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ORIGINAL ARTICLE

Effects of neurodevelopmental stimulation on premature infants in neonatal intensive care: Randomized controlled trial

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Abstract The purpose of the current study was to identify effects of neurodevelopmental stimulation as administered by board certified music therapists to premature infants admitted to the neonatal intensive care unit. Premature infants ($N = 108$) admitted and meeting inclusion criteria were included. Experimental subjects received the developmental multimodal stimulation protocol paired with live singing ($n = 25$) or live singing with guitar accompaniment ($n = 29$). The no contact control group received standard neonatal intensive care unit care ($n = 54$). An ANCOVA analyses with birth weight as a covariate resulted in significant main effects found for infant length of stay ($p < .05$). When comparing the means, differences were found between gender and types of music paired with the developmental multimodal stimulation. The results of this study suggest an increase in neurodevelopment for infants receiving developmental multimodal stimulation as hypothesized.

Abbreviations: NICU, neonatal intensive care unit; ANCOVA, analysis of covariance; LOS, length of stay; DMS, developmental multimodal stimulation; SD, standard deviation; rCBF, regional cerebral blood flow.

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Introduction

Many variables affect length of stay (LOS) in the NICU including but not limited to the gestational age at birth, birth weight, time on the ventilator, the provision of oxygen at 36 gestational weeks or later, and retinopathy of prematurity (Beeby, 2003). LOS research has shown that treatment is highly differentiated across NICUs and differences can be attributed primarily to problems with monitoring/treating apnea and poor feeding ability (Eichenwald et al., 2001). For infants born at 28 weeks gestation or earlier, higher numbers of painful procedures experienced and earlier gestational age resulted in decreased blood cortisol levels and behavioral stress response reactivity over time (Grunau et al., 2005). This points to possible changes in underlying stress response systems for premature infants during their time in the NICU. At eight months corrected chronological age, infants born at 28 weeks gestation or earlier had significantly higher levels of salivary cortisol when exposed to a positive novel stimulus than infants born between 29 and 32 weeks gestation and term infants. The cortisol response to novelty was predicted by neonatal pain and gestational age at birth, while higher basal cortical levels at 8 months old was associated with higher numbers of skin-breaking painful procedures (Grunau et al., 2004). One explanation is a possible "resetting" of the basal arousal systems for premature infants born extremely early. If infants are experiencing shifts in their set point for arousal, the arousal system could be influenced by the processing of environmental experiences. Infants who engage in an intervention that elicits pleasurable responses at the same stage of development that painful NICU treatment occurs may be able to alter their set point of arousal and, therefore, allow better self-regulation.

The abilities to self-soothe, modulate emotions, and tolerate changes in stimulations experienced within an environment are all related to the development of regulation (DeGangi, 2000; Kopp, 1982). The biological factors contributing to behavioral regulation abilities have been discussed not only in relation to gestational age at birth but also the disruption of brain maturation in regionally specific areas. Neuroanatomical studies using magnetic resonance imaging have identified neurological abnormalities seen in early cerebral white matter volume loss, cystic abnormalities, and immature patterns of myelination (Clark et al., 2008; Nadeau et al., 2003; Peterson et al., 2000; Stewart et al., 1999; Taylor et al., 2004; Woodward et al., 2006). The region of the brain primarily affected for premature infants is the periventricular zone which affects neuronal integration and cortical projection. Disorganization of fiber tracts connecting subcortical and cortical regions as well as disruption of myelination formation is attributed to damage in this region (Clark et al., 2008; Counsell et al., 2003; Huppi et al., 2001). This type of white matter damage may inhibit infants' abilities to learn how to regulate emotional responses and respond appropriately to stimulation as the brain is forming the intricate coordination of neural processes.

The existing literature addressing the effects of developmental music protocols for premature infants provides support for the acquisition of coordinating advanced behavioral regulation skills (Standley, 1998, 2002; Standley and Swedberg, 2008; Whipple, 2000, 2008). To date, the studies utilizing behavioral measures indicate that premature infants improve oxygen saturation rates, are discharged home sooner, return to homeostasis sooner after painful procedures, and show trends of consistent patterns of increases in weight gain in response to developmental music interventions.

