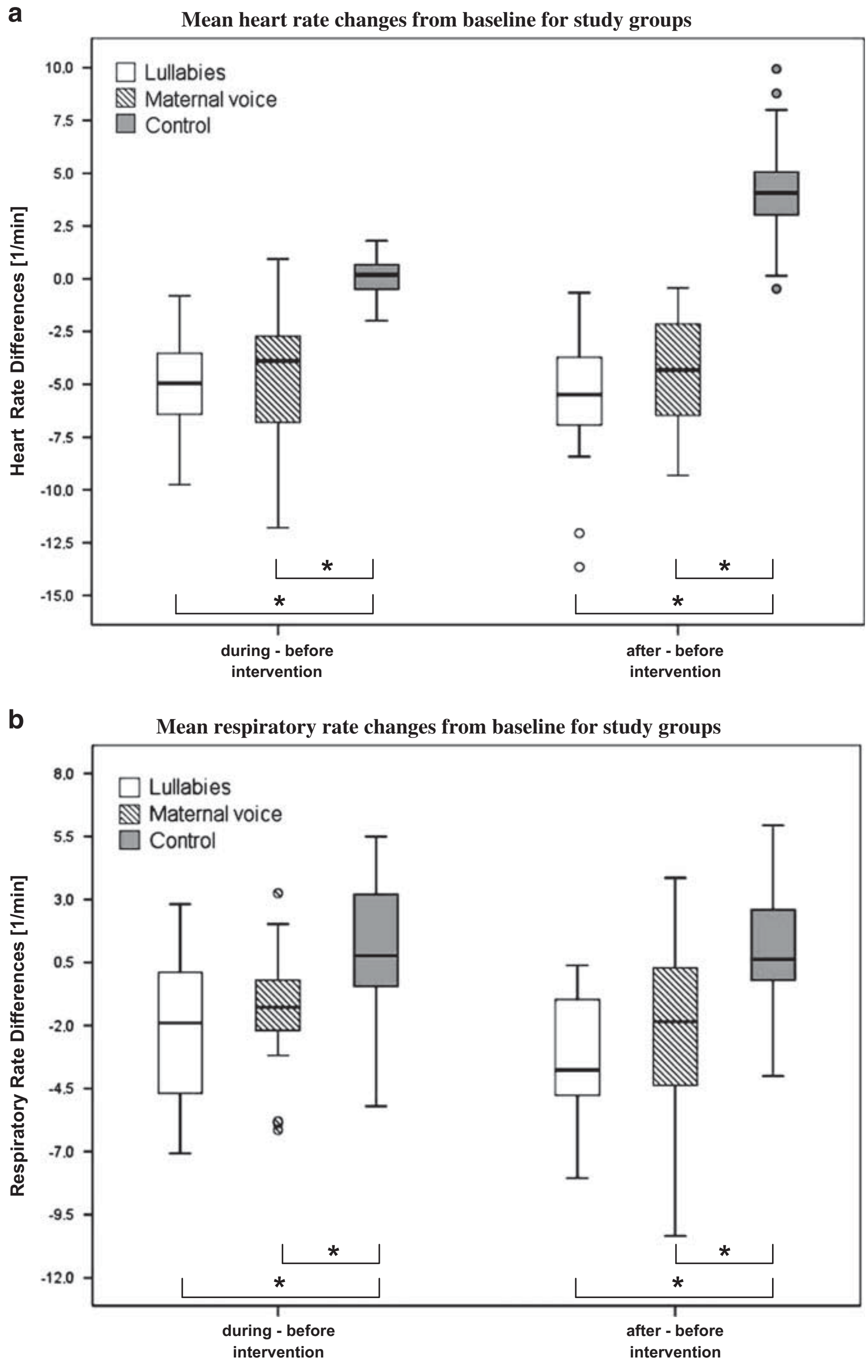

Figure 2. Mean changes from baseline in heart rate (**a**) and respiratory rate (**b**) for the three study groups. The figure reveals the differences between the stimulation period and the period before stimulation (left panel), and the differences between the period after stimulation and the period before stimulation (right panel); °outliers and *statistically significant ($P<0.05$).

