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REGULAR ARTICLE

Music exposure and maturation of late preterm sleep–wake cycles: a randomised crossover trial

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ABSTRACT
Aim: To determine the effect of music on sleep–wake cycle (SWC) patterns in late preterm neonates.
Methods: In a masked crossover study, infants between 32 and 36 6/7 weeks gestation were randomised to music exposure either during the first six or last six hours of a 12-hour observation period. SWC characteristics were determined by continuous amplitude-integrated electroencephalography (aEEG) read by two coders masked to exposure sequence. Analysis was performed in paired comparisons. ANOVA was used to assess the effects of music exposure, period and crossover on SWC outcomes: (i) Burdjalov Scores (BS) during active sleep (AS) (ii) per cent and duration of quiet sleep (QS).
Results: Thirty infants were studied. A total of 222 QS cycles (median seven per patient; range five to 12) were analysed. Music exposure was associated with higher BS ($F = 10.60$, $p = 0.0019$) in AS and decreased interruptions during QS. The advanced postconceptual age (PCA) SWC pattern during AS was equivalent to a one-week mean. Number, duration and ratio of QS cycles did not change with music exposure.
Conclusion: Music exposure elicits an increasing PCA pattern in AS and fewer interruptions in QS. Music may benefit sleep in late preterm infants.

BACKGROUND
Despite improved survival due to advances in neonatal care, preterm infants remain at high risk for neurodevelopmental impairment. Neonatal sleep patterns predict neurodevelopmental outcomes; specifically intelligence quotient, expressive language, fine motor abilities verbal skills and executive functions (1,2). Onset of sleep–wake cycling (SWC) within the first two weeks of life is associated with higher neuro-cognitive scores (3,4). The sound experience in the NICU, a dynamic influence on sleep quality, remains suboptimal (5–7).

We hypothesised that exposure to music would lead to a more mature SWC as evidenced by one or more of the following; higher Burdjalov Scores (BS) (8), rise in the upper and lower margins of amplitude-integrated electroencephalography (aEEG), increased amplitude of the lower margin of quiet sleep (QS), decreased bandwidth, longer duration of QS, greater percentage of time spent in QS, and/or more continuous QS.

Abbreviations
aEEG, Amplitude-integrated electroencephalography; AS, Active sleep; BS, Burdjalov score; DOL, Day of life; GA, Gestational age; NICU, Neonatal intensive care unit; PCA, Postconceptual age; QS, Quiet sleep; QSC, Quiet sleep cycle; REM, Rapid eye movement; SWC, Sleep-wake cycle.

PATIENTS AND METHODS
This study was approved as minimal risk by the institutional review boards (IRBs). Infants that were 0–28 days of age, born between 33 0/7 and 36 6/7 weeks, who had passed a hearing screen were eligible for the study. Infants were excluded for encephalopathies, seizures, abnormal

Key Notes
- This study provided the first objective evidence of the effect of music on neonatal sleep—wake cycling using amplitude-integrated electroencephalography (aEEG).
- An association was found between music exposure and more advanced PCA sleep–wake cycle patterns, specifically during active sleep, with no interruption to quiet sleep.
- Further research is indicated to determine effect of other sound exposure on sleep–wake cycling and actual effect of music exposure on long-term developmental outcomes.

neurologic examination, meningitis, neonatal abstinence syndrome or scalp lesions affecting the sensor application or signal transduction. Critically, ill infants requiring mechanical ventilation, positive pressure respiratory support or pharmacologic pressors were excluded. In addition to prematurity, admission diagnoses included suspected sepsis (N = 17), respiratory distress (N = 13), transient tachypnea (N = 4), small for gestational age (N = 3), feeding intolerance (N = 2), magnesium exposure (N = 2), pneumothorax (N = 2), hypoglycaemia (N = 2), twin-to-twin transfusion (N = 2), anaemia (N = 2), presumed neonatal pneumonia (N = 1) and thrombocytopenia (N = 1). Although not an exclusion, none of the infants were receiving caffeine.

The infant's prestudy environment was maintained (i.e. bassinet or open crib) with no changes in their feeding or care regiment. Per bedside documentation, 13 infants took all feeds PO bottle feeds, of which one infant also went to breast, 13 required partial NG feeds and one infant was solely NG fed (three not documented). Infants received scheduled feeds every three hours.