Many nurses and neonatologists are reluctant to add another type of stimulation to the NICU environment. Some researchers have suggested there is not enough conclusive evidence supporting the use of music with premature infants since most studies have small sample sizes (Hartling et al., 2009). However, a review of twenty years of music therapy in the NICU discovered significant effects across multiple measures including behavioral, length of stay, and physiological measures (Standley, 2011). There are multiple NICUs incorporating developmental multimodal interventions across the nation provided by trained NICU Board Certified music therapists. This controlled study was designed to investigate how a specific music therapy protocol impacts premature infant development.

Patients and methods

Participants

Infants admitted to four different NICUs in Florida and Texas were invited to participate in this study from October, 2008, to March, 2010. Infants were referred by NICU physicians or nurses for music therapy intervention and then randomly assigned to experimental or control condition groups with

randomization order generated by a computerized random number generator. Parents were informed of the study by the staff music therapists working at each participating hospital and written informed consent was obtained from parents. Inclusion criteria stated that infants must be born between 32 and 36 weeks gestation as determined by early ultrasound date or Dubowitz score, weigh $<$2500 g at birth, and be at least 32 weeks gestation and ten days old at the time intervention began. Exclusion criteria consisted of infants born after 32 weeks gestation, infants transferred to a different hospital, infants who died before discharge, or infants who did not pass a hearing screening. The study was approved by the participating institutional review boards and human subject committees.

Study design and procedures

This study utilized a control condition and two types of experimental conditions. NICU medical staff members were blind to infant condition groups. Infants in the control group received standard NICU care and were not exposed to music therapy. All four sites collected data on control infants.

Each participating site was assigned an experimental music protocol for experimental infants. Two sites administered developmental multimodal stimulation (DMS) with unaccompanied live lullaby singing and two sites added chordal guitar accompaniment to the lullaby singing during the DMS. Daily approval of the nurse providing care for each infant was obtained before the DMS was administered. Infants in the experimental group received DMS sessions lasting 20 min in length at least once per week for the duration of their stay. The DMS protocol progressively layers multiple modes of stimulation per infant tolerance in the following order: auditory, tactile, vestibular, and visual stimulation. The music stimuli volume, both singing and guitar playing, was monitored to remain in the low 70's dB (scale C) range which corresponds to approximately 60 dB (scale A) as per pediatric guidelines. The guitar accompaniment and singing used minimal rhythmic emphasis, a constant rhythm, and slow tempo. The tactile stimulation consisted of massaging or stroking the infant body parts according to cephalocaudal development in the following order: head, back, neck, arms, chest, abdomen, legs, cheeks, forehead, ending with nose to ear strokes. Infants were observed for signs of overstimulation and all stimuli ceased with any sign exhibited by the infant. The stimulation was then re-introduced to the infant one stimulus at a time, beginning with auditory, followed by tactile, and ending with vestibular stimulation as per tolerance of each preceding level of stimulation.

Measures

All information was gathered from infant charts. Length of stay was calculated as the number of days between admission and discharge. Average daily weight gain was calculated by dividing the difference between birth and discharge weight by infant length of stay. Gestational age at discharge was reported in days and was calculated by adding the length of stay to the infant gestational age at birth. Number of days to full feeds was calculated by counting the days from birth to PO feeding. Number of days receiving IV nutrition was counted for any day receiving IV nutrition.

Power calculations

The study size was calculated originally to detect a difference in length of stay and weight gain variables ($\alpha = .05$; $\beta = .80$). This analysis indicated that 52 infants were needed for each preterm group. To allow for withdrawals and establishing of equality between groups for birth weight and gender, the target size was set at 85 infants each in experimental and control groups ($N = 170$).