Primary outcome

Whereas heart rate did not significantly change during the daily study period in the control group, it significantly decreased in both intervention groups during the interventions from baseline before intervention ($HR_{dur\text{-}bef}$: 'Lullabies group' vs 'control group,' $P<0.001$, 95% CI: −6.23 to −3.32; 'Maternal voice group' vs 'control group,' $P<0.001$, 95% CI: −6.5 to −3.24). A significant difference between both intervention groups was not observed ($HR_{dur\text{-}bef}$: $P=0.95$, 95% CI: −1.72 to −2.14) (Figure 2a and Figure 3).

Secondary outcomes

Heart rate was significantly lower after stimulation than before stimulation in both intervention groups ($HR_{aft\text{-}bef}$: 'Lullabies group' vs 'control group,' $P<0.001$, 95% CI: −10.72 to −6.95; 'Maternal voice group' vs 'control group,' $P<0.001$, 95% CI: −10.41 to −6.72). No significant difference was observed between the two intervention groups ($HR_{aft\text{-}bef}$: $P=0.85$, 95% CI: −2.33 to 1.81) (Figure 2a).

The decrease in heart rate during stimulation $HR_{dur\text{-}bef}$ ($P<0.001$) and after stimulation $HR_{aft\text{-}bef}$ ($P=0.019$) was related to gestational

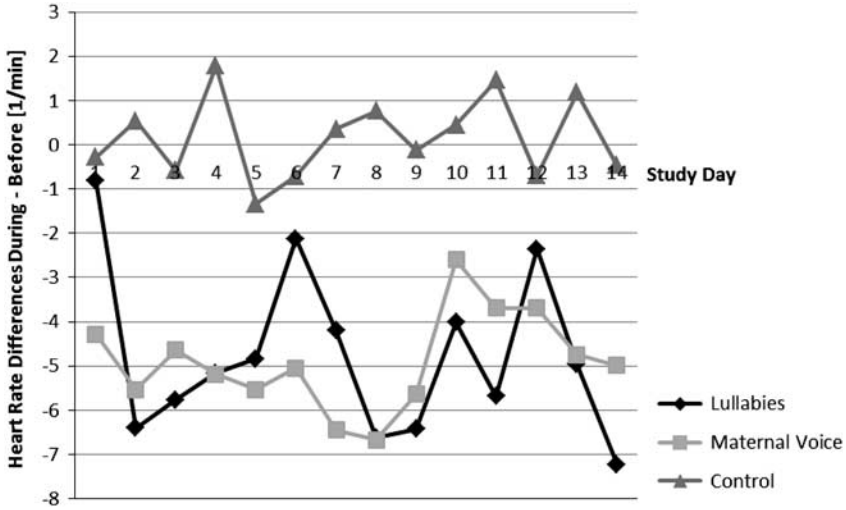

Figure 3. Mean changes from baseline in heart rate for the three study groups. Negative and positive values denote decreasing and increasing heart rate during acoustic stimulation.

