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MUSIC AND VOICE INTERVENTIONS IN THE NICU: A NOVEL ADAPTIVE PERSONALIZED AUDITORY CARE BASED ON BIOPHYSICAL FEEDBACK

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ABSTRACT

Neonatal Intensive Care Units are an extremely noisy and stressful environment, known to be detrimental to the neurological outcome of preterm born infants. In a time when the sensory environment is critical for the infants' development, implementing new acoustic solutions relying on evidence-based research is key for offsetting these risks. Music and voice interventions have shown beneficial effects on preterm infants' brain, behavior, and physiological development, increasing our understanding of the effects and mechanisms of acoustic interventions for well-being. Newborns can distinguish between vocal and instrumental melodies, and music intervention creates musical memories and influences the resting state of preterm infants. Maternal voice interventions stabilize the newborns, promote the maturation of their autonomous nervous system, and protect them from pain by increasing oxytocin levels. Structured and meaningful acoustic interventions can improve the bioecological niche where preterm infants mature in the first weeks of life, traditionally an acoustically unpredictable and noisy environment. Based on these results, future research aims at collecting, analyzing, and interpreting data from the infant's physiology and well-being in order to provide each hospitalized newborn with a personalized and individually modulated sound environment that will be tailored to the infants' needs, and potential health perspectives.

Keywords: *neonatal intensive care units, premature infants, sound environment, individualized acoustic care, biophysiological feedback.*

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1. INTRODUCTION

Our mature brain consists of a complex network of some 100 billion neurons connected by synapses. From birth, the brain develops according to a programmed order, with precise genetic expression guiding the proliferation of cells, their morphogenesis and subsequent migration, dendritic differentiation, synaptogenesis, apoptosis and myelination. These processes occur at certain crucial moments in the development of the foetus and newborn child and depend in part on sensory input.

Disruption of one of these processes has as a direct consequence in the typical development of brain structures and functions, with potentially associated long-term alterations at both the macro- and micro-structural levels, in the cortical layering and/or number of neurons and axonal projections. The repercussions in terms of neurological and behavioral development are well known.

Prematurity exposes the infant to many risk factors for later neurodevelopmental deficits, including focal brain injury with subsequent alteration of brain development. In addition to strictly medical factors, the environmental factors that expose the newborn to an atypical sensory environment (maternal womb vs. neonatal intensive care) also affect brain development [1]. Advances in neonatal therapy, for example, have significantly reduced the incidence of focal brain injury, but this reduction has not always had an equally positive and protective impact on overall long-term neurodevelopmental deficits [2]. This means that other factors in the early care of children born prematurely also influence long-term development.

1.1 Fetal and neonatal sound environment

The prenatal acoustic environment in humans has been described as a chamber filled with dense water and surrounded by flexible walls that vary in thickness as the fetus develops [3].

The intrauterine auditory environment is characterized by two major sound sources: maternal sounds and externally generated sounds, which reach the fetus through airborne or vibroacoustic stimulations. The sounds produced internally cross the uterine wall and are transmitted via bone conduction or the amniotic fluid. They are created by the organs and the maternal cardiovascular system, in a continuous and very variable dynamic movement; they are mainly constituted by low frequencies [4] even if high frequencies, at specific intensities, can cross the maternal abdomen filter.

The maternal heartbeat is most likely audible to the baby in utero from very early on [5], but is far from being a precise rhythmical stimulus, as it depends on the maternal state – active or sleeping – on her stress level and on the various external stimulations to which she responds at a physiological level. Interestingly, during the third trimester of pregnancy, the fetus does not only detect variations in the mother's breathing rhythm, but can adjust its rate of activation in response to it [6], showing the ability to synchronize with its auditory environment. For fetuses, the mother's voice is a very prominent stimulus and it is transmitted both internally through bone and tissue conduction and as an external stimulus, and it has a minor attenuation.

Fetuses are also exposed to the external sounds which are differently attenuated in terms of intensity, according to their frequency: low frequencies, for example, pass unaltered through the tissues of the abdomen and placenta; external sound waves at middle frequencies are partially reflected by the maternal abdomen, and the sound is reduced by around 6 dB Sound Pressure Level (spl) per octave. External voices, both male and female, conversing at an average volume of about 60 dB spl are very well audible for the fetus and remain intact and audible even if in utero they reach about 40dB spl, the sound level of a whisper.

