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Music processing in preterm and full-term newborns: A psychophysiological interaction (PPI) approach in neonatal fMRI

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ABSTRACT

Neonatal Intensive Care Units (NICU) provide special equipment designed to give life support for the increasing number of prematurely born infants and assure their survival. More recently NICU's strive to include developmentally oriented care and modulate sensory input for preterm infants. Music, among other sensory stimuli, has been introduced into NICUs, but without knowledge on the basic music processing in the brain of preterm infants. In this study, we explored the cortico-subcortical music processing of different types of 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. Additionally, we investigated if early exposure during NICU stay modulates brain processing of music in preterm infants at term equivalent age. We approached these two questions using Psychophysiological Interaction (PPI) analyses. A group of preterm infants listened to music (Original music) starting from 33 weeks postconceptional age until term equivalent age and were compared to two additional groups without music intervention; preterm infants and full-term newborns. 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. Increased connectivity between auditory cortices and thalamus and dorsal striatum 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 previously listened music induces a more arousing and pleasant state. Our results suggest that music exposure in NICU's environment can induce brain functional connectivity changes that are associated with music processing.

Introduction

Music is the art of combining and organizing sounds to obtain a harmonious combination of frequencies and thus, a pleasant melody, which positively influences physiological and behavioral states (e.g. Panteleeva et al., 2017). Music listening involves auditory, cognitive, motor, and emotional functions across cortical and subcortical brain regions (Koelsch, 2014). Thus, music listening, because of its beneficial effects, has been used in post-stroke rehabilitation and in patients with aging related neurological disorders (Johansson, 2011; Särkämö et al., 2014; Särkämö, 2017). In adult intensive care units, music listening has been shown to have an impact on anxiety states, physiological indices,

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and sleep duration of critically ill patients (Hu et al., 2015; Lee et al., 2017). Therefore, there has been an increased interest in introducing music interventions in neonatal intensive care units (NICU). A number of authors have considered the effects of music listening in preterm infants and many have shown stabilizing effects on heart and respiratory rates, reduction of apnea or bradycardia, improved resting energy expenditure, improved feeding, better weight gain and more mature sleep patterns; and most of them report a beneficial effect on at least one of these outcomes (Haslbeck, 2012; Filippa et al., 2017; Pineda et al., 2016; Anderson and Patel, 2018). Nevertheless, these music interventions have been proposed for enhancing neonatal intensive care environments without knowing the preterm brains ability to process music. Perani et al. (2010) using functional magnetic resonance imaging (fMRI) observed a differential processing of altered (music acoustic structure alteration: dissonance; and music-syntactic structure modification: key shift) *versus* consonant music in full-term newborns. Furthermore, a right lateralized auditory cortex activity in response to consonant music was observed in these newborns. In contrast, two other studies performed in few days old newborns, one using fMRI (Dehaene-Lambertz et al., 2010) and one using near-infrared spectroscopy (Kotilahti et al., 2010), showed no lateralization during music processing in newborns and mainly primary auditory cortex activation.

The ability to process music may therefore already be present in full-term newborns either be innate or learned by sound and tissue vibrations exposure in the womb, which may provide experience for the fundamental temporal organization of music elements; i.e., detection of regular patterns as is present in rhythm and meter (mothers' heart and respiratory sounds) and pitch and melody (mothers' voice) (Teie, 2016).

The ability to mirror musical tempo by rhythmic movements has been shown in infants between 5 and 24 month of age (Zentner and Eerola, 2010). Similarly, listening to a 15% tempo change, faster or slower than spontaneous non-nutritive sucking tempo has been found to slow down sucking tempo in newborns and two month-old infants (Bobin-Bègue et al., 2006). In addition, a number of authors reported an ability of two to six months old infants to remember a tempo and perceive tempo modifications using a head-turn paradigm (Baruch and Drake, 1997; Trainor et al., 2004; Trehub and Hannon, 2009). Thus, these early behavioral responses speak for an ability to detect rhythm and tempo and violation of these temporal patterns have been detected by electroencephalogram studies in two month-old infants (Otte et al., 2013) and in newborns (Háden et al., 2015). Recently, using magnetoencephalography in 9-month-old infants, Zhao and Kuhl (2016) showed that a music intervention in a social environment for one month (12 sessions of 15 min) increased mismatch responses in auditory and prefrontal cortical regions to temporal violation in music and speech. Thus, the authors suggested that repeated music intervention might modify not only music processing abilities, but also speech processing.

