



REVIEW ARTICLE

Early vocal contact and music in the NICU: new insights into preventive interventions

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It is now clearly established that the environment and the sensory stimuli, particularly during the perinatal period, have an impact on infant's development. During the last trimester of gestation, activity-dependent plasticity shapes the fetal brain, and prematurity has been shown to alter the typical developmental trajectories. In this delicate period, preventive interventions aiming at modulating these developmental trajectories through activity-inducing interventions are currently underway to be tested. The purpose of this review paper is to describe the potentialities of early vocal contact and music on the preterm infant's brain development, and their potential beneficial effect on early development. Scientific evidence supports a behavioral orientation of the newborn to organized sounds, such as those of voice and music, and recent neuroimaging studies further confirm full cerebral processing of music as multisensory stimuli. However, the impact of long-term effects of music exposure and early vocal contact on preterm infants' long-term neurodevelopment needs to be further investigated. To conclude, it is necessary to establish the neuroscientific bases of the early perception and the long-term effects of music and early vocal contact on the premature newborns' development. Scientific projects are currently on the way to fill this gap in knowledge.

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PREMATURITY AS A WINDOW OF OPPORTUNITIES:

MECHANISMS OF ACTIVITY-DEPENDENT NEURAL PLASTICITY

Premature birth exposes the developing brain to a dramatically different environment with diverse noxious stimuli in the neonatal intensive care unit (NICU) and deprives it from daily-rhythm mothers-linked sensory inputs, relevant for activity-dependent plasticity¹ during a critical period of brain development.

The third trimester of pregnancy is a period of striking sequential brain developmental changes and, consequently, a period of important vulnerability. Numerous neurodevelopmental events take place across the developing brain and continue during the third trimester, including growth of white matter tracts (outgrowth of axons, pathway finding, axonal guidance, target selection, and in growth in the cortical plate),² dendritic proliferation, migration, molecular specification, and differentiation, as well as synaptogenesis, gliogenesis, myelination, and physiological cell death.³

The activity-dependent dendritic and axonal growth is mainly regulated by the early cortical synaptic activity. It starts between 17 and 25 weeks of gestation and it rapidly increases in complexity (branching) and growth between 27 and 32 weeks of post conceptual age.¹

The penetration of thalamocortical and basal forebrain fibers into the cortical plate is a major event in the axonal pathway development taking place after 24 weeks of gestational age (GA),

coinciding with the establishment of the first synapses in the human telencephalon and making possible functional interactions between the thalamic afferents and cortical plate cells.^{2,3} Indeed, the most significant event related to the establishment of thalamocortical connectivity is the appearance of somatosensory-evoked potentials. In the human fetal cerebral cortex, the existence of an early functional cortical connectivity offers new insights on early activity-dependent processes. In perspective, it shows an original outlook on sensory expectant brain organization and on the potentialities of environmental-protective modifications.⁴

Additionally, myelination and apoptosis phenomena are presumably particularly more intense in this period than at any other time of an individual's life.⁵ Myelination is a process that, although genetically controlled, is markedly influenced by neuronal activity.⁶ Synaptogenesis and synapse elimination hold a major role in the plasticity of the developing nervous system and environmental experiences might have important effects on the development of neural function during this organizational period.⁷ In fact, enrichment and deprivation studies have evidenced the powerful role of experience on brain development.^{8–10} More specifically, deprivation of sounds or specific auditory stimuli in the NICU have been shown to impact on the auditory cortex maturation.¹¹ Thus, the integrity of the brain developmental process depends absolutely upon the presence of the right neural

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elements appearing at the appropriate developmental moment,¹² based on an optimal interaction with environmental stimulations and endogenous activity. Because of the extreme complexity inherent to brain development across different GAs, the nervous system displays individual and specific responses to early life events. Literature has evidenced early developmental brain abnormalities in preterm infants that can hold a negative impact on development, correlating with later specific neuropsychological deficits, comprising regional cortical and subcortical volumes loss,^{13–19} as well as alteration of connectivity patterning of brain networks and their microstructural characteristics.^{20,21}

Sound environment in the NICU is an example of a drastic change in environment that preterm infants have to face, exposing them to a direct, erratic, unpredictable, and noisy auditory environment, different from the rhythmical, coherent, familiar, and indirect auditory environment of the mother's womb. Indeed, the advanced equipment present in the NICU implicates frequent high sound pressure levels and high-pitched sounds,²² often exceeding the general recommendations.²³ This loud, unorganized, and unpredictable noise might contribute to the neurocognitive burden observed in preterm birth, comprising behavior and socio-emotional deficits, such as attention deficit disorders²⁴ and/or alterations in early communicative skills.^{25,26}

On the other hand, some networks might develop early in response to events such as prematurity, which occurs in a period when the brain has the capacity to re-organize its networks. It has been shown that, in comparison to full-term infants, preterm infants at term-equivalent age evidence a decreased connectivity between thalamus and prefrontal, insular, and anterior cingulate cortex, but an increased functional connectivity between thalamus and lateral primary sensory cortex, suggesting the role of early experiences of premature extra-uterine life in network modulation and development.²⁷ Moreover, in a clinical study, premature babies with higher neuronal activity measured by electroencephalography (EEG) during the first 72 h of life subsequently showed better growth and myelination of the brain.²⁸

Environment has definitely been shown to play a major role in child development,²⁹ and the preterm infant is an active participant in its world and actively selects specific elements of his or her environment.³⁰ Additionally, parents do not simply mediate environmental stimuli, but are part of the environment itself, changing their interaction according to the infant's needs, reactions, and requests and impacting on his socio-emotional development.

A number of protective actions are nowadays at the core of early intervention programs in the NICU, and their aim is to sustain preterm infants' development by empowering their potentialities.

Early interventions in the NICU, well known as "developmental care" or "brain care" interventions, aim to protect the preterm infant from the noxious environmental sources of stress, such as pain or exceeding levels of sound or light, using specific behavioral techniques and the parental early involvement in infant's care.³¹

Early interventions in preterm infants have been shown to hold a significant impact on cognitive, behavior, and motor outcome at preschool age, although it is still not known what specific environmental factors ultimately contribute to enhance brain development.^{32–36} In sum, one of the key points in preventive perinatal medicine is the timing of the intervention (i.e., the level of maturation of the brain at the moment of the intervention) and, thus, the degree of activity-dependent plasticity of the developing brain. The intensity of neuronal plasticity mechanisms during the third trimester of life, whether in or ex utero, could imply that early interventions in this specific period are more effective than later in life.

