The Effect of *MUSIC* in the Neonatal Brain

A neuroimaging investigation of Music structural effects in preterm infants' brain

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INTRODUCTION

Preterm birth disrupts normal brain maturation, exposing preterm infants to variate insults and depriving them from meaningful sensory inputs relevant for activity dependent plasticity during early brain development, being thus associated to long-term neurodevelopmental impairments.[1,2,3]

Music, as an extrinsic multisensory stimulus, was shown in adults to modulate neural networks that are known to be formed in early development and that can be affected by prematurity. These networks are relevant for later cognitive and socio-emotional functions and comprise: [4,5]

- Auditory cortex
- Temporal/frontal/parietal subcortical areas → Attention, Memory, Motor functions
- Limbic and paralimbic regions → Emotional processing

Amygdala, a primary structure of the limbic system, is reduced in volume in preterm infants[6] and has been shown to play a central role in emotion modulation during music processing.[7,8]

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging (MRI) technique that allows to study the microstructure of brain water matter (WM) fibers in vivo and thus access brain maturation.[9] It provides measures such as FA, describing the anisotropy of diffusion, and MD, reflecting the overall dispersion of diffusion. During brain maturation, FA has been shown to increase and MD to decrease. Diffusion measures indicative of WM injury have been proved to correlate with later motor, cognitive and socio-emotional impairments in preterm children.[10,11]

AIM

Study the impact of a music intervention on structural brain development of premature infants.

MATERIALS & METHODS

	Preterm		Term
GA (weeks)	$24^{0/7}$-$32^{6/7}$		$37^{0/7}$-$42^{6/7}$
Condition	Music	No Music	No music
N	15	15	15
	headphones	headphones	
	10' music 5x week	10' no noise suppression 5x week	
MRI	Term-equivalent age		Term

Table 1 – Study population was divided into three groups: preterm with music, preterm control without music and full-term newborns. An MRI brain image was performed at term or at term-equivalent age. GA, gestational age.

Music by Andreas Vollenweider
Volume <65 dBA

Figure 1 – Baby listening to the music with the headphones in the neonatal unit.

Region of interest (ROI) DTI analysis

- MRI data were acquired on a Siemens 3T scanner (Siemens, Erlangen, Germany). T2-weighted structural images were obtained prior to DTI. DTI was acquired in 30 non-collinear directions with a b-value of 1000 s/mm^2.
- DTI preprocessing and diffusion tensor reconstruction for each subject was done with FSL (FMRIB Software Library). FSL EDDY function adapted for neonatal data was used to address distortions caused by motion and eddy currents.[12,13]
- 20 regions of interest (ROI) were drawn manually in a specific study template, generated with DTI-TK and back transformed to each subject space in order to compute ROI-average estimates of DTI measures (FA, MD).[14,15]

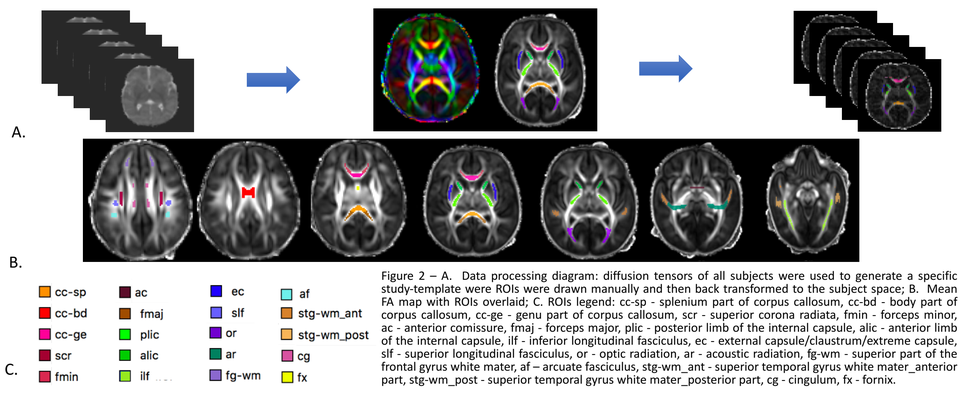
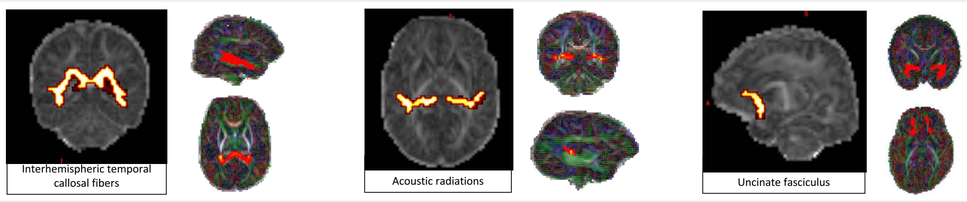