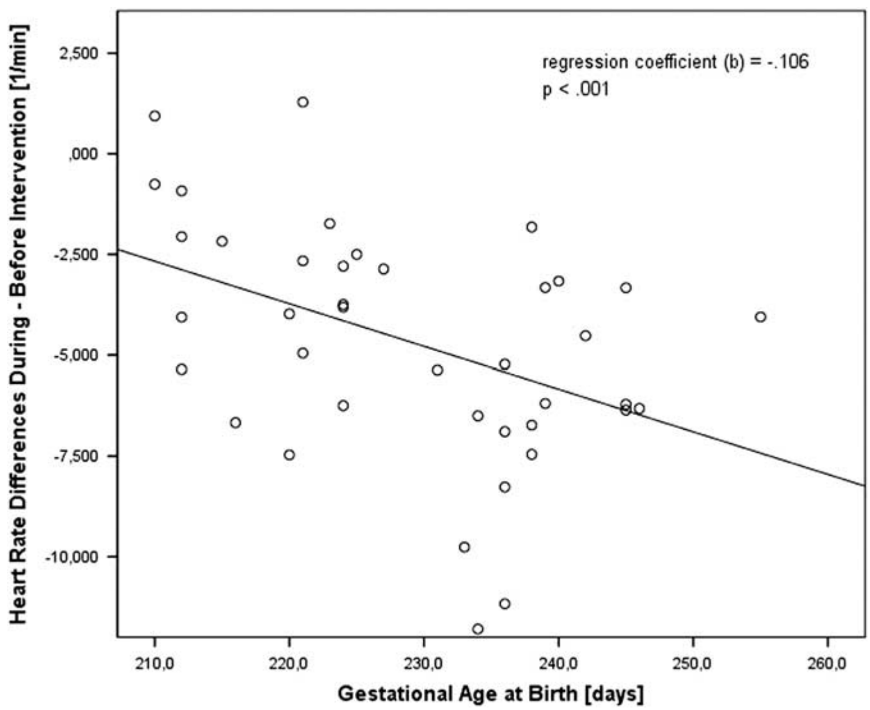

Figure 4. Effects of gestational age at birth on heart rate changes during acoustic stimulation. The circles reveal the differences between the stimulation period and the period before stimulation.

age and was more pronounced in more mature infants (Figure 4). A significant correlation of the change in heart rate and the infants' postnatal age at entering the study could not be observed.

Similar to heart rate, respiratory rate decreased during and after acoustic stimulation as well: $RR_{dur\text{-}bef}$ ('Lullabies group' vs 'control group,' $P < 0.001$, 95% CI: -5.51 to -1.61; 'Maternal voice group' vs 'control group,' $P = 0.0004$, 95% CI: -4.44 to -1.29) and $RR_{aft\text{-}bef}$ ('Lullabies group' vs 'control group,' $P < 0.001$, 95% CI: -5.90 to -2.09; 'Maternal voice group' vs 'control group,' $P = 0.003$, 95% CI: -4.82 to -1.15). However, a significant difference between the two intervention groups for $RR_{dur\text{-}bef}$ and $RR_{aft\text{-}bef}$ was not found ($RR_{dur\text{-}bef}$: $P = 0.53$, 95% CI: -2.67 to 1.10; $RR_{aft\text{-}bef}$: $P = 0.29$, 95% CI: -3.08 to 1.04) (Figure 2b).

Activity during stimulation and no stimulation (control group) was recorded on day 1 (onset), day 7 (midpoint) and day 14 (end point) of intervention. On day 1 ($P = 0.011$, 95% CI: -583.59 to -56.59) and day 14 ($P = 0.037$, 95% CI: -703.35 to -2.19), infants in the 'Maternal voice group' had a significantly lower activity level than the infants in the 'control group'. On day 7, activity in the 'Maternal voice group' was not only lower than in the 'control group' ($P = 0.005$, 95% CI: -507.20 to -50.01) but also lower than in the 'Lullabies group' ($P = 0.021$, 95% CI: 7.19 to 352.12). Activity was lower in the 'Lullabies group' than in the 'control group,' but this difference did not reach statistical significance. When summarizing the 3 days of activity recording, infants in the 'Lullabies group' had significantly less activity during stimulation