Neonatal care is evolving towards integrating the approach of precision medicine, which aims at identifying early precursors of developmental problems as well as early windows of

opportunities for prematurely born newborns. The main atypical neurodevelopmental trajectories of prematurity, such as cognitive and socio-emotional difficulties, are in the center of the efforts for a precision medicine approach in newborn care. Biomarkers have been developed to identify early precursors of such atypical trajectories in the first weeks of life in the NICU, and neuroimaging tools including magnetic resonance imaging (MRI) and EEG, have proven valuable in assessing sensitive or critical periods of brain plasticity and resilience. Masten and Obradovic³⁷ define resilience as the ability to cope with biological or environmental stressors normally linked to adverse outcomes. Genes and their expressions are considered to play a crucial role in the individual infant's resilience and his ability to positively respond to environmental stressors,³⁸ but individual variations regarding the quality of early socio-emotional experience can impact the infants' regulatory capacities and, thus, his or her resilience. Each infant shows different abilities to re-organize his or her development in co-regulation with the caregivers and the general social context.³⁹ These abilities to re-organize the brain and behavioral functions encounter variations in parental care and might modulate the degree of severity of the disabilities.

Future research challenges comprise the link of specific early interventions with neurobehavioral development through dedicated assessments, brain development owing to neuroimaging techniques, and genetic and epigenetic factors through devoted specific analysis techniques allowing researchers to understand further how epigenetic factors modulate gene expressions in interaction with environmental contexts.

In this paper, we introduce early vocal contact (EVC) and music as two resilience-inducing actions, which share the important auditory sensory medium as a basis and that the trained medical staff and nurses can implement in their daily routine.

In the first part, we briefly outline the main aspects of voice and music perception in newborns. In the second part, we describe the potential protective and preventive actions of EVC and music in the NICU.

NEWBORNS ORIENT TO THE HUMAN VOICE

In adults, vocal sounds elicit significantly greater activation than non-vocal sounds in several regions of non-primary auditory cortex and there are no regions of human brain showing greater activation for non-vocal than for vocal stimuli.⁴⁰ The voice-selective regions are mainly located along the bilateral superior temporal gyrus (STG) and sulcus (STS).⁴⁰ In adults, several findings have demonstrated the implication of the anterior part of the STS in voice recognition and speaker identity processing.^{41–45} Familiar voices, when contrasted with unfamiliar voices, activate predominantly the right anterior STS and other brain regions, such as the right amygdala, the parietal lobe (e.g., precuneus), and the fusiform gyrus.⁴³

Already few hours or days after birth, neonates are orienting to human voices and they possess a strong endowment to process speech:⁴⁶ they can process phonetic differences between syllables,^{47,48} they can discriminate between different speakers,⁴⁷ and they are sensitive to small changes in prosody.^{49,50} Even if neural substrates underlying spoken language were found in both hemispheres, comprising the left and right temporal cortices and the left inferior frontal cortex,⁵¹ human infants seem to show a left-hemisphere predominance to process specific properties of speech,⁴⁹ but the emotional characteristics of the speech⁴⁶ and the novelty-related responses^{52,53} are mainly processed in the right hemisphere. Interestingly, newborns can also discriminate between singing and speech, sharing the same linguistic content, and are more activated by rich prosodies.⁵⁰

Furthermore, full-term newborns have a clear preference to familiar voices and languages. They can recognize familiar components of the language,⁵⁴ which suggests the development

of a sophisticated cortical organization towards voices well before birth.

The ability to recognize their mothers' voice develops in utero, already between 33 and 34 weeks of GA.⁵⁵ A number of studies have demonstrated the abilities of the newborn to respond differently to the maternal voice compared to an unknown female voice.^{52,56,57} Further neuroimaging studies have revealed that the mother's voice elicits a left-dominant brain activation pattern in the temporal lobe, whereas the stranger's voice elicits more voice-specific responses in right temporal lobe, which was also evidenced in 2-month-old infants.⁵⁸

In contrast, the processing of maternal voice by premature infants develops in an atypical acoustic and human environment. As a result, unlike full-term newborns, premature newborns at term-equivalent age showed altered recognition capabilities when compared to full-term newborns.⁵⁹ However, also preterm infants show specific abilities and orientations to voices. Their ability to perceive their own mother's voice is evidenced around 34 weeks of corrected age, based on studies using the mother's voice or sounds as an early intervention.^{60–62} Moreover, the repeated exposure to maternal sounds during the first month of life of preterm infants may enhance the anatomical development of their primary auditory cortex, suggesting an adaptive and experience-dependent brain plasticity specific to maternal sounds.⁶³

Preterm infants, before term corrected age, react differently to vocal and non-vocal sounds, significantly decreasing their heart rate in response to human voices whereas their heart rate was increased following artificial sound peaks of similar intensities.⁶⁴ They can discriminate a change of syllable (/ba/ vs. /ga/), as showed by functional optical imaging (functional near-infrared spectroscopy (NIRS)) through an activation of a network of temporal and frontal areas, but limited responses were found to a novel voice (male vs. female voice).⁶⁵ Additionally, 10 weeks before term they show discriminative responses for subtle phonetic contrasts based on a fine-grained temporal coding.⁶⁶ Preterm infants at around 30 weeks GA also seem to discriminate their mothers' voices from the voices of other women, as suggested by differences in cortical activation in the left and right frontal areas to the voices of their mothers and female nurses.⁶⁷ Their response to linguistic stimuli seems to be related to the GA at birth, with an increase in GA associated with greater ERP differences in response to various speech sounds (Table 1).^{68,69}