Finally, it is important to note that the fetus is also exposed to vibroacoustic stimuli, i.e. those that mechanically vibrate the mother's body or abdomen. These sounds, often aggressive and uncontrolled, can originate simultaneously in the air through direct contact of the mother's body with vibrating surfaces, such as mechanical frames or agricultural vehicle seats. Even leaning against a musical resonant instrument like a drum or travelling in a closed car with a loud stereo causes powerful mechanical vibration. Women are advised to be careful and to protect their fetuses as much as they can from aggressive, continuous, loud noises and mechanical vibrations.

1.2 Atypical sound environment in the NICU vs sound environment in the womb

As seen in the introductory paragraph, the environment plays an important role in the development of the infant; genes and the environment interact to guide the maturation of the infant's neural circuits, in a continuous exchange between a brain that needs and depends on external sensory stimuli, and the physical and human environment that provides the nourishment necessary for development.

In the first months of a foetus' and child's life, various brain functions (visual, auditory and somatosensory) mature thanks to this continuous and vital positive interaction. Unfortunately, premature birth drastically reduces some positive stimuli, such as the familiar maternal voice, contact, nourishment and warmth that were provided by the mother's body, which are replaced with artificial forms of nourishment (nasal cannula, parenteral), thermoregulation (incubator) and oxygenation (ventilation, CPAP or supplemental oxygen in the incubator). The "natural" fetal sound environment described above (section 1.1) is replaced by an artificial environment consisting mainly of non-adaptive sounds, such as opening and closing mechanisms of cabinets and doors, alarms and sudden opening of taps for sterilizing hands. High-risk premature infants admitted to the neonatal intensive care unit spend an important period, even several months, in this environment deleterious for neurosensory development (critical for subsequent neurobehavioural functions) where the stimulations, visual, olfactory and auditory, are often not in an optimal relationship with the infant's individual needs. In addition to the non-adaptive sensory environment, there are numerous stressful events imposed by necessary care, such as painful procedures, disruption of sleep patterns, often due to the absence of appropriate responses to the infant's behavior. For high-risk infants, optimizing their neurological development in this early period of life is of utmost importance.

Figure 1. Preterm infant in the NICU. Picture obtained with permission in the HUG NICU in Geneva by Craig Kutler

1.3 Short and long-term effects on early auditory discrimination in preterm infants

The development of neural networks in the perinatal period is highly dependent on the intrinsic and extrinsic multisensory activity [7, 8] including meaningful sounds such as human voices or music, which drive maturation of neuronal circuits [9].

The preterm infant develops in an auditory environment characterized by high environmental noise and reduced exposure to the mother's voice. As we pointed out in the previous section, when stimuli in the environment are not functional and suitable for the infant's brain maturation and activity, the deprivation of specific sounds and auditory stimuli prevents the auditory cortex from maturing which also has long-term effects [10]. In the short term, preterm infants show atypical responses at the presumed age of birth - term equivalent age - when compared to term infants [11]. For example, they do not show clear signs of distinguishing the mother's voice from that of a foreign mother and use additional cortical regions for processing these stimuli [7]. In both hemispheres and in several frequency bands, the preterm newborns demonstrate different activations for mothers and stranger voices when compared to terms [12]), and they show less mature and selective response for emotional prosody with respect to their pars at term [13].

2. RETHINKING NEONATAL CARE: NICU SOUND ENRICHMENT USING BIOPHYSICAL FEEDBACK

2.1 Music and Voice in NICU

Auditory interventions, mainly based on live or recorded music and on the administration of the maternal voice have been at the center of several investigations and systematic reviews in the past years [14, 15]. More specifically, we report here a study conducted by our research group, demonstrating the beneficial effect of music exposure in the NICU. In [8], authors used a multi-instrumental musical composition. In this randomized clinical trial study, three different musical compositions were presented to the infants depending on their behavioral state: falling asleep, waking up, staying awake. This dedicated stimulus was intended at engaging infants in multisensory perception, but also at providing them cues to manage their SWC cycles. This music exposure positively correlated to an increase in functional connectivity in brain regions implicated in multisensory and emotional processing, strengthening involvement of salience network otherwise weakened after prematurity [8], fMRI further indicating strong engagement of musical memories, and disengagement of default-mode network due to the aforementioned cognitive processing [16]. In addition, infants that were exposed to the music intervention during their NICU stay presented significantly larger brain amygdala volumes in comparison to those receiving standard-of-care, as well as maturation of major white matter fiber tracts such as the acoustic radiation and the uncinate fasciculus, an important network in limbic functions.