Figure 2 – A. Data processing diagram: diffusion tensors of all subjects were used to generate a specific study-template were ROIs were drawn manually and then back transformed to the subject space; B. Mean FA map with ROIs overlaid; C. ROIs legend: cc-sp - splenium part of corpus callosum, cc-bd - body part of corpus callosum, cc-ge - genu part of corpus callosum, scr - superior corona radiata, fmin - forceps minor, ac - anterior comissure, fmaj - forceps major, plic - posterior limb of the internal capsule, alic - anterior limb of the internal capsule, ilf - inferior longitudinal fasciculus, ec - external capsule/claustrum/extreme capsule, slf - superior longitudinal fasciculus, or - optic radiation, ar - acoustic radiation, fg-wm - superior part of the frontal gyrus white mater, af – arcuate fasciculus, stg-wm_ant - superior temporal gyrus white mater_anterior part, stg-wm_post - superior temporal gyrus white mater_posterior part, cg - cingulum, fx - fornix.

Tractography analysis

- FSL seed-based probabilistic tractography was performed using FSL Bedpostx and Probtrackx functions.
- Sets of "seed", "waypoint", "stop" and "exclusion" masks were defined for each tract in the subject diffusion space, where the probabilistic tractography was performed.
- The reconstructed tracts were: acoustic radiations, interhemispheric temporal callosal fibers and uncinate fasciculus



Amygdala Segmentation and Volumetric analysis

- Right and left amygdala segmentations were performed manually in each subject T2-weighted structural image, always by the same operator, using the manual contour editing function of a visualization software (ITK-snap).
- Segmentation was based on anatomical guidelines for the localization of amygdala, according to published literature and a neonatal atlas comprising a protocol for amygdala manual segmentation.[6,16] Segmentations were corrected by a neurosurgeon with expertise in neuroanatomy.
- Amygdala volumes were obtained using ITK-snap and corrected for intracranial cavity (ICC) volume, gestational age at MRI (GA-MRI) and sex for statistical analysis.

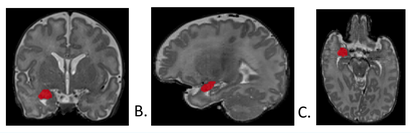
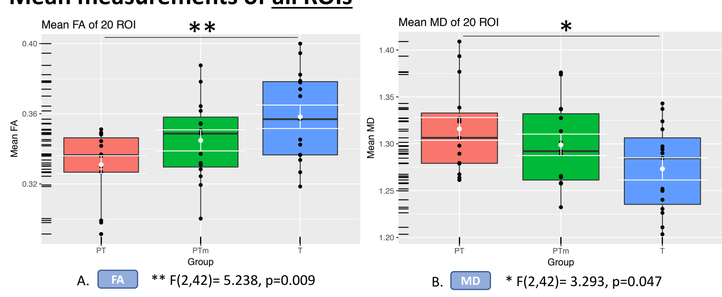


Figure 3 – Delineation of right amygdala on T2-weighted MRI using the ITK-snap software: (A) coronal view; (B) sagittal view; (C) axial view.

RESULTS

DTI measures in the selected ROIs

- **Mean measurements of all ROIs**



Preterm control at term age evidence a significantly lower **FA** and higher **MD** vs Full-term, while mean **FA** and **MD** values are not significantly different between Preterm Music vs Full-Term.