MUSIC PERCEPTION IN NEWBORNS

Music listening implies a complex process in the brain that involves multisensory responses,⁷² triggering both cognitive and emotional components with distinct neural substrates.^{73,74} In fact, human neural processing of music involves a widespread bilateral network of cortical and subcortical areas, extending well beyond the auditory cortex and including temporal, frontal, and parietal subcortical areas and, in particular, limbic and paralimbic regions, integrating several auditory, cognitive, sensory-motor, and emotional functions.^{74–76} Functional neuroimaging studies on music-evoked emotions show changes in activity in various regions, comprising amygdala, hippocampal formation, ventral striatum (including nucleus accumbens), ventral pallidum, pre-supplementary motor area (SMA), cingulate cortex, insula, and the orbitofrontal cortex, which constitute brain core regions involved in emotion processing⁷⁷ and are also key areas of deficits in preterm infants.^{20,75,78,79}

In a recent review, the existing studies on neural processing have been summarized and provide evidence for early existence of music processing capacities.⁸⁰ Indeed, distinct event-related potential response has been observed in full-term newborns in response to variation of relative pitch,^{81–83} timber,⁵⁸ resonance

scale,⁸⁴ and minor/major chords.⁸⁵ Full-term newborns have also been shown to detect beat alteration⁸⁶ and variation in tones presentation rate.⁸⁷ Also, full-term newborns seem to be able to extract pitch trends from a sound sequence and a discriminative mismatch response to deviation from the pitch trends has been observed using EEG.⁸⁸ Using fMRI, Perani et al.⁸⁹ observed differences in brain activations in full-term infants, of 1 to 3 days old, when listening to either consonant music or altered versions (dissonant or with sudden key shifts). Consonant music led to activation of the right auditory cortex as well as of the amygdalo-hippocampal complex, whereas altered music led to an increased activation of the left inferior frontal gyrus and the left amygdalo-hippocampal complex. In contrast to the aforementioned results, a study using NIRS⁹⁰ showed no lateralization during music processing in full-term newborns.

The ability of learning music seems to be present already in the fetus, with behavioral and electrophysiological studies evidencing in full-term newborns a preferred response for melodies heard during fetal life.⁹¹ In full-term newborns exposed to music during the last weeks of pregnancy, a decreased heart rate was demonstrated while listening to the same music.⁹² When listening to an altered melody (12.5% of notes changed within the extract), EEG at birth and at 4 months resulted in a different electrical brain response than when listening to the original melody heard during fetal life. In addition, the magnitude of this difference was correlated with the number of antenatal exposure to the melody.⁹³ These cardiac and brain electrical responses have been linked by these authors to memory for the melody heard during the fetal life.

The ability of newborns to process music could have its origins in exposure to sounds present during the last trimester of pregnancy, in the mother's womb, where the fetus can acquire the basics for the treatment of the fundamentals of the music and language, such as rhythm, metrics (sounds from the heart and the mother's breathing), pitch, and melody referring to prosodic aspects (mother's voice), and so on (Table 2).⁹⁴

THE EARLY VOCAL CONTACT IN THE NICU

The EVC is a special form of early intervention that actively involves parents in emotional and meaningful vocal contact with their infants.⁹⁵ It sustains preterm infant's physiological stability,⁶¹ it increases the amount of time that parents spend in face-to-face interactions with their infants in the NICU, extending the occurrences of early co-regulations within the dyad, by means of voice.⁹⁶ Finally, it enhances emotional contact between parents and preterm infants in the NICU,³⁷ with potential long-term impacts on parent-infant synchrony. However, no studies until now evaluated the effect of EVC on preterm infant's brain development through neuroimaging techniques.

The rational basis of EVC has been conceived and presented in its multiple perspectives.⁹⁵ In particular, three arguments on which the EVC is based have been identified and are following described.

EVC supports synchrony and facilitates intuitive parenting skills. In the past decades, there has been an exponential increase in studies evaluating the effects of the maternal and other voices, either direct or recorded, on the preterm hospitalized infant.^{98,99}

The majority of studies evaluate the effects of maternal voice, direct or recorded, on short-term indicators of a mainly physiological nature. The most evident result is that maternal vocal intervention promotes the stabilization of physiological and behavioral parameters of the premature infant, with a decrease in critical events, regulation of the heart rate and stabilization of the respiratory rate. It is therefore assumed that this intervention may have effects on the regulation of the autonomic nervous system both directly and indirectly through, for example, the hormonal system.

Table. 1. Neural evidences for voice processing at birth

Author, ref.	Population (N; age)	Stimuli		Type of intervention	Stimulus details (duration; intensity; repetitions)	Neuroimaging technique	Results
		Type of stimulus					
1 deRegnier et al. ⁶⁹	32 full-term newborns and 25 control with diabetic mothers (DM); age at test: 10.7 ± 2.0 days and 12.8 ± 1.9 days, respectively	Maternal voice vs. stranger's voice. Speech sound (the sound "ba" in a female voice) and a non-speech sound (a computer chime)		No	400 ms; 80-dB SPL, 100 repetitions	EEG	Both groups demonstrated increased amplitude and latency for the "P2" peak elicited by the maternal voice compared with the stranger's voice. In the control group the stranger's voice also elicited a negative slow wave, which was attenuated in the IDMs
2 Dehaene-Lambertz and Pena ⁴⁷	16 full-term newborns; age at test: 2–6 days, mean 3.5 days	Two syllables /pa/ and /ta/ produced by four female speakers were used		No	Syllable duration varied across speakers; 78-dB SPL	EEG	Difference between standard and deviant trials in the "different speaker" trials
3 Cheour et al. ⁷⁰	45 full-term newborns: experimental group, n = 15, age at test: 1–7 days; two control groups, n = 15 in both, age at test: 2–7 days	Vowel sounds /y/ ("standard"), /i/, and /y/i/ ("deviants")		2.5–5.0 h during sleep	Vowels duration: 100 ms; 75-dB SPL; presented in blocks of 300	EEG	Difference between pre- and post-training sessions. Trained sleeping newborns are better able to discriminate the speech sounds /y/ and /y/i/ after training. Control group not exposed to any training, and control group trained to discriminate between other vowel sounds, show no difference between the two sessions
4 deRegnier et al. ⁵⁶	18 preterm newborns; 20 full-term newborns; 21 full-term experienced; age at test: ≤1 week old	Maternal voice vs. stranger's voice. A speech sound (the sound "ba" in a female voice) alternating with a non-speech sound (a computer chime)		No	400 ms; 80-dB SPL, 100 repetitions	EEG	Neonates born between 35 and 38 wGA did not distinguish between the syllable "ba" spoken by their mother and the same syllable said by another woman, contrary to those born between 39 and 42 wGA
5 Peña et al. ⁴⁹	14 full-term newborns; age at test: 2–5 days, mean 2.7 days	Forward and backward speech samples from two mothers; children's stories using infant-directed speech		No	15 s.; 10 blocks per condition, presented in random order	NIRS	Left hemisphere (LH) temporal areas showed significantly more activation when infants were exposed to normal speech than to backward speech or silence. We conclude that neonates are born with an LH superiority to process specific properties of speech
6 Kujala et al. ⁴⁸	10 full-term newborns; age at test: 1–25 days, mean 6 days	Long vowels [a:] and [i:] recorded female voice, and the vowel [a:] with a rising pitch (change of intonation)		No	300 ms; about 60-dB SPL	MEG	The magnetic mismatch-negativity response was obtained and successfully modelled to the speech sound quality change in all infants and to the intonation change in six infants