In general, auditory stimuli have been integrated in the therapy of neurodegenerative disease as modulators of brain tissue inducing activity-dependent plasticity. Simple 40Hz external tone stimuli can trigger electrical brain activity in the gamma band, while improving the otherwise decreased gamma activity and mental capacities [17]. In preterm born children electroencephalogram (EEG) based oscillations have been reported to be altered in both the alpha, beta and potentially gamma bands [18]. Primary sensory stimuli are ideal stimuli for eliciting brain activity in the newborn, as auditory neural pathways develop early and become functional during the third trimester of pregnancy or early in life in high-risk infants. A mechanistic study in ferrets suggested that extrinsic auditory stimuli would be able to activate neurons in the transient subplate compartment which would influence the organization of the future auditory cortex [19]. The first question that arises is how to present these stimuli to high-risk newborns, as stimulating brain tissue in the newborn brain needs to be done non-invasively and taking into account the comfort of the newborn, his personal needs and health conditions.

2.2 A step beyond: adaptive personalized auditory care using biophysical and behavioral feedback

The general state and well-being of newborns (as of humans in general) has diverse measurable effects on their cognitive, nervous, cardiovascular and respiratory physiology, as well as behavior.

2.2.1 Continuous monitoring in the NICU

In recent years, long-term monitoring and automatic interpretation of vital parameters and behavior have also been substantially improved thanks to key advances in wearable monitoring technologies, and in data science based on artificial intelligence (AI). Optical sensors such as photoplethysmography (PPG) and motion sensors such as accelerometers, in particular, have now been successfully integrated in diverse compact wearable devices such as wristbands, armbands and smartwatches. Advances in signal processing and analysis have then made it possible to extract multiple physiological and activity parameters from these sensors in real-time: heart rate (HR), heart rate variability (HRV), respiratory rate (RR), oxygen saturation (SpO2) and even blood pressure (BP) from PPG [20]; postural changes, activity type and energy expenditure from motion sensors. Likewise, specifically for newborn infants, PPG has been found to provide excellent estimates of this type of cardiovascular and respiratory parameters, with the crucial additional benefit of being non-invasive and considerably less cumbersome than more traditional techniques such as electrocardiography (ECG) [21]. Wearable motion sensors (accelerometry) have also been successfully tested in premature infants in the NICU, with promising performance in the identification of cramped-synchronized general movements, for instance [22].

2.2.2 Sleep in neonates

Sleep is an important determinant of brain development in preterm infants. It is a major contributor in neural development as sleep-specific motor activity evokes somatotopic cortical activity. Sleep has been linked to improved memorization and to the consolidation of learning capacities as well as neural plasticity. On the contrary, the suppression of sleep behavioral patterns can impair cortical activity levels and synaptic plasticity. As such, the correct management of sleep-wake cycles (SWC) creates a component of self-regulatory competence [23]. Well-developed SWC are already present in healthy term-born infants immediately after birth. They are characterized by regular variations in the EEG bandwidth that show higher uncertainty in the case of preterm infants. Low REM behavior is found in groups of neonates with developmental delays and has been linked to behavioral problems and smaller cortical size in animal studies [24]. Identifying the different sleep stages in an univocal way, together with the adaptation of care procedures to these sleep stages, is of utmost importance for the later neurodevelopment of preterm infants.

Recent developments using deep-learning classifiers have shown that this task can be accomplished with relatively high accuracy based on recordings from single-channel EEG [25], which is considerably more comfortable and suitable for long-term recordings than high-channel density EEG.

2.2.3 Behavioral monitoring

Behavioral cues from facial expressions, crying, gaze and body movements are traditionally well known to represent specific states and needs, such as pain and hunger. Yet, continuous monitoring of infants' state is time consuming and adds a considerable burden to nurses' work. Video-based body motion monitoring is a promising tool, due to its non-contact and unobtrusive nature. With the cost of off-the-shelf digital video cameras continuously decreasing, methods to detect motion in neonates have been widely investigated in recent literature, with methods raging from background subtraction (BS), sparse optical flow (SOF), dense optical flow (DOF), and oriented FAST [1] and rotated BRIEF [2] (ORB). With the extensive research work that exists in the field of computational methods for video analysis that can be combined with physiological measures to determine the specific states and needs of the infants, such as pain and hunger, this represents an interesting approach for assessing preterm infant stress or well-being features.