In addition to tempo and rhythm, pitch cues are key elements for music processing. Using a head-turn preference testing Plantinga and Trainor (2005) observed no difference in 6 month-old infants responses to a familiar music and the same melody transposed (absolute pitch modification). This absence of preference suggested either that infants did not process the absolute pitch of the music or that they remembered the melody, but not the absolute pitch of it. Opposing to this, another study from Volkova et al. (2006) using a similar behavioral assessment showed a preference for transposed music in 7 month-old infants after 14 days of exposure, assuming a processing of and a memory for absolute pitch. These divergent findings between the two studies could be explained by a longer exposure in the latter or by differences of the age of the participants.

Lastly, even exposure to music during fetal life (during the 35th 36th and 37th weeks of gestation) was shown to reduce heart rate in the newborn when listening to the music, played to the fetus antenatally, one month after birth. Authors suggested that this cardiac response may be linked to memory for the melody heard during the last weeks of pregnancy (Granier-Deferre et al., 2011). Furthermore, full-term newborns that have been exposed to a specific melody during the last weeks of pregnancy presented larger brain event-related responses when hearing the known music than newborns without music intervention (Partanen et al., 2013b). Also, middle-syllable raise of pitch (relative pitch modification) within pseudo-words of three syllables (e.g. [tatata]) elicited larger mismatch response amplitudes in newborns with fetal exposure to these pseudo words than in newborns without fetal exposure (Partanen et al., 2013a). Furthermore, mismatch responses for alteration of the middle-syllable duration of the pseudo word were also observed. Thus fetal exposure to music or pseudo words seems to induce learning for the processing of some features of words and music such as relative pitch processing and duration of the stimuli.

However, for preterm infants, sound exposure is different and exposure to voices, noise and potentially music happens earlier and non-attenuated by surrounding fluid. Brain networks implicated in processing and remembering tempo and in the processing of absolute pitch in newborns remain to be explored, as well as the effect of music exposure during NICU stay on this processing.

How music introduction to preterm infants contributes to cortical processing of the listened music is an important question to ask, before promoting enrichment of the neonatal environment by music.

We hypothesize that prematurely born newborns have existing music processing abilities that could be enhanced by enrichment of NICUs' environment with repetitive music listening. To test for this hypothesis, we have used functional MRI to observe tempo and absolute pitch processing in full-term newborns at birth and preterm newborns with or without early music intervention at term equivalent age (TEA) using an effective connectivity approach; i.e., a psychophysiological interaction (PPI) analysis.

Materials and methods

Participants

Preterm and full-term newborns were recruited from the University Hospital of Geneva neonatal units. Ethical review board approval of the study and parental informed consent was obtained for each newborn prior to participation in the study. 35 preterm infants (GA at birth <32 weeks) were randomized to either music intervention or control condition (without music). The Preterm-Music group consisted of eighteen preterm newborns who were exposed to music with closed headphones (isolating from noise) during the hospitalization in the NICU. The Preterm-Control group consisted of seventeen preterm newborns, who had open headphones (which do not isolate babies from noise around them) without music five times per week during the hospitalization. At term equivalent age all preterm infants underwent magnetic resonance imaging including a fMRI music exposure paradigm. The Full-term group consisted of twenty-one full-term newborns scanned in the first days of life with the same fMRI music paradigm protocol. Few infants were excluded from further analysis because of major brain lesions or large-scale movement on MR-Imaging. Infants with no auditory cortex activation to sound were also excluded (see 2.4 Image Processing). The final sample of infants used for further analysis was as follow: 9 Preterm-Music (4 females/5males, mean GA at birth: 28.70 ± 2.46 weeks, mean GA at MRI: 40.25 ± 0.51 weeks), 9 Preterm-Control (5 females/4 males, mean GA at birth: 28.7 ± 2.01 weeks, mean GA at MRI: 40.4 ± 0.77 weeks) and 9 Full-term infants (4 females/5males, mean GA at birth: 39.32 ± 1.03 weeks, mean GA at MRI: 39.63 ± 1.02 weeks). No significant difference between the Preterm-Music and the Preterm-Control groups was found in demographic and perinatal variables: gestational age at birth; weight, height and head circumference at birth; gender; neonatal asphyxia; bronco-pulmonary dysplasia; intraventricular hemorrhages grade 1 and 2; sepsis (positive blood culture); mean number of music/no-music intervention; gestational age at MRI and socio-economic parental status (Largo et al., 1989) (*see* Appendix A.).