A sample size of 27 was calculated for a power of 80% to detect a 10-minute increase in QS per epoch, with a standard deviation of 12 minutes for paired within subject comparison of music exposure and ambient noise, with a 0.05 two-sided significance level.

This study was a randomised, masked, crossover trial. The randomisation sequences were generated by a secure website (Sealed Envelope) in blocks of four and were stratified according to GA and day of life (DOL). A total of 30 infants were randomised and completed the study with acceptable quality aEEG recordings; 15 in Sequence A/B (Music First) and 15 in Sequence B/A (Music Last). There was no washout period between exposure to music and ambient noise. The crossover allowed for collective, within group and within subject analysis of the effect of music.

Chloe Agnew's lyrical version of Brahms' Lullaby, a highly consonant tune sung in soprano, was selected as the intervention measure based on studied neonatal preferences for music (9).

Aim was to play music at <60 dB-based safe sound recommendations, but approximately 10 dB above ambient noise in order to be audible (10). Noise levels were measured with a Sper Scientific mini sound meter placed at each infant's ear. Median ambient noise levels in dB were 49.9 (IQR 48–49.9). Median music levels in dB were 58 (IQR 56–58.9), with three infants exposed to music just above 60 dB. aEEG data was obtained using five electrodes – two biparietal on each hemisphere, with one grounding electrode on the shoulder. Brahms' Lullaby was played on repeat for 6 of the 12 hours. At the end of six hours, music was either discontinued or initiated, depending on sequence randomisation. Subjective comfort and activity levels were documented using the COMFORT neo scale (11), a validated behavioural pain instrument using six behavioural dimensions to assess neonatal comfort alertness; calmness/agitation; respiratory response or crying; body movement; facial tension; muscle tone. Alertness was a subjective tool with numerical values to analyse sleep state.

Two coders masked to music sequence assignment analysed the aEEG recordings, reaching agreement on scoring parameters. Measurements in millimetres were converted into μV using a logarithmic equation provided by Natus Medical Inc. (Pleasanton, CA, USA) Continuity (frequent variations in the aEEG electrical activity) and cyclicity (sinusoidal variations in amplitude and continuity, alternating between narrow and broad bandwidths) were analysed (8). Active sleep (AS) and wakefulness are indistinguishable on aEEG, both defined as a narrow bandwidth representing lower voltage and more continuous activity. QS is defined by broadening of bandwidth representative of discontinuity, with a drop in the minimum amplitude. Interrupted QS is QS disturbed by brief narrowing then return to broadening of the bandwidth with completion of the QS cycle.

Number of sleep cycles per hour, duration of QS, frequency of interruptions and duration of intervals between QS were measured. Qualitative continuity of QS was evaluated. Study outcomes were the effect of music exposure on the ratio of QS to total duration of time observed and the BS, a score 'devised to assess objectively the developmental maturation of the neurologically unimpaired premature infant' (8).

Data are presented as mean ± SD, difference of the means with 95 % confidence intervals. Continuous data were analysed by paired *t*-test, the McNemar's exact symmetry test was performed for paired nominal data. Treatment effect was analysed by adjusting for possible period and crossover effect using ANOVA (pkcross; STATA 11). Estimation of treatment, period and crossover effects were analysed for the primary endpoint of QSC Ratio (%) and secondary endpoints of number of QSC (N/hour), total BS and calculated postconceptual age (PCA).

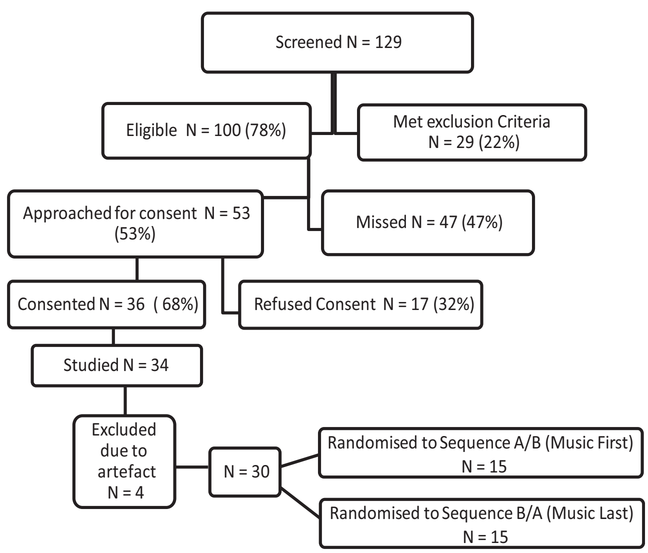

Figure 1 Subject screening, exclusion and randomisation. A total of 34 infants completed the 12 hour study, 4 were subsequently excluded due to aEEG artefact, leaving 15 infants in each randomisation sequence.