2.3 Identifying infants' status: the well-being score

Allowing for the correct timing of the medical treatments and examinations as well as medical care such as changing diapers, cleaning, and bathing may help reduce the stress induced to the infants as well as the consolidation of the SWC. Neonatal care in the NICU generally relies on the nurses' appreciation and it is generally triggered by the system's alarms due to a critical situation of the infants (desaturation, bradycardia). Here, we propose to dynamically enrich the NICU environment using a soundscape based on infants' biofeedback through real-time feature estimation algorithms responses. The overall idea is to collapse all the information coming for physiological and behavioral monitoring in a single index able to provide real-time information for the "well-being status" of the infants. As such, we will develop algorithms for real-time estimation of relevant physiological parameters from the neonate based on non-obtrusive sensors (video, audio, PPG, low-density EEG), and then develop a model capable of combining these parameters to estimate a so-called "well-being score" (WBS). The physiological parameters of interest will include:

- Cardiovascular and respiratory parameters, including HR and HRV, RR and RRV. These will be estimated from the PPG sensor, employing a combination of algorithms previously developed for adults. These algorithms will be adapted for neonatal signals to account for their particular characteristics (e.g. substantially higher baseline HR).
- Motor activity, including the smoothness and frequency of movements and postural changes, tremors, startles, facial twitches and autonomic movements. These will be estimated from video acquired with a combination of thermal and RGB cameras (infrared cameras will also be considered if compliant to limited near-infrared radiation). Infants will be recorded from birth to discharge at 25 frames per second with MPEG-4 encoding.
- Sleep-wake state, based on characteristic patterns in low-density EEG and cues from motility patterns and cardiorespiratory fluctuations. The algorithm will be in line with well-accepted criteria for neonatal sleep staging, with further optimizations for use specifically with low-density EEG [25].
- Acoustic sensing: Crying and infant sounds such as hiccups, gagging, comfort/discomfort and the type of vocalization (cry-like vs. positive vocalization). Mechanical noise vs. voice

The well-being indicators of premature infants in the NICU

	Well-being (green light)	Stress (red light)
Physiological Level	Regular respirations and heart rate (no fluctuations above 15% of the mean values) Good healthy color No spontaneous tremors or startles No facial twitches or autonomic movements	Apnea episodes, or considerable tachypnea dusky color, or very pale or very "webbed" or flushed red color Tremors, hiccoughing, gagging, spitting up Facial twitches, eye rolling
Motor level	Smooth postural changes and adjustments	Flaccid posture Brief episodes of hyperextension and/or hyperflexion (sudden, abrupt changes and jerky adjustments) Very jerky movements with dramatic arm and leg extensions into midair (salute)
Infants' state	Regular breathing, relaxed facial expression; Eyes closed, no eye movements under closed lids, No spontaneous activity except isolated startles Solid sleep state slow EEG waves **Best state for interrupting environmental stimuli (sleep)** Alert with a bright shiny look. Motor activity at minimum **Best state for starting the interaction stimuli (awake)**	Intense crying, Intense grimace and cry face, yet, cry sound may be very strained or very weak or even absent

Figure 2. Well-being/stress indicators for premature infants in the NICU. Created with BioRender.com

2.4 Environmental acoustic modulation in the NICU

The monitoring of the well-being score as a function of the NICU environment being the key objective of the project, a particular emphasis is put on technical means to modulate acoustic stimulations. To that end, a dedicated sound rendering device will be deployed for such environmental acoustic modulation. The specifications of this instrument will be two-fold: In a first phase, an active noise control environment will be developed to allow reducing the impact of stressful external stimuli such as pumps, fans,

[1] FAST: Features from Accelerated Segments Test

[2] BRIEF: Binary Robust Independent Elementary Features

alarms, etc. The closed environment of the NICU is favorable to implement active sound absorption principles [26], that are extremely efficient at reducing emissions at low-frequencies, where most of these adverse noises occur. In combination with such standard active noise control techniques, active vibration techniques could be efficient at improving the glazing soundproofing performance, either employing state-of-the-art shaker-based active techniques [27]. The incubator environment can also be a playground for testing innovative membraneless solution such as the recently developed "plasmacoustic metalayer" in the bulk of the incubator's glazing [28].

In a second step, a sound rendering environment will be deployed using dedicated headphones, implementing binaural sound. For that, the individual HRTFs will be collected from MRI acquisitions [29]).

2.5 NICU environment enrichment

The integrity of brain development is based on an optimal interaction between "well-timed" environmental stimuli and endogenous brain activity. Hence, a meaningful auditory experience is essential for the brain maturation and may be a contributing factor to healthy neurodevelopment [30]. Parental vocalizations are also fundamental for preterm infant's development, and for the neuroendocrine regulation of social bonding in humans.