Figure 4 - Boxplot of mean DTI measurements with mean±SD (in white) computed of all selected ROIs, A. FA – Fractional Anisotropy, B. MD – Mean Diffusivity. Lines indicate significant differences between groups. One way ANCOVA with correction for GA-MRI was performed with Bonferroni post hoc test.

- **FA measurements per ROI**

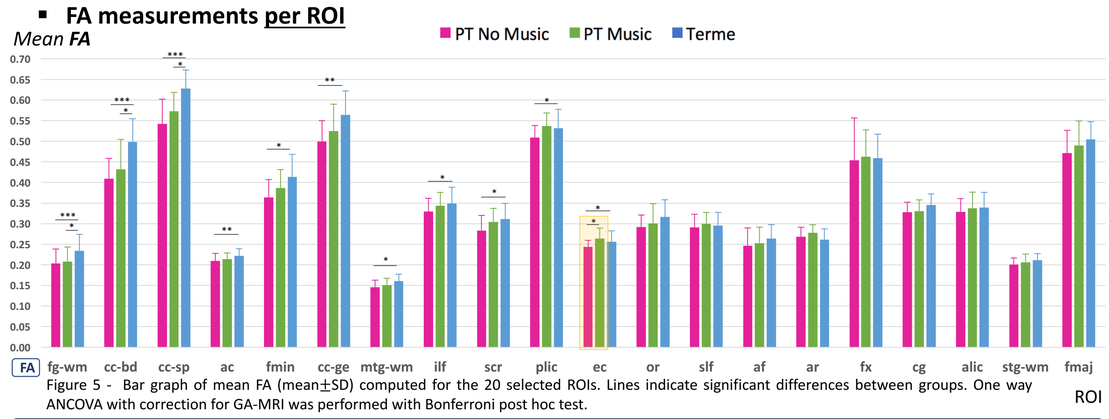
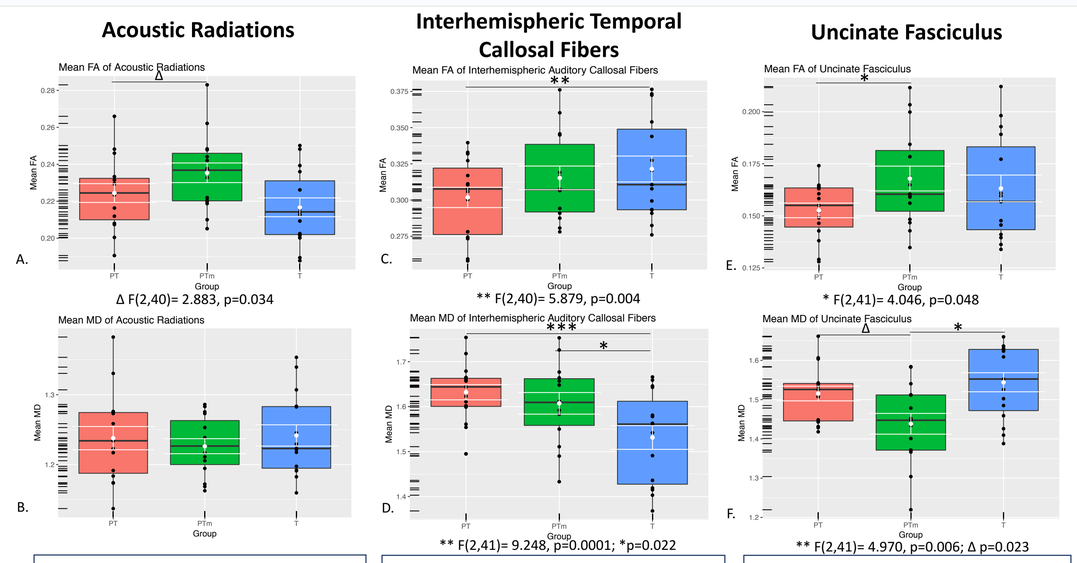


Figure 5 - Bar graph of mean FA (mean±SD) computed for the 20 selected ROIs. Lines indicate significant differences between groups. One way ANCOVA with correction for GA-MRI was performed with Bonferroni post hoc test.