Table 1 Subject demographics

Variable	N = 30
Gender	
Female	12 (40%)
Male	18 (60%)
Race	
Black	18 (60%)
White	9 (30%)
Hispanic	2 (6.6%)
Other	1 (3.3%)
Gestational age, mean (SD), week	35 0.8/7 (1.08)
Birthweight, mean (SD), g	2330.9 (586.42)
DOL at time of study, median (25–75 quartile), days	5 (2–9)
CGA at time of study, mean (SD), week	36 (1)
Five-minute Apgar, mean (SD)	8 (1.51)
Gestation	
Singleton	19 (63.3%)
Twin	11 (36.7%)

Characteristics of the 30 subjects are described. Each subject served as a reflexive control for the music intervention.

RESULTS

A total of 129 infants were screened; of which 100 infants were eligible to participate (Fig. 1). Table 1 shows demographic characteristics. As shown in Table 2, there was no difference in the number of QS cycles/hour, median duration in minutes of QS or ratio of time spent in QS with music compared to without music. There was no difference in the minimum amplitudes in μV of QS, maximum amplitudes in μV of QS or bandwidths (μV) of the QS cycles with music compared to without music. However, there were 62% fewer interruptions of QS during music exposure periods. There was no treatment effect ($p = 0.84$), no period effect ($p = 0.54$) nor carryover effect ($p = 0.84$) on the ratio of QS time to total time of each exposure. There was no treatment effect ($p = 0.62$), no period effect ($p = 0.38$) nor carryover effect ($p = 0.99$) on the number of QS cycles/hour. Paired *t*-test analysis of Comfort neo Scores (11), with isolation of the Alertness parameter, showed no difference at baseline, three hours of music exposure, six hours of music exposure, three hours without music or six hours without music.

Burdjalov Scores score analysis is presented in Table 3. Music exposure was associated with higher BS ($F = 10.60$, $p = 0.002$) independent of period or crossover effects. Figure 2 represents a linear regression curve plotting the effect of music on the BS, demonstrating a consistent score increase with the influence of music.

DISCUSSION

Our study provides the first objective evidence, using aEEG monitoring, correlating music exposure with SWC patterns corresponding to increased PCA. This correlation is equivalent to an increase in approximately one-week PCA based on BS analysis of AS. Significance of this change in SWC lies in its association with brain maturation and stabilisation (1–3). AS is specifically involved with mechanisms thought to be fundamental to learning formation of memories (12) and completion of neuronal development (13).

In agreement with our findings, QS characteristics are thought to be biologically determined and not responsive to environmental modifications (14,15). In contrast to our findings, Olischar et al. (16) reported a trend towards significant changes in QS in their music exposure group when compared to controls (16). Premature infants are extremely sensitive to environmental stimulation precipitating state change and arousal from sleep (17,18), which can significantly interfere with the early processes of sensory development (19). In our study, music did not increase arousals or disrupt QS, demonstrated by no difference in the number, duration, ratio or bandwidth of the QS epochs and association with fewer interruptions.

Lullabies have been correlated with other beneficial effects for preterm infants, such as improved oxygen saturations, reduced initial weight loss, increased daily average weight, increased caloric intake, reduced length of stay and reduced stress behaviours (20–22).

Our study is limited by the small sample size and lack of control for other environmental auditory input in the NICU setting. However, the testing environment represented the real-world NICU setting. Clinical sleep/wake states (eyes closed or open) were not consistently correlated with aEEG

Table 2 The effect of music on parameters of quiet sleep

aEEG analysis (N = 30)	On music	Off music	Difference (95% CI)	p-Value
Number of QSC (N/hour)	0.7 (0.31)	0.65 (0.23)	0.05 (−0.09 to 0.19)	0.47
Median duration of QSC (minute)	21.07 (3.82)	21.13 (4)	−0.07 (−1.84 to −1.71)	0.94
QSC ratio (%)*	24 (10)	24 (10)	0.2 (4 to 5)	0.93
Any interrupted QSC (%)	20 (40)	53 (50)	−33 (−21 to −46)	<0.001
COMFORTneo scale total score (Mean ± SD)	12.7 ± 5.9	13.65 ± .7	−0.9 (−3.7 to 1.8)	0.47
COMFORTneo scale alertness score (Mean ± SD)	2.7 ± 0.3	2.6 ± 0.2	0.1 (−0.61 to 0.77)	0.81

Reported are means (SD); difference of means and 95% confidence intervals. p-values were generated by paired-samples *t*-test.
*Ratio of QSC (quiet sleep cycles) to total duration of observation. No significant differences were observed in number of QSC, median duration of QSC or QSC ratio. There were significantly lower number of interrupted QSC in the presence of music. Subjective findings of COMFORTneo scale are included and did not show any differences in total score or alertness component with or without exposure to music.

Table 3 Burdjalov scoring

	Agreement change with music exposure agreement	p-Value
Cycling score [means (SD)]	Decrease 0/30	0.002
	Unchanged 18/30	
	Increase 12/30	
Interrupted [Number (%)]	Decrease 0/30	0.002
	Unchanged 20/30	
	Increase 10/30	
Maturity score [means (SD)]	Decrease 0/30	<0.016
	Unchanged 16/30	
	Increase 14/30	

Reported are case matched agreements of Burdjalov score items based on if music exposure decreased, unchanged or increased the score item within same subject. p-values were generated by McNemar's exact symmetry test (#). Music is correlated with significant changes in cycling score, number interrupted and total Burdjalov Maturity Score.

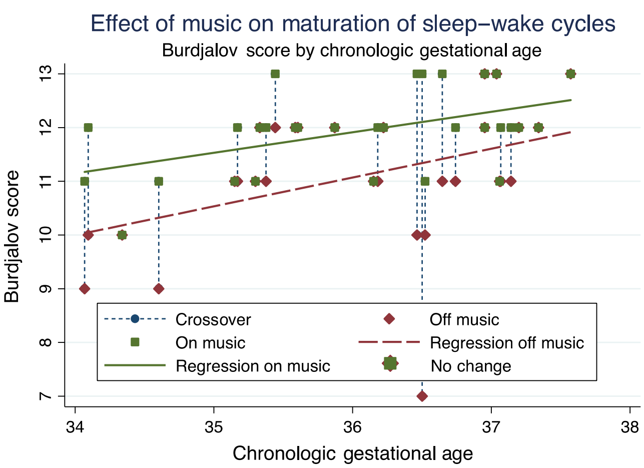

Figure 2 Linear regression of effect of music on Burdjalov Maturity scores. Actual chronologic gestational ages are plotted against Burdjalov Scores. Regression lines show an increase in scores with the intervention of music, which is equal to a mean of one-week gestational age. Each subject is plotted with and without exposure to music, allowing all subject with increases as well subjects with no change in score to be visualised. There were no score decreases with music.

data. As the music exposure was temporary, and duration of effects postexposure was not measured, the short- and long-term effects of either temporary or repeated music exposures are not known. It is noted that optimal music exposure would be catered to each infant-specific cultural background, ideally delivered in the maternal voice. Best administration of recorded music for optimal neonatal processing remains to be determined with additional studies; however, available evidence has demonstrated beneficial outcomes without detrimental side effects, and recorded music has remained a conventional therapy (20). For the purpose of this study, we were limited by the inability to record the maternal voice as an intervention for each infant but are able to demonstrate a feasible solution for similar NICUs where this is also not an option. The effect of maternal voice on SWC, as well as other sounds, compared to music will be of interest for further studies.

Recently, quantitative polysomnography analyses (23) and visual assessment of neonatal sleep EEG (24) have shown useful defining characterisation of sleep–wake states. PSG measures show association with neurologic examination scores (25). Future directions involve improving interrater agreement and validity confirming among all three modalities, creating a gold standard.

CONCLUSION

We demonstrated the utility of the aEEG to assess the effect of a NICU environment modification, specifically music, to facilitate sleep patterns in late preterm infants that correlated with advancing PCA using BS. Music did not increase arousals or disrupt sleep; it was associated with fewer interruptions in QS. Music may be a noninvasive, inexpensive modality to promote maturation of SWC in the NICU. Further studies are warranted to evaluate long-term effects of music on neurodevelopmental outcome.

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CONFLICT OF INTEREST

There is no conflict of interest to report.

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