Statistical analysis

The primary outcomes measure for this study was length of hospital stay. Secondary outcome measurements were average daily weight gain and gestational age at discharge. Means, SDs, and checks for normality were calculated for all variables. A *t*-test was used for gestational age at birth data to determine if differences between groups existed before intervention was administered. Comparisons of overall differences in the length of stay, average daily weight gain, and gestational age at discharge measurements between groups was performed using separate analyses of covariance with birth weight as the covariate for each analysis. Assumption of homogeneity of error variance was met for each ANCOVA analysis. All analyses were performed by using PASW Statistics 18 (IBM Corp, Somers, NY) and p values $< .05$ were considered significant.

Results

A total of 168 infants born prior to 37 weeks gestation and meeting all enrollment criteria were

enrolled in the current study. One parent chose to remove their infant from study participation after providing parental signed consent. This parent stated she did not want to take the chance that her infant would not receive music therapy intervention if he/she was assigned to the control group. No infants admitted in the study died nor were any transferred to another hospital. Prior research has shown gender differences in premature infant responses to music and differentiated responses to more complex music stimuli (Standley, 1998, 2002; Standley and Swedberg, 2008). Therefore, this study controlled for those variables. Since LOS is affected by birth weight, after random assignment to condition groups infants were removed from analysis who did not meet criteria to equalize participant demographics. Criterion for removal was met if an infant was not found in the opposite condition group with the same gender and birth weight $+/-$ 2 ounces. A total of 59 infants met criterion for removal. For the remaining 108 infants ($n = 54$ control, $n = 54$ experimental), demographic and infant characteristics are listed in Table 1.

When comparing groups by condition a significant main effect was found for length of stay, $F(1,103) = 4.67$, $p < .05$, partial $\eta^2 = .04$. No significant interactions were found for length of stay by gender or gestational age at discharge by gender. Means for days of length of stay by gender showed differences by the type of music paired with the developmental multimodal stimulation (Table 2). Experimental babies went home an average of 12.9 days sooner than control babies. Differences were found by gender (Fig. 1) with experimental males going home 8.2 days sooner and experimental females discharged 15.7 days sooner. Experimental males who were only sung to went home 15.7 days sooner than experimental males who received guitar in addition to singing. On the other hand, experimental females had an opposite response to the type of music paired with the developmental multimodal stimulation. Experimental females who received guitar in addition to singing went home 12 days sooner than females who were only sung to.

No significant differences were found between groups for gestational age at birth $t\ (106) = -1.01$, $p > .05$ confirming that infants in both groups were born at similar gestational ages. No significant main effects were found for gestational age at discharge $F(1,103) = 2.25$, $p > .05$ or average daily weight gain between groups $F(1,103) < 1$, $p > .05$ (Table 3) indicating no group differences for how old infants were when discharged home or how much weight was gained over the course of their hospitalization. A positive trend was discovered for number of days to full feeds and number of days receiving IV nutrition, with infants receiving DMS taking less time to integrate feeding behaviors than control infants (Table 1).

Table 1 Infant Characteristics and Demographics.

Characteristic	Experimental infants	Control infants
Gender, %		
Male	54	54
Female	46	46
Race, %		
Black	35	31
Non-Hispanic White	48	41
Hispanic	15	22
Asian	0	4
Other	2	2
Birthweight, %		
Under 1000 g	20	20
1000–1499 g	43	43
>1500 g	37	37
RDS %	70	70
IVH Grade 3 or 4%	9	11
ROP %	31	24
Average number of days to full feeds	23.5	31.7
Average number of days on IV nutrition	9.9	15.7

Discussion

This study demonstrates that premature infants who received Developmental Multimodal Stimulation with music had positive neurodevelopmental gains as measured by significantly shortened LOS. There were differences by gender in type of music

Table 2 Means and standard deviations for length of hospital stay.

	Length of Stay (days)	
	Mean	SD
Overall Experimental Infants	52.9[a]	33.0
Experimental Singing Males	51.4	31.5
Experimental Guitar Males	67.1	39.0
Experimental Singing Females	52.1	29.2
Experimental Guitar Females	40.2	26.5
Overall Control Infants	65.8[a]	48.8
Control Males	68.2	39.9
Control Females	61.5	58.8

[a] Adjusted mean values reported for overall mean scores by group.