Music intervention

Infants were randomly assigned to either the Preterm-Music or the Preterm-Control group. Parents, music intervention providers and caregivers were blind to group assignment.

The Music group listened to 8 min of a music especially created by Andreas Vollenweider (http://vollenweider.com/en), composed of a background, bells, harp and punji (charming snake flute), five times per weeks, from 33 weeks gestational age until TEA. This music was chosen based on behavioral and physiological responses of preterm newborns to the instruments (for more details see Appendix B.). The music was either presented on B (4 infants) or Eb key (5 infants).

Preterm-Control group followed the exact same protocol but had headphones placed without music. Preterm-Music infants listened to music about 5 times per week (mean: 4.96 ± 1.54) and Preterm-Control infants had the headphones put on without music at the same frequency (mean: 4.91 ± 2.60).

MRI acquisition

All infants received breast or formula feeding before the MRI and were swaddled in a blanket and set up in a vacuum pillow for immobilization. No sedation was used; infants were scanned while resting quietly in the scanner or sleeping. Infants were monitored (heart rate and oxygen saturation) during imaging. To protect infants from the noise of the scanner and to deliver the music, MR-compatible headphones were used (MR confon, Magdeburg, Germany).

A Siemens 3 T scanner (Siemens Trio: 11 out of 18 Preterm-Music, 9/17 Preterm-Control, 15/21 Full-term infants and Siemens Prisma) was used to acquire T2*-weighted gradient-echo EPI images (260 images, TR = 1600 ms, TE = 30 ms, 30 slices, voxel size = $2.5 \times 2.5 \times 3.0$ mm^3, flip angle = 90°, Matrix size 64×52) as well as T2-weighted structural image for anatomical reference (113 coronal slices, TR = 4990 ms, TE = 151 ms, flip angle = 150°, Matrix size = 256×164; voxel size = $0.78 \times 0.78 \times 1.2$ mm^3).

During the EPI sequence, music stimuli were presented in a pseudo-random block design protocol of 5 conditions: Silence, Original music, Tempo music, Transposed music and Background music. Each block lasted 8 s and each condition was repeated ten times. Original music stimuli consisted of 10 different extracts, lasting 8 s, of the music heard during NICU stay (known music). All contained background music as well as at least one of the instruments (bells, harp and/or punji) and all instruments were represented in the 10 extracts. Tempo music stimuli were composed of these same extracts played 40% faster, and transposed music were the same extracts but transposed on a different key (B/Eb).

Image processing

Functional MRI sequences were preprocessed and analyzed using Statistical Parametric Mapping software SPM8 [Wellcome Department of Imaging Neuroscience, London (www.fil.ion.ucl.ac.uk/spm/software/spm8/)], including: (i) realignment; (ii) slice-timing; (iii) rigid body coregistration with the T2 structural image; (iv) normalization of the T2 structural image (1×1x1mm^3) and the EPI (2×2x2mm^3) using a newborn template (N = 20 term and preterm at TEA newborns); and (v) smoothing with a Gaussian kernel of 6-mm full-width at half-maximum. To correct for motion, 24 motion-related parameters (the 6 realignment parameters and their Volterra expansion) (Friston et al., 1996) were reduced into 6 components using Singular Value Decomposition (SVD) and included in the model as covariates to remove any residual motion-related variance. First, infants with brain lesions were excluded. Next, only infants with absolute motion (framewise displacement) under 1 mm for more than 180 consecutive images (70% of the total run) were used for subsequent analyses. Finally, all subsequent analyses were performed only on infants showing activations induced by the overall sound > silence contrast, at $p < 0.05$ uncorrected in auditory regions. The final number of infants per group was 9.

Data analysis

In order to define the long-range connectivity during music processing a