Precision NICU Music Medicine: Paternal Complex-Stimulus Singing Surpasses Maternal Delivery in Boosting Developmental EEG Activity of Very-Preterm Infants

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Background

- Early music exposure modulates fetal autonomic regulation and neonatal neural plasticity (Massimello et al., 2022; Qiu et al., 2025).
- Music-Based Interventions' (MBI) improvement of premature infants HR, respiration, feeding, stress, and neurobehavioral outcomes show a dose-response effect (Santos et al., 2015; Yue et al., 2020; Shahbazi et al., 2025).
- NICU sensory ecology and prematurity risks highlight the need for structured, low-intensity MBI (Seassau et al., 2023).
- Electroencephalography (EEG) is a safe, non-invasive, feasible (≤1 h) measure of preterm infants' brain maturation (Anne & Malhotra, 2024; Pavlidis et al., 2025).
- qEEG and MBI integration enables precise analysis of spectral power, coherence, and kinship-linked voice effects (Papatzikis et al., 2024).

Methodology

Protocol Overview

- Participants: 14 infants (GA ≤ 32 weeks; EEG measurement PMA 35 weeks)
  - a priori power of 0.83 (α = 0.05; pre-study MESI =0.35)
- Duration: Four consecutive days, once per day
- Site: NICU room in Greek Hospital

Session Structure

- Silence1: 180 seconds
- Sustained Note A: 60 seconds
- Silence2: 180 seconds
- Study Lullaby: 90 seconds
- Silence3: 180 seconds

Facilitator Variation

- Music Facilitators (Mother, Father, Male Music Therapist, Female Music Therapist)
- Voice Characteristics (F0):
  - High Fundamental Frequency (Female)
  - Low Fundamental Frequency (Male)
- Kinship Level (close relationship and no relationship)

Electroencephalography (EEG)

- MatLab 2024a and EEGLab 2024.02
  - Custom preprocessing code
  - Adapted code by Toole & Boylan (2017)
- Data collection sampling rate: 512 Hz

Auxiliary Video Recording

- Parallel neural/behavioral observation
- Protocol consistency

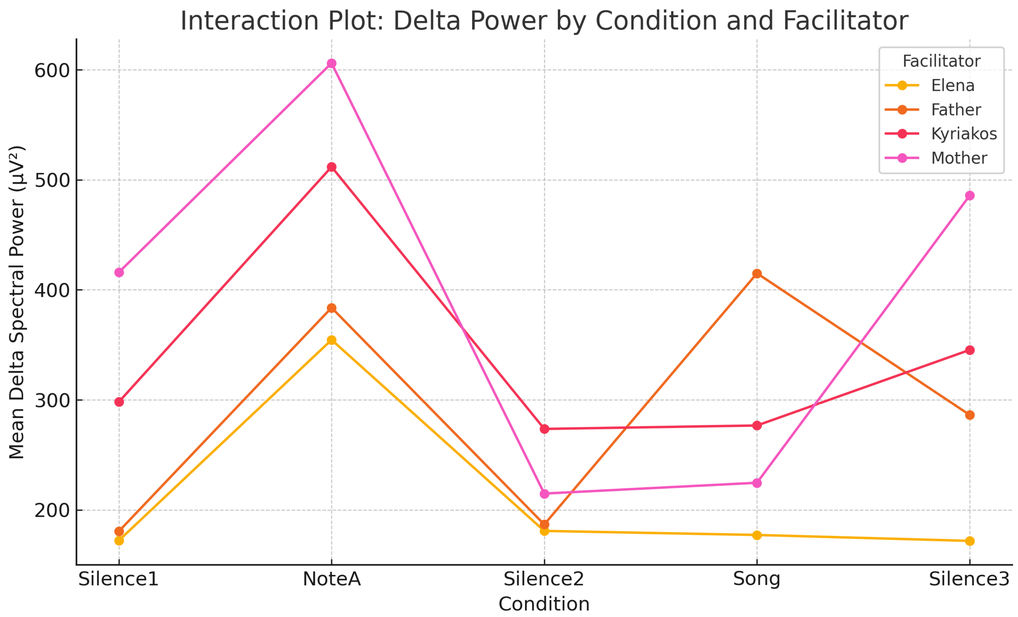
Statistical Analysis

- Primary outcome: mean delta spectral power (0.5–3 Hz) (well studied developmental index)
- Secondary outcome: delta spectral entropy (not reported here)
- Analysis: mixed-effects model

Ethics and Oversight

- Approved by IRB (see www.clinicaltrials.gov NCT06398912)

Results



Main Effects

- Condition significantly influenced delta-band power
  - ($\chi^2_{(4)}$ = 9.65, p = .047)
- Facilitator main effect was not significant
  - ($\chi^2_{(3)}$ = 5.79, p = .123)

Interaction Profile (Condition × Facilitator)

- Highest mean delta power (lullaby): paternal singing (415 ± 574 μV^2).
- **Contradicts the original hypothesis favoring maternal dominance.**
- Largest response for Note A: maternal singing (606 ± 1164 μV^2).

Sex-Based Comparison (Lullaby Condition)

- Male voices (low F0) vs Female voices (high F0):
  - higher delta power (Δ ≈ +142 μV^2; dz ≈ 0.46)
  - Wilcoxon test: V = 81, p = .039.

Variance Components

- Between-infant variance: 12 % (σ^2 = 26 517 μV^2)
  - Moderate inter-individual differences.

Hypothesis

- H1: We hypothesize that when premature newborns are exposed to a live singing intervention provided by their mother (high fundamental frequency – biological kinship) compared to the father (low fundamental frequency – biological kinship) or an unrelated male/female music therapist, they show statistically more visible short-term positive oscillatory differentiations in their brain activity.

Research Gap and Aim

- Earlier studies used uniform facilitators, merging maternal and non-kin voices.
- This study isolates kinship-specific singing, comparing high-F_0 mothers, low-F_0 fathers, and music therapists.
- Focuses on short-term cortical dynamics in very-preterm infants.

Benefits

- MBI for preterm infants may enhance brain maturation, mitigating neurodevelopmental delays.
- Male low F0 voices may enhance sensory integration.
- EEG monitoring as objective biomarkers for developmental progress during MBIs.

Future Clinical Applicability

- Personalized Medicine in the NICU.
- Broader Use of MBIs.
- Predictive Modeling and Longitudinal Studies

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References