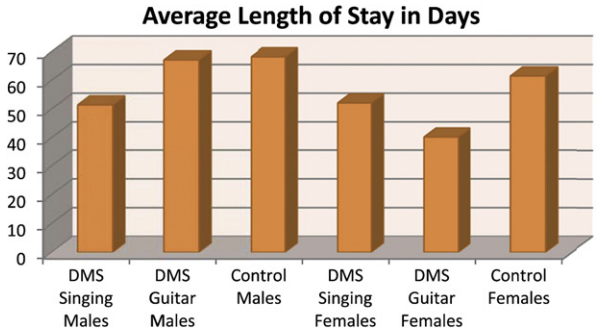

Fig. 1 Average length of stay by type of music intervention and gender.

stimulation received. These findings are similar to the smaller study previously conducted (Standley, 1998) finding gender differences in length of stay for DMS using only singing. The differences found by gender and types of music stimulation are interesting and warrant further analysis. Males showed the greatest benefit when exposed to singing only as opposed to singing paired with guitar stimuli, with an average discharge of 15.7 days sooner. However, premature females had the opposite response and went home 12 days sooner with guitar and singing paired together than with singing only. Prior research has shown that premature males have demonstrated lower sensitivity to high frequencies in hearing screenings than premature females (Cassidy and Ditty, 2001). The current findings provide more evidence that the differences in hearing sensitivities are causing premature infants to integrate the music stimuli with very different neurologic and developmental responses. These differences support the adherence to separate intervention protocols for male and female infants receiving DMS.

It is theorized that the improved outcomes observed among infants receiving DMS is attributed to the brain integrating new information while maintaining homeostasis via music listening. The theoretical concept supporting the use of developmental multimodal stimulation postulates that as the infant interprets and responds appropriately to the music and other layered stimuli, positive emotion activation and decreases in negative emotion activation occur in the brain allowing greater integration of stimuli to advance self-regulation skills. Stimulating activities such as transferring out of the isolette, being held, being touched, moving through space, and eye contact are tolerated by the infant with increasing frequency as DMS interventions progress. We theorize that this systematic progression fosters neural activation, maturation of the regulation system, and integration of multiple sensory inputs. When infants spend more time in homeostasis and respond positively to stimulation, their development occurs at a faster rate than infants still reacting negatively to stimulating procedures.

Music is a unique auditory stimulus with unique neurologic processing. Music listening activates several areas of the brain including the prefrontal cortex, paralimbic, and neocortical regions (Blood et al., 1999; Blood and Zatorre, 2001). Music listening has also been effective in structuring causal learning for pacing of non-nutritive sucking for premature infants ages 30—36 weeks gestation (Standley, 2000, 2003; Standley et al., 2010). These results suggest that music is a pleasurable stimulus for premature infants, and one that is rewarding enough to structure causal learning very early in development.

Paralimbic and neocortical regions of the brain are activated when listening to consonant and dissonant unfamiliar music, areas associated with certain emotional processes (Blood et al., 1999). Decreases of regional cerebral blood flow (rCBF) in the amygdala are accompanied by rCBF increases in the ventral striatum when responding to intensely pleasurable music stimuli. This finding supports the idea that when processing music, the reward system activation which maximizes pleasure does so by simultaneously decreasing activity in brain structures that elicit negative emotions (Blood and Zatorre, 2001).

Current models of care for the premature infant focus on reducing stimulation through decreasing environmental sound levels, clustering care to maximize the amount of time available for sleep, and minimizing movement of the infant out of the isolette or crib (Als and Gilkerson, 1997). Conclusive

Table 3 Means and standard deviations for gestational age at discharge and average daily weight gain.