Table 1 continued

Table 1 continued

Author, ref.	Population (N; age)	Stimuli		Type of intervention	Stimulus details (duration; intensity; repetitions)	Neuroimaging technique	Results
		Type of stimulus					
7 Therien et al. ⁵⁷	35 preterm newborns <32 weeks GA at birth; age at test: at term age; 40 healthy, term newborns; age at test: 1–3 days	A: speech sounds /bi/ and /gi/, male voice; B: the mother's voice vs. a stranger's voice; the word "baby"		60 interventions	A: 230 ms; 75-dB SPL; B: 750 ms; 78-dB SPL; 120 repetitions	EEG	Speech sound differences were observed at the frontal and temporal sites for preterm infants, and at the midline frontal–central sites for the full-term infants
8 Kushnerenko et al. ⁷¹	12 full-term newborns; age at test: 1–4 days	Clicks, chirps, simulations of bird vocalizations, vowels, and syllables. Standard sound vs. deviant sounds		No	100 ms; 57.7–81.9-dB SPL; 1 block of 800 stimuli for each condition	EEG	Newborns present the largest and most stable ERP with white-noise sounds. Late discriminative ERP response also for the other deviants, indicating novelty in acoustic stimulation
9 Saito et al. ¹²⁷	20 full-term newborns; age at test: 1–9 days	Readings of Little Red Riding Hood, digital voice; two conditions: variably pitched speech and monotonous flat-pitched speech		No	30 s; 60–70-dB SPL	NIRS	Variable speech produced a greater increase of oxygenated blood to the frontal area of the brain area than monotonous flat-pitched speech
10 Gervain et al. ¹¹	44 full-term newborns each; age at test: 3–14 days, range, 1–6 days	A: Repetition of ABB artificial grammar and an unstructured ABC control B: BA grammar containing nonadjacent repetitions vs. the same ABC control		No	A: 18 s; 270 ms each syllable; B: same procedure	NIRS	A: The repetition sequences evoked greater activation than the random sequences; over the subsequent trials, activation increased further in response to the repetition sequences but not in response to the random sequences. B: no discrimination was observed
11 Sambeth et al. ⁵⁰	11 full-term newborns; age at test: 1–5 days (mean age 2 days)	Finnish Christmas carol, female voice. Four conditions, Singing, Speech, without variations in the fundamental frequency, and low-pass filtered (formants not audible).		No	Variable duration; 60–75-dB SPL	MEG	Brain response elicited to the prosodically rich singing and continuous natural speech conditions decreased dramatically when the prosody in the speech was impoverished
12 Saito et al. ⁶⁷	26 preterm newborns; age at test: 35 + 6–38 + 5, 18–81 days PNA	The mother's voice and a female Nurse's voice. White noise as a control auditory stimulus		No	10 s every block and 20 s white noise; 60–70-dB SPL; two blocks; repeated four times	NIRS	The mother's and the nurse's voices were activated in the same way in the left frontal area, but showed different reactions in the right frontal area
13 Beauchemin et al. ⁵²	16 full-term newborns; age at test: 8–27 h	Samples of the French vowel /a/ pronounced by the natural voice of different speakers, all females		No	212 ms, total duration 24 min; four blocks of 390 stimuli; 75-dB SPL	EEG	Mother's voice processing more active than that of strangers at both an early and a late stage of processing. The mother's voice is preferentially processed in the left temporal lobe at early latencies before activating central right regions. In contrast, the stranger's voice elicited

Table 1 continued

Author, ref.	Population (N; age)	Stimuli		Type of intervention	Stimulus details (duration; intensity; repetitions)	Neuroimaging technique	Results
		Type of stimulus					
14 Kotilahti et al. ⁹⁰	13 full-term newborns; age at test: 1–4 days	Speech: Fairy tale “Little red riding hood”	No	5 s	NIRS		predominant right temporal lobe voice-specific response On both hemispheres, speech and music responses were significantly correlated. Response to the speech stimuli was greater than zero in the left hemisphere, whereas responses on the left hemisphere did not differ significantly from zero
15 Perani et al. ⁵¹	15 full-term newborns; age at test: 1–3 days after birth	Tale for children in normal speech, hummed speech, and flattened speech	No	About 84-dB SPL	fMRI		Language-related neural substrate is fully active in both hemispheres with a preponderance in the right primary and secondary auditory cortex. These brain regions were strongly activated in normal speech and to a lesser extent also in hummed speech, but not in flattened speech; strong connectivities only between the two hemispheres
16 Benavides-Varela et al. ¹³⁰	44 full-term newborns; age at test: 1–4 days (mean: 2.5 days)	Words (/sisi/, /mama//titi/, /lala/),	No	700-ms duration each word; 70-dB SPL	fNIRS		Right frontal regions showed a characteristic neural signature of recognition when newborns listened to the same vowel. Novelty response when a test word had different vowels than the familiar word, despite having the same consonants
17 Cheng et al. ⁴⁶	98 full-term newborns; age at test: 1–5 daysvs.	Emotionally spoken syllables “dada” vs. correspondent non-vocal sounds; experiment 1, happy syllables vs. nonvocal sounds; experiment 2, fearful syllables vs. happy or neutral syllables; experiment 3, angry vs. happy syllables		550-ms duration each syllable; 70-dB SPL (min: 57 dB; max: 62 dB)	EEG		Happy syllables relative to non-vocal sounds elicited an MMR lateralized to the right hemisphere. Fearful syllables elicited stronger amplitudes than happy or neutral syllables, and this response had no sex differences. Angry vs. happy syllables elicited an MMR, although their corresponding non-vocal sounds did not. Cerebral specialization for human voice and emotion processing emerges over the right hemisphere during the first days of life
18 Key et al. ¹⁹			No	250-ms duration each syllable; 75-dB SPL; random	EEG		An increase in either GA or PNA was associated with greater ERP