Preterm control evidenced significantly lower **FA** vs Full-term in 11 of the 20 ROI. Preterm Music a significantly higher **FA** vs Preterm control at term age in "**ec**".

DTI Tractography analysis



Mean **FA** was higher in Preterm Music at term age vs Preterm control newborns.

Preterm control evidenced a significantly lower **FA** and higher **MD** vs Full-term newborns.

Mean **FA** was significantly higher in Preterm Music vs Preterm control at term age.

Figure 6 - Boxplot of mean FA and MD measurements with mean±SD (in white) computed per selected tract, FA (A) and MD (B) of Acoustic Radiations; FA (C) and MD (D) of Interhemispheric Temporal Callosal Fibers; FA (E) and MD (F) of Uncinate Fasciculus. Lines with "*" indicate significant differences between groups that survived One-way ANCOVA analysis with correction for GA-MRI and Bonferroni post hoc test, while lines with "Δ" indicate differences not surviving the multicomparison test correction.

Amygdala Volumetric Analysis

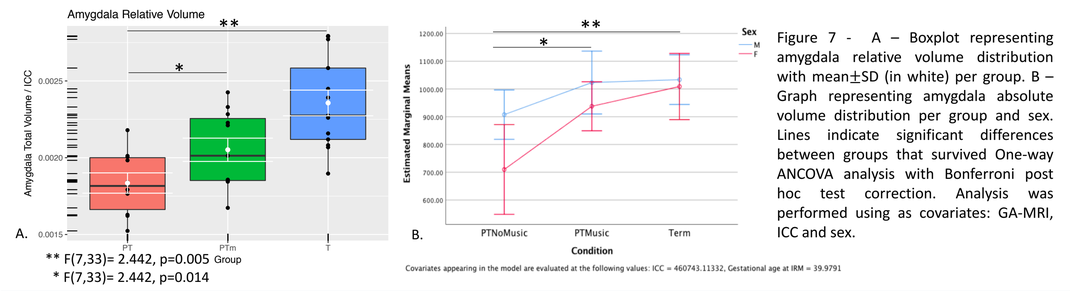


Figure 7 - A – Boxplot representing amygdala relative volume distribution with mean±SD (in white) per group. B – Graph representing amygdala absolute volume distribution per group and sex. Lines indicate significant differences between groups that survived One-way ANCOVA analysis with Bonferroni post hoc test correction. Analysis was performed using as covariates: GA-MRI, ICC and sex.

Covariates appearing in the model are evaluated at the following values: ICC = 460743.11332, Gestational age at IRM = 39.9791

Preterm control present a significantly lower amygdala volume vs Full-term, whereas Preterm Music a significantly higher amygdala volume vs Preterm control.

CONCLUSIONS

- Overall, **brain microstructural maturation** was **decreased** in **Preterm Control** at term vs **Full-term**:
  - . Significantly lower **FA** in the "average of 20 ROI" and namely in "fg-wm", "ac", "fminor", "cc-ge", "cc-bd", "cc-sp", "mtg-wm", "ilf", "scr", "plic" and "ec" ROIs in Preterm Control at term vs Full-term.
  - . Significantly lower **Amygdala volumes** in Preterm Control at term vs Full-term.
- **Preterm exposed to Music** when at term :
  - . **FA** values not different from Full-term in the "average of 20 ROI" and "Interhemispheric temporal callosal fibers".
  - . Significantly higher **FA** in "ec" ROI, Acoustic Radiations and Uncinate Fasciculus vs Preterm Control.
  - . Significantly higher **Amygdala volumes** vs Preterm Control.

Music ❯

- Improves **WM maturation**, namely in **Emotional processing** neural pathways
- Non-invasive early postnatal neuroenhancement intervention to preterm infants during NICU stay.

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