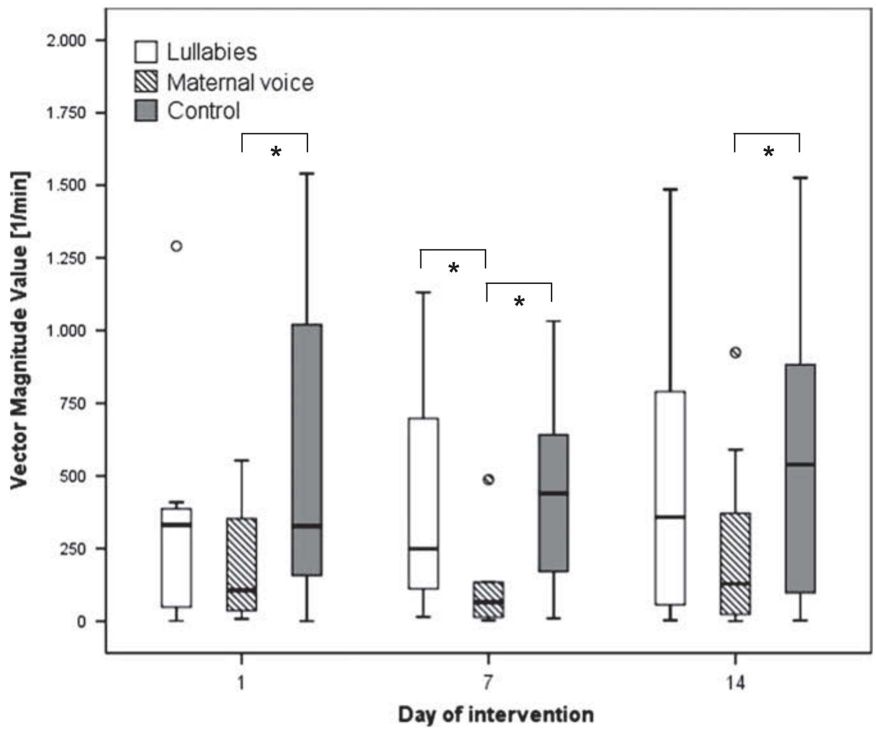

Figure 5. Activity (given as Vector Magnitude Values = acceleration from all three axes calculated on 1-min epoch basis) during acoustic stimulation on days 1, 7 and 14 of the intervention. It is noteworthy that the algorithm used for calculation leads to values between 0 and several thousands; °outliers and *statistically significant ($P < 0.05$).

than infants in the 'control group' ($P = 0.04$, 95% CI: − 172.74 to − 4.87) (Figure 5).

Maternal voice showed the highest effect on activity in preterm infants when summarizing the 2 weeks ('Maternal voice group' vs 'control group,' $P = 0.01$, 95% CI: − 444.91 to − 186.24; 'Maternal voice group' vs 'Lullabies group,' $P = 0.04$, 95% CI: 2.53 to 287.00).

DISCUSSION

To study the effect of standardized acoustic stimulation, we randomly assigned 62 preterm infants into three groups as follows: a 'Maternal voice group,' a 'Lullabies group' and a control group. Our data indicate that standardized acoustic stimulation during the first weeks of life influences heart rate and respiratory rate, as well as physical activity in stable preterm infants with 30 to 36 completed weeks of gestation. A daily acoustic stimulation of 30 min in the evening with recorded lullabies or taped maternal voice led to a decrease in heart rate and respiratory rate during and 15 min after this intervention. Both kinds of acoustic stimulation were associated with lower activity during intervention when compared with the control group.

To our best knowledge, only two other studies with comparable design have been published to date. Malloy *et al.*[15] studied the effects of three study arms, maternal voice, lullabies and standard care on behavior, days to discharge and weight gain. They found no statistically significant differences between the three groups with the exception that infants exposed to lullabies reached the objected weight significantly earlier. As that study was performed before recommendations for safe sound levels within the NICU were made, they used stimuli of 70 to 75 dB(A).[17] These high sound levels might have inhibited potential positive effects. As it is recommended for NICUs that noise in general should not exceed 50 dB(A), we used sound levels that were lower than those in the study of Malloy *et al.*[15] Nevertheless, they were slightly higher than recommended, in order to overcome the surrounding sound level in our units.

In the study of Standley *et al.*[18] comparing lullabies and maternal voice, oxygen saturation and frequency of pulse-oximeter alarms were measured. The findings of that study suggest that stimulation with lullabies stabilizes infants' oxygen regulation more effectively than with maternal voice.[18] Since the time these two studies[15,18] were performed, remarkable changes in performance and environmental conditions in the NICU have occurred.