Table 1 continued

Table 1 continued

Author, ref.	Population (N; age)	Stimuli		Type of intervention	Stimulus details (duration; intensity; repetitions)	Neuroimaging technique	Results
		Type of stimulus					
	50 preterm newborns; weeks GA at birth: 29.6; age at test: after 32 weeks post-conceptual age	Six computer-synthesized consonant-vowel syllables (i.e. /ba/, /da/, /ga/, /bu/, /du/, /gu/)			order, 25 times each, for a total of 150 trials		differences in response to various speech sounds. These effects were more pronounced for consonant than vowel contrasts. Increasing PNA was associated with greater sound discrimination in infants born at or after 30 weeks GA, while minimal postnatal age-related changes were observed for infants with GA <30 weeks
19 Chipaux et al. ⁶⁸	46 preterm infants; weeks GA at birth: 29–30 (n = 12), 31–32 (n = 22), 33–34 (n = 11), and 35 (n = 1); age at test 31–38 postmenstrual weeks (PMW)	Stimulus 1: a recorded male voice pronouncing the word “bébé”; peak intensity of around 70–75 dB (SPL)	Stimulus 2: “click” and voice, peak intensity of 56–62 dB (SPL)	No	Stimulus 1: recorded male voice = peak intensity of around 70–75-dB SPL Stimulus 2: “click” and voice = peak intensity of 56–62-dB SPL	EEG	Before 34 PMA voice and “click” stimuli evoked cortical responses. Auditory responses to stimuli mimicking ambient sounds were maximal on temporal areas before 35 PMA and consisted of slow waves mixed with rapid oscillations. A switch in human preterms around 35 wGA in quiet sleep, from an undifferentiated response to tone and voice stimuli. Auditory evoked delta-brushes both sleep stages and in response to both verbal and non-verbal stimuli
20 Mahmoudzadeh et al. ⁶⁵	12 preterm newborns; weeks GA at birth: 30.3 ± 1.6 wGA; age at test: 3.4 ± 1.2 days, corresponding to 30.7 ± 1.5 wG	Four digitized syllables /ba/ and /ga/, naturally produced by a French male (ba, ga) and a French female speaker		No	Total duration 285 ms; about 70-dB SPL; three types of blocks, total duration of 108 m		Neonates discriminated a change of syllable (/ba/ vs. /ga/) by means of a network of temporal and frontal areas fairly similar to that described subsequently, whereas the response to a novel voice (male vs. female voice), although present, was more limited.
21 Gómez et al. ¹³¹	24 full-term newborns; mean age at test = 2.9 days	Well-formed syllables (e.g. blif) vs. ill-formed syllables (e.g., lbif, bdif)		No	70 dB	NIRS	Significant differences between conditions in oxyhemoglobin concentrations in both left temporal and right fronto-parietal values). In both areas, well-formed syllables elicited lower oxyhemoglobin concentrations than ill-formed syllables
22 Webb et al. ⁶³	40 preterm newborns, 25–32 wGA at birth; age at test: 30 days PNA	Mother’s voice and heartbeat sounds,		Yes	3 hours per day; loud peaks >65 dBA; repetitions: four	Cranial ultrasounds	Larger primary auditory cortex in infants with auditory intervention; the magnitude of

Table 1 continued

Author, ref.	Population (N; age)	Stimuli	Type of intervention	Stimulus details (duration; intensity; repetitions)	Neuroimaging technique	Results
Type of stimulus						
23 Vannasing et al. ⁵³	29 full-term newborns; age at test: 15–37 h after birth (mean: 28 ± 6.75 h)	The story <i>Snow White</i> was recorded in the native language (forward French: Ffwd) and non-native language (forward Arabic: Afwd) by a bilingual female reader	No	times per day for a duration of 45 min each 40 min; 64–76 dB; repetitions: total stimulation time was 40 min for both French and Arabic in either forward or backward condition	fNIRS	the right and left auditory cortex thickness was significantly correlated with GA but not with the duration of sound exposure Comparisons between left and right hemisphere oxyhemoglobin (HbO ₂) concentration changes over the temporal areas revealed clear left hemisphere dominance for native language, whereas non-native stimuli were associated with right hemisphere lateralization. In addition, bilateral cerebral activation was found for non-linguistic stimulus processing
24 Mahmoudzadeh et al. ⁶⁶	90 preterm infants; 30-wGA at birth; age at test: 3 days, range: 1–6 days, corresponding to 28–32 wGA	Four syllables were presented by series of 4 to constitute either standard trials (4 repetitions of the same syllable, e.g., ba ba ba) or deviant trials (3 repetitions followed by a change, e.g., ba ba ba ga), which were presented randomly	No	Duration: series of 4 syllables, 600 ms each; intensity = ≈70 dB, via speakers placed at the infant's feet	EEG	The syllables elicited four peaks with distinct topographies with a processing hierarchy; repetition induced a decrease in the amplitude of these peaks, but their latencies and topographies remained stable. A change of stimulus generated mismatch responses, which were more precisely time-locked to event onset in the case of a phonetic change than in the case of a voice change
We included studies from 2000, conducted with neuroimaging measurement techniques, in the first days of life for full-term infants and up to term age for preterm infants						
dB decibel, dBA decibel A weighted, EEG electroencephalography, fMRI functional magnetic resonance imaging, Hz Hertz, fNIRS functional near-infrared spectroscopy, GA gestational age, MEGmagnetoencephalography, NIRS near-infrared spectroscopy, PMA post-menstrual age, PNA postnatal age, s seconds, ms milliseconds, SPL sound pressure level, w weeks						