In an earlier music-only intervention, authors showed a beneficial effect of music on both structural and functional development of the preterm brain [7, 8]. Yet, a parental voice enriched soundscape should enhance the structural maturation of multisensory and emotional processing neural pathways including amygdala and orbitofrontal cortex, as vocal emotions are decoded using a subcortical route involving the amygdala [7]. Indeed, while it has been shown that extensive musical experience increases insula-based connectivity, significantly higher activation in the left posterior insula is seen in response to human voices when compared to artificial voices.

Here, we propose to dynamically enrich the NICU environment using a soundscape based on infants' biofeedback through real-time feature estimation algorithms responses (the WBS, SWC and the NICU noise levels). The soundscape exposure will be triggered by the psychological and behavioral cues (see section 2.3) and will also include vocal stimuli in a binaural set-up. The final goal of this combined soundscape enrichment and personalized audio-devices is to reduce NICU stressors and to help at establishing a well-developed sleep–wake cycle in the preterm infants.

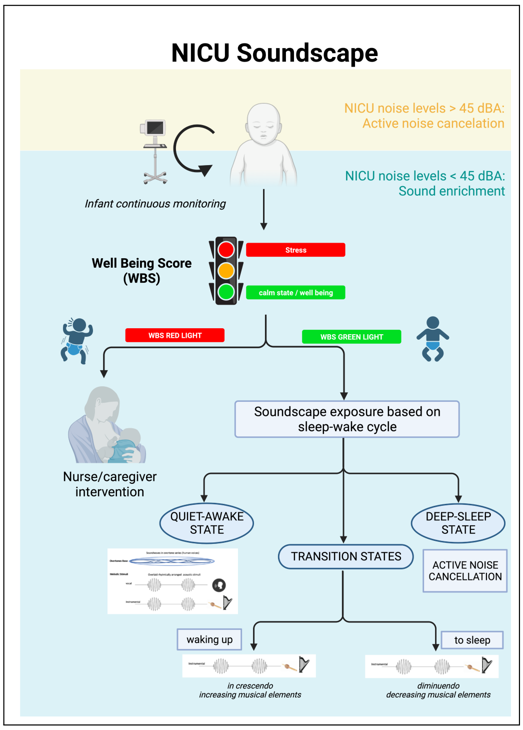

Figure 3. Proposed intervention pipeline. Image created with BioRender.com

Specifically, the personalized environmental enrichment will be triggered by the NICU noise level, the WBS and the SWC, following (but not being restricted to) specific behavioral and physiological cues (see Table 2 and Figure 3):

- If noise levels exceed the recommended maximum (45 dBA following the WHO guidelines) the active noise cancellation will be automatically activate. This sound cancellation will be total if the infants in deep sleep state but not in case that the infant is in quiet state (awake).
- The well-being score will mainly trigger the soundscape enrichment. If the infant is in green-light state WBS, we will enable the soundscape exposure. If in red WBS, we will try to modulate the infant's state (either by noise cancellation or soundscape exposure or a combination of both). A caregiver intervention will be requested. The action will be annotated to allow the automatic detection to learn.

- The sleep-wake-cycle will modulate the soundscape (which soundtrack will be played and for how long) and if noise cancellation will be performed. In summary:
  - If in deep-sleep state: To protect deep sleep, we will never use soundscape exposure but only active total noise cancellation.
  - If in a quiet-awake state: best moment for soundscape exposure, to allow infants interaction with the environment. The soundtrack will be harmonics based instrumental embedded with vocal sounds and if parents are available, we will encourage the skin-to-skin and kangaroo care as regularly performed in the NICU.
  - If the baby needs to sleep (detected by phase of SWC): trigger soundscape exposure aiming at helping him to sleep (lullaby-like) to avoid fuzziness and increased stress.
  - If the baby needs to wake up (transition from sleep to awake): trigger soundscape exposure to wake up smoothly.

3. FUTURE PERSPECTIVES

Neonatal intensive care neonatal units (NICUs) generally rely on standardized protocols with little, if existing, individual patient-driven intervention. Additionally, NICUs are an extremely noisy environment, providing a stressful background noise that represents a serious threat to newborn infants, having been shown to affect their neurological condition [3]. Moving towards personalized care, i.e. having the ability to identify patient-specific parameters from data that is both patient-specific and time-varying (the needs of a one-day-old infant are not the same after one week yet alone after one month), is key for better managing the individual needs of neonatal critical care patients and offset risk factors that may lead to developmental impairments. Our vision is to provide neonatal healthcare centers with a personalized environmental monitoring and modulation to NICU care, in order to personalize newborn critical care and reduce the environmental risk factors for developmental impairment.

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