More recent studies showed a positive effect with respect to physiological and behavioral responses of preterm infants to acoustic stimulation.[10–12] Owing to the wide variety of acoustic stimuli, most studies pursued different approaches, mainly by either comparing different types of musical stimuli[10] or focusing on different forms of presentation such as live versus recorded music.[10,13]

As recorded music with multiple musical elements is suspected to cause overstimulation in preterm infants, some authors prefer stimulation with live music.[11] Focusing on physiological and behavioral parameters, Arnon *et al.*[13] found a superiority of live music compared with recorded music and to a control group.

It is well known that an early physical and verbal contact provided by the mother has a positive impact on neonates.[6,19] However, in contrast to musical stimuli, only limited data are available on the physiological and behavioral responses of preterm infants to maternal voice.[20] A previous study by Doheny *et al.*[21] suggests a positive effect on cardiorespiratory regulation in preterm infants.

We observed a positive correlation between the infants' gestational age and their physiological response to standardized acoustic stimulation. Preterm infants with higher gestational ages showed significantly stronger effects on heart rate during stimulation than infants with lower gestational ages. These results are in accordance with those of Doheny *et al.*,[21] who reported an effect of maternal voice on the cardiorespiratory regulation only in infants ⩾33 weeks of gestation. Owing to the fact that major active neurological maturation occurs during the third trimester of fetal life, Bowden *et al.*[22] assumed that preterm infants are not able to coordinate autonomic responses to environmental stimuli before 32 to 34 weeks of gestation.

Although most other studies are restricted to only a few days of acoustic stimulation,[10,14,23,24] infants in our study were stimulated daily over a period of 14 consecutive days.[23–25] This enabled us to investigate whether a habituation effect as a response to repeated stimuli may occur. Neither for lullabies nor for maternal voice, infants showed a decreasing response to repeated acoustic stimulation over time.[25] Thus, no habituation or negative effect of repeated stimulation could be observed in our trial (Figure 3). Interestingly, the decrease in heart rate during stimulation showed a larger variation over the 14 days of intervention in the maternal voice group than in the two other groups (Figure 3).

In only one pilot study including eight premature infants, the effect of acoustic stimulation on activity was measured.[14] In other studies, behavioral responses of premature infants to acoustic stimulation have been assessed by behavioral scores.[11,15] As these scores rely on subjective evaluation, conflicting findings have been published. By using accelerometers, we were able to measure activity of preterm infants during stimulation independently of the observer's impression. Using this design, we were able to show that activity was lower in preterm infants during a standardized acoustic stimulation than in control infants without acoustic stimulation.

The acoustic stimulation used in our study is easily reproducible and feasible. Although live music provides the possibility to individually adjust stimulation, its integration into the NICU routine is difficult to establish. Furthermore, specially trained staff is needed, whereas recorded stimulation can easily be performed by parents or staff even in the absence of the parents.

The strength of our study is the randomized design. By using a standardized stimulation including consistent timeframes and duration, as well as a controlled sound volume, a high comparability between the groups was provided.

Our results are limited to relatively mature and stable preterm infants and cannot be applied to very immature and very ill preterm infants. Moreover, our results are restricted to short-term outcomes and give no information on long-term effects. A further limitation of the present study is that the lullabies and the novel, which was read by the mother, were in German language. Therefore, they may not fit to families with a migration background.

It can be speculated that the decrease in heart rate and respiratory rate, and the lower activity during standardized acoustic stimulation reflects a decrease in stress. As autonomic parameters and activity levels can reflect many cortical and brainstem processes, this needs to be investigated in further studies.

In conclusion, we could show that acoustic stimulation with recorded lullabies or taped maternal voice leads to a decrease in heart and respiratory rate during and after stimulation, and a lower activity during stimulation in preterm infants of 32 to 36 completed weeks of gestation. These findings may indicate a reduction of stress; however, further studies are needed to validate this assumption and to look for long-term effects of acoustic stimulation in preterm infants.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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