	Gestational age at discharge (days)		Average daily weight gain (grams)	
	Adjusted mean	SD	Adjusted mean	SD
Experimental Males	267.2	24.9	20.1	6.2
Experimental Females	263.9	15.1	19.1	8.4
Control Males	271.1	28.6	19.4	7.2
Control Females	276.4	46.7	19.9	13.1

evidence is necessary for the inclusion of an augmentative treatment such as developmental multimodal stimulation (Jacobs et al., 2002; Philbin et al., 1999; Symington and Pinelli, 2003). We feel this study provides evidence for integration with NICU developmental care. Current data consistently support the use of music stimulation for premature infants to minimize the effects of being born prematurely (Standley, 1998, 2002; Standley and Swedberg, 2008; Whipple, 2000, 2008).

A critical barrier to progress in this line of research is music use by individuals without specialized training for the NICU environment. Board certified therapists trained in NICU specializations are able to behaviorally assess each infant's responses to music stimulation and adapt the intervention immediately. The change in NICU developmental care models suggested by this application is to include an additional intervention for premature infants that is stimulating in theory but which is designed to increase tolerance for stimulation over time.

There were some limitations in this study. First, not all study sites investigated both types of music stimuli. Each participating site utilized one type of music stimuli, either singing or singing accompanied by guitar. This presents a possible site bias in the implementation of the treatment variable. Additionally, differences could have been present in the timbre and resonance produced by guitars and voices used in this study.

Conclusions

This study is the largest examination of the neurodevelopmental effects of developmental multimodal stimulation for premature infants to date. Adding DMS to standard patient care in the NICU is a safe and low cost intervention to improve neurodevelopmental outcomes of premature infants. Future research recommendations include investigating gender differences by birth weight and type of music stimuli to refine clinical protocol recommendations. Longitudinal analysis investigating effects of developmental music stimulation across the first years of life may also reveal unknown developmental benefits for children born prematurely.

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Conflict of interest

No authors have any conflict of interest with the completion of this study.

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References

Als, H., Gilkerson, L., 1997. The role of relationship-based developmentally supportive newborn intensive care in strengthening outcome of premature infants. Semin. Perinatol. 21, 178—189.

Beeby, P., 2003. How well do diagnosis-related groups perform in the case of extremely low birthweight neonates? J. Paediatr. Child. Health 39, 602—605.

Blood, A.J., Zatorre, R.J., 2001. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc. Natl. Acad. Sci. 98, 11818—11823.

Blood, A.J., Zatorre, R.J., Bermudez, P., Evans, A.C., 1999. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat. Neurosci., 382—387.

Cassidy, J.W., Ditty, K.M., 2001. Gender differences among newborns on a transient otoacoustic emissions test for hearing. J. Music Ther. 38 (1), 28—35.

Clark, C.A.C., Woodward, L.J., Horwood, L.J., Moor, S., 2008. Development of emotional and behavioral regulation in children born extremely preterm and very preterm: biological and social influences. Child. Dev. 79, 1444—1462.

Counsell, S.J., Allsop, J.M., Harrison, M.C., Larkman, D.J., Kennea, N.L., Kapellou, O., et al., 2003. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. Pediatrics 112, 1—6.

DeGangi, G., 2000. Pediatric Disorders of Regulation in Affect and Behavior. Academic Press, San Diego, CA.

Eichenwald, E., Blackwell, M., Lloyd, J., Tran, T., Wilker, R., Richardson, D., 2001. Inter-neonatal intensive care unit variation in discharge timing: influence of apnea and feeding management. Pediatrics 108, 928—933.

Grunau, R.E., Weinberg, J., Whitfield, M.F., 2004. Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. Pediatrics 114, e77—e84.

Grunau, R.E., Holsti, L., Haley, D.W., Oberlander, T., Weinberg, J., Solimano, A., Whitfield, M.F., Fitzgerald, C., Yu, W., 2005. Neonatal procedural pain exposure predicts lower cortisol and behavioral reactivity in preterm infants in the NICU. Pain 113, 293—300.