We included studies from 2000, conducted with neuroimaging measurement techniques, in the first days of life for full-term infants and up to term age for preterm infants
dB decibel, dBA decibel A weighted, EEG electroencephalography, fMRI functional magnetic resonance imaging, Hz Hertz, fNIRS functional near-infrared spectroscopy, GA gestational age, MEG magnetoencephalography, NIRS near-infrared spectroscopy, PMA post-menstrual age, PNA postnatal age, s seconds, ms milliseconds, SPL sound pressure level, w weeks

Table 2. Neural evidences for music processing at birth

Author, ref.	Population (N; age)	Stimuli	Music or voice intervention		Neuroimaging technique	Results
			Type of stimulus	Stimulus details (duration, intensity, repetitions)		
Novitski et al. ⁸¹	19 full-term newborns; age at test: 2 days	Tones: Standard: 250, 1000, and 4000 Hz Deviant: 5 and 20% higher or lower than standard	No	100 ms tones, 80-dB SPL at 250 Hz, 75-dB SPL at 1000 Hz, and 65 dB SPL at 4000 Hz	EEG	Full-term infants show positive deflection in the ERP 200–300 ms after deviant stimuli
Stefanics et al. ⁸²	12 full-term newborns; age at test: 2–3 days	Two complex tones with three harmonic frequencies added to the base frequency. Base frequency of the low tone: 500 Hz and that of the high tone: 612 Hz	No	50 ms, presentation of the stimuli in grouped condition: SSSD, in random condition: pseudo-randomized, 75 dB, 1000 repetitions	EEG	Deviant condition elicited more negative fronto-central ERP response between 150 and 250 ms than standard tones. Deviant tones also elicited strong γ -band oscillations approximately 200 ms from stimulus, whereas standard tones induced a decrease in amplitude 140–270 ms from stimulus. These differential responses between standard and deviant stimuli were observed only in the random condition but not in the grouped condition
Bisiacchi et al. ⁵⁹	39 preterm newborns; age at birth: 23–34 wGA; age at test: 35 wGA	Tones, standard tones: 1000 Hz Deviant tones: 2000 Hz	No	100 ms, 75 dB, 990 repetitions	EEG	Extremely preterm infants (born <32 weeks) showed smaller auditory event-related potentials in response to deviant tone than more moderately preterm infants (born >32 weeks)
Håden et al. ⁵⁸	12 full-term newborns; age at test: 2–3 days of age	Standard: tones with two different pitches: 139 Hz and 175 Hz Deviant tones: seven resonator-size variants (different timbre) for each pitch	No	600 repetitions	EEG	Deviant timbre elicited an early negative and a later positive discriminative response in central electrodes
Stefanics et al. ⁸³	15 full-term newborns; age at test: 2–3 days	Pairs of tones	No	50 ms, 75 dB, 1000 repetitions	EEG	Second tone of deviant pairs elicited differential event-related potential in frontal areas than second tone of the standard pairs
Vestergaard et al. ⁸⁴	17 full-term newborns; age at test: 2–3 days of age	2 notes: pitch 175 Hz, different resonance scale (size of sound)	No	545 ms, 2000 repetitions	EEG	For larger resonance-scale deviant: lower-amplitude central (Cz) response than the standards 212–252 ms latency range. For smaller resonance-scale deviant: higher-amplitude central (Cz) response than standards at 204–244 ms latency range
Winkler et al. ⁸⁶	30 full-term newborns; age at test: 1–3 days of age	Instrumental: Snare, bass, and hi-hat spanning. Standard eight notes equally spaced vs. beat violation (=standard with omitted sound)	No	306 repetitions	EEG	Violation of the beat of a rhythmic sound sequence elicited event-related potentials in central areas

Table 2 continued

Table 2 continued

Author, ref.	Population (N; age)	Stimuli	Music or voice intervention	Stimulus details (duration, intensity, repetitions)		Neuroimaging technique	Results
		Type of stimulus					
Kotilahti et al. ⁹⁰	13 full-term newborns; age at test: 1–4 days of age	Instrumental, Mozart	No	No	5 s, 60 dB, 64 repetitions	NIRS	No lateralization of music processing in the auditory cortex. Response to music is inconsistent between newborns
Mento et al. ¹¹⁶	39 preterm newborns; age at birth: 24–34 wGA; age at test: 35 wGA	Standard tones: 1000 Hz Deviant tones: 2000 Hz	No	No	100 ms, 75 dB, 990 repetitions	EEG	Preterm infants had a higher electrophysiological activity in the right hemisphere for both pitch detection (standard condition) and discrimination (deviant condition)
Perani et al. ⁸⁹	18 full-term newborns; age at test: 1–3 days	Major–minor tonal (“Western”) instrumental classical music, average tempo of 124 beats per minute	No	No	21 s blocks pseudo-randomized, two times 7 min sequence. Three types of stimuli: consonant music, dissonant, or with sudden key shifts	fMRI	Consonant music led to activation of the right auditory cortex as well as of the amygdalo-hippocampal complex, while altered music led to increased activation in the left inferior frontal gyrus and the left amygdalo-hippocampal complex
Suppiej et al. ¹¹⁵	26 preterm newborns; age at birth: 25–35 wGA; age at test: 40 wGA	Tones, standard: 1000 Hz Deviant: 2000 Hz	No	No	100 ms, 75 dB nHL	EEG	In active sleep, preterm infants showed an increased frontal negativity in the time period from 200 to 300 ms after a deviant tone
Virtala et al. ⁸⁵	28 full-term newborns; age at test: 1–3 days	Triad chords comprised of three tones. Standard: major chords Deviant: minor chords and dissonant chords	No	No	250 ms, 60 dB SPL, 551 repetitions	EEG	Full-term infants differentially process minor vs. major chords and consonant vs. major chords. Major chords (standards) stimuli elicited early frontal negative response around 20–120 ms and a later central and parietal positive response around 250–350 ms. Dissonant chords elicited a large positive mismatch response in frontal areas. Minor chords elicited a negative mismatch response in parietal electrodes
Partanen et al. ⁹³	24 full-term newborns; 12 with fetal music exposure; age at test: at birth	Instrumental music, including Twinkle twinkle little star	Twinkle twinkle little star and with speech phrases		600 ms. Original melody: Twinkle twinkle little star; Altered melody: 12.5% of notes’ pitch changed within the extract, 70 dB SPL, 9 repetitions	EEG	Original vs. Altered melody: positive mismatch response to changed sounds between 200 and 300 ms after stimulus onset. The magnitude of this difference was correlated with the number of antenatal exposure to the melody
Håden et al. ⁸⁷	33 full-term newborns; age at test: 1–3 days	Standard: Six tones descending in pitch in three semitone steps Deviant: train included a deviant ascending step at position 2 or 5	No	No	50 ms, 75 dB SPL, 600 repetitions	EEG	Full-term infants showed discriminative mismatch response for deviants delivered in the 5th but not in the 2nd position
Håden et al. ⁸⁸	14 full-term newborns; age at test: 2–3 days	Train of tones, tone duration: 50 ms, uniform pitch. Half of the	No	No	65 dB SPL, 170 repetitions	EEG	

Table 2 continued

Author, ref.	Population (N; age)	Stimuli	Neuroimaging technique		Results
			Music or voice intervention	Stimulus details (duration, intensity, repetitions)	
Lordier and Loukas ¹²⁴	35 preterm newborns; age at birth: 24–32 wGA; age at test: 40 wGA; 21 full-term newborns; age at test: 1–4 days of age	train at a slow rate: IOI: 200 ms, half at a fast rate: IOI: 100 ms Instrumental, composed for the study by A. Vollenweider, harp, bells, punji	17 preterm newborns without music intervention; 21 full term	8 s blocks, Original, Key transposition, Tempo modification, 10 repetitions	In full-term infants, variations in presentation rate elicited and early fronto-central negative response No difference was found between Original and Key transposed and between Original and Tempo modification stimuli in preterm controls and full term Preterm infants with music intervention processed equally Original and Key transposed music. When compared to preterm control group, preterm group with music intervention showed a stronger connectivity between the right primary auditory cortex and right thalamus, left middle cingulate cortex and the left caudate nucleus when listening to known music than tempo modified music condition. In the same condition comparison, preterm-music group, compared to the full-term group, increased their functional connectivity between the left primary auditory cortex region and the left superior temporal gyrus and the left middle cingulate cortex and between the right primary auditory cortex and left middle cingulate cortex and putamen
			18 preterm newborns with music intervention: 8 min of recorded music via headphones, 5 times per week, from 33 wGA until discharge, <55 dBA		
Lordier et al. ¹²⁵	35 preterm newborns; age at birth: 24–32 wGA; age at test: 40 wGA; 21 full-term newborns; age at test: 1–4 days of age	Instrumental, composed for the study by A. Vollenweider, harp, bells, punji	17 preterm newborns without music intervention; 21 full term	No stimulus: infants at rest	Rs-fMRI When compared to full-term infants, preterm controls infant had a decreased connectivity in three modules with the salience network connecting these three modules: medial superior frontal, auditory, and sensorimotor networks; thalamus, precuneus, and right posterior temporal gyrus networks; and orbitofrontal cortex, posterior cingulate cortex, visual cortex and left posterior temporal gyrus networks In preterm infants with music intervention, RS-functional

Table 2 continued

Author, ref.	Population (N; age)	Stimuli	Music or voice intervention	Stimulus details (duration, intensity, repetitions)	Neuroimaging technique	Results
		Type of stimulus				
			8 minutes of recorded music via headphones, 5 times per week, from 33 wGA until discharge, <55 dBA			connectivity was more similar to those of full term in these very same networks shown to be altered by prematurity, namely, the salience network with the superior frontal, auditory and sensorimotor networks, and thalamus and precuneus networks

IOI inter interval onset, *dB* decibel, *dBA* decibel A weighted, *ERP* event-related potential, *fMRI* functional magnetic resonance imaging, *fNIRS* functional near-infrared spectroscopy, *GA* gestational age, *NIRS* near-infrared spectroscopy, *SPL* sound pressure level, *nHL* normal adult hearing level, *w* weeks

Several studies of multidimensional parental intervention—for example, during the skin-to-skin contact—have shown that EVC during the hospitalization period also has positive effects on reducing parental anxiety and also can sustain early attachment processes.^{100,101}

In this context, EVC can be a preferred tool for maintaining synchrony in early social interactions with hospitalized premature infants.

The synchrony between human beings is based on a shared rhythmic experience that coordinates exchanges during social interactions. Reciprocal synchrony-regulated exchanges are not only vocal and auditory, but lead to biological co-regulation in which hormones and physiological responses play a fundamental role, whereas a lack of synchrony can have a detrimental impact on communication.¹⁰² A kind of asynchrony has been described in premature dyads: biological dysregulation of premature infants affects parenting behavior and their mothers tend to have less consistent and less synchronized social contact with their infants.¹⁰³ Early contact experiences, such as skin-to-skin contact, can change these patterns into more cohesive styles. This brings mothers and fathers to be more sensitive and less intrusive and preterm infants to have better arousal modulation and more sustained exploration abilities.¹⁰⁴

EVC is multisensory and redundant contact
Defining the optimal sensory experience for premature newborns is complex. However, some indications can be made by observing the characteristics of the prenatal and postnatal sensory and cerebral development of the fetus and the newborn.¹⁰⁵

In the early stages of newborn development, the senses work in synchrony and the various sensory systems provide intermodal information about objects and events.¹⁰⁶ Since birth, newborns are sensitive to audiovisual synchrony,¹⁰⁷ especially for speech and faces. The maternal voice facilitates the recognition of the maternal face from birth.¹⁰⁸ prior experience with the mother's voice and face together is necessary for the development of facial recognition, which shows that intermodal perception is evident at birth. Thus, the ability of newborns to recognize the mother's face is more likely to be rooted in the prenatal learning of the mother's voice.

In conclusion, the vocal contact, during development, supports the coupling with visual stimulus (looking at the mother's face) and encourages the experiences of neonatal mimicry (gestures and voices).

EVC can impact the communicative and social skills of the premature newborn
The etiology of language disorders in premature infants is multifactorial and is related to the "degree of prematurity, neonatal morbidity, severity of the disease, gender, language environment in the intensive care unit and at home, the level of maternal education, the social and environmental status of the family, and access to early intervention".¹⁰⁹ Although there are other factors involved, the loss of biologically significant auditory stimuli, in particular with the maternal voice, seems to have a particularly important role in the development of language and communication skills for premature newborns.

Premature babies react to emotional voices and voice of the mother with the typical characteristics of the "baby talk," which can regulate their behavior.¹¹⁰ In turn, the mother's direct voice is regulated by changes in the baby's condition and behavior,⁹⁶ and early exposure to adult language during hospitalization¹¹¹ improves their language development.¹¹² As social and communication skills are acquired, for the newborn at term, from the first moments of life, in contexts of social interaction, the prematurity can affect synchrony in the mother-baby dyad, with subsequent differences in language and socio-emotional abilities.¹¹³

MUSIC INTERVENTION IN THE NICU

For about a decade neonatologists have been investigating the potential role of music in the NICU¹¹⁴ and for designing such interventions is relevant to understand how the preterm infant's brain processes music. Using EEG, the ability to process relative pitch has been shown to be present in near-term premature infants.¹¹⁵ Furthermore, a right functional lateralization when processing pitch deviant was shown in 35-week-old preterm infants.¹¹⁶ However, at 1 month of age, extremely preterm infants showed smaller auditory event-related potentials in response to deviant tone than moderately preterm infants.⁵⁹ Thus, the ability to process tones may be impaired by extremely early birth or by increased time spent in NICUs, with loud noise and deprivation of meaningful sounds. As stated above, the presence of meaningful sounds is necessary for an appropriate maturation of the auditory system^{117–119} and music has been thought as a developmental care intervention in NICU that may provide meaningful sounds when presented in a meaningful context. It comprises both sound and silence expressively organized in time and is known to involve a widespread bilateral network of cortical and subcortical areas, extending well beyond the auditory cortex. Music intervention during NICU stay might thus hold the potential to modulate neural networks known to be affected early in development by prematurity.

A number of authors have considered the effects of listening to music on premature infants' physiological data. Studies on early enrichment of NICUs environment by music have used different types of music and different protocols regarding the amount of music exposure, delivery method, GA of the infant, leading to equivocal results.^{63,120–122} However, although some studies have not shown any effect of exposure to music on the newborn, none have noted a negative effect and most of them observed a stabilizing effect of music on heart and respiratory rhythms, a decrease in apnea and bradycardia counts per day, an improvement in diet, greater weight gain, and more mature sleep patterns.^{120,121,123}

Nevertheless, so far there is little data regarding the effects of a music intervention on preterm infants' brain development. Webb et al.⁶³ evaluated the effects of recorded sound intervention on brain development through ultrasonography. They described a larger auditory cortex in preterm infants who had an enrichment of their environment for 1 month through filtered maternal voice and heartbeat sounds. These results suggest an effect of NICUs sound enrichment on preterm brain maturation. A recent study by our group¹²⁴ explored the cortico-subcortical music processing of different types of music conditions (Original music, Tempo modification, Key transposition) in newborns shortly after birth to assess the effective connectivity of the primary auditory cortex with the entire newborn brain, showing that music stimuli are indeed processed on multiple cortical levels beyond auditory cortex only. This study also for the first time assessed the effect of a music intervention during the NICU stay from 33 weeks to term-equivalent age, when the intervention group listened to specifically composed tunes of 8 min. The results showed that neural music processing was influenced by the music intervention. Auditory cortex functional connectivity with cerebral regions known to be implicated in tempo and familiarity processing were identified only for preterm infants with music training in the NICU. The increased connectivity between auditory cortices and thalamus and dorsal striatum, as found in this study, may not only reflect their sensitivity to the known music and the processing of its tempo as familiar, but these results are also compatible with the hypothesis that the music that they listened previously induces a more arousing and pleasant state. Furthermore, we recently showed that this music intervention also changed resting state functional connectivity in preterm infants. Indeed, decreased functional connectivity was observed in preterm control infants when compared to full-term newborns in a neural circuitry involving the Salience Network, a network thought to be implicated in relevant internal or external stimuli detection and generation of appropriate behavioral response. Functional connectivity was

decreased in preterm control infants between Salience Network and regions implicated in sensory processing, as well as networks underlying cognitive functions and behavioral and emotional regulations. Preterm infants with music intervention showed brain functional connectivity more similar to those of full-term newborns between these same regions, namely, the salience network with the superior frontal, auditory and sensorimotor networks, and thalamus and precuneus networks. Thus, music intervention seems to lead to a functional brain circuitry in preterm infants more similar to those of full-term newborns.¹²⁵

Finally, emotional regulation capacities of these patients were evaluated at 12 and 24 months of corrected age using four episodes of the Laboratory Temperament Assessment Battery (assessing expressions of joy, anger, fear, and sustained attention). Preterm infants in the music group showed more similar fear reactivity at 12 months of age and anger reactivity at 24 months of age to full-term infants than preterm control infants. Thus, early music intervention in NICU seems to have long-lasting effects on neurodevelopment in preterm infants and especially on emotion regulation capacities.¹²⁶ However, the effect of music interventions, including type of music and amount of exposure in the NICUs on the future brain development, music processing abilities and later cognitive and behavioral outcome remains to be further explored.

CONCLUSIONS

Despite the reported short-term benefits of maternal, direct and recorded voice and music, there is still a lack of scientific evidence of the long-term effects of these early interventions, both in terms of cerebral anatomical development and infant neurodevelopment. To evaluate the effectiveness of direct and recorded maternal voice interventions, it is necessary to clarify what factors determine the observed effects and the conditions under which interventions are delivered. The direct maternal voice has been subject of very few studies, particularly with regard to its potential long-term effects on parenting skills. The long-term effects on dyads and triads, with both parents involved in the intervention, must be carefully considered.

A recent review of the literature¹¹⁴ points out that it is necessary to examine the long-term neurodevelopmental outcomes of early voiced and musical interventions. Specific assessments of their impact on brain growth, structural, and functional connectivity in preterm infants are underway, but long-term functional outcome regarding language development, the effect on behavior, and emotional regulation of children, as well as their abilities to establish or use social interactions for their regulation, need to be explored.

Nevertheless, these interventions could have an important role in the family-centered developmental care strategies and deserve to be considered and discussed by the scientific and medical community.^{127–129}

AUTHOR CONTRIBUTIONS

All authors were involved in study design, review, and editing of the manuscript and approved the final version of the manuscript.

ADDITIONAL INFORMATION

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