Hartling, L., Shaik, M.S., Tjosvold, L., et al., 2009. Music for medical indications in the neonatal period: a systematic review of randomized controlled trials. Arch. Dis. Child. Fetal Neonatal. Ed. 94, F349—F354.

Huppi, P.S., Murphy, B., Maier, S.E., Zientara, G.P., Inder, T.E., Barnes, P.D., et al., 2001. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. Pediatrics 107, 455—460.

Jacobs, S., Sokol, J., Ohlsson, A., 2002. The newborn individualized care and assessment program is not supported by meta-analysis of the data. Pediatrics 140, 699—706.

Kopp, C.B., 1982. Antecedents of self-regulation- A developmental perspective. Dev. Psychol. 18, 199—214.

Nadeau, L., Tessier, R., Boivin, M., Lefebvre, F., Robaey, P., 2003. Extremely premature and very low birthweight infants: a double hazard population? Soc. Dev. 12, 235—248.

Peterson, B.S., Vohr, B., Staib, L.H., Cannistraci, C.J., Dolberg, A., Schneider, K.C., Ment, L.R., 2000. Regional brain volume abnormalities and long-term cognitive outcomes in preterm infants. J. Am. Med. Assoc. 284, 1939—1947.

Philbin, M.K., Robertson, A., Hall, J.W., 1999. Recommended permissible noise criteria for occupied, newly constructed or renovated hospital nurseries. J. Perinatol. 19 (8), 559—563.

Standley, J.M., Swedberg, O., Nov. 2008. NICU Music Therapy: A 1-year Post Hoc Clinical Analysis of Premature Infant Characteristics and MT Intervention. American Music Therapy Association Annual Conference Research Poster Session, St. Louis.

Standley, J.M., Cassidy, J., Grant, R., Cevasco, A., Szuch, C., Nguyen, J., Walworth, D., Procelli, D., Jarred, J., Adams, K., 2010. The effect of music reinforcement for non-nutritive sucking on nipple feeding of premature infants. Pediatr. Nurs., 36.

Standley, J.M., 1998. The effect of music and multimodal stimulation on responses of premature infants in neonatal intensive care. Pediatr. Nurs. 24, 532—538.

Standley, J.M., 2000. The effect of contingent music to increase nonnutritive sucking of premature infants. Pediatr. Nurs. 26, 493—499.

Standley, J.M., 2002. A meta-analysis of the efficacy of music therapy for premature infants. J. Pediatr. Nurs. 17, 107—113.

Standley, J.M., 2003. The effect of music-reinforced nonnutritive sucking on feeding rate of premature infants. J. Pediatr. Nurs. 18, 169—173.

Standley, J.M., 2011. 20 years Of Music Therapy Research in the NICU: An Updated Meta-analysis. Proceeding from 19th Annual International Symposium for Research in Music Behavior Barcelona, Spain.

Stewart, A.L., Rifkin, L., Amess, P.N., Kirkbride, V., Townsend, J.P., Miller, D.H., et al., 1999. Brain structure and neurocognitive and behavioral function in adolescents who were born very preterm. Lancet 353, 1653—1657.

Symington, A.J., Pinelli, J., 2003. Developmental Care for promoting development and preventing morbidity in preterm infants (Review). Cochrane Database Syst. Rev. 4, 1—72.

Taylor, H.G., Minich, N., Bangert, B., Filipeck, P.A., Hack, M., 2004. Long-term neuropsychological outcomes of very low birth-weight: associations with early risks for periventricular brain insults. J. Int. Neuropsychol. Soc. 10, 987—1004.

Whipple, J., 2000. The effect of parent training in music and multimodal stimulation on parent-neonate interactions in the neonatal intensive care unit. J. Music Ther. 37, 250—268.

Whipple, J., 2008. The effect of music-reinforced nonnutritive sucking on state of preterm, low birthweight infants experiencing heelstick. J. Music Ther. 45, 227—272.

Woodward, L.J., Anderson, P.J., Austin, N.C., Howard, K., Inder, T.E., 2006. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N. Engl. J. Med. 355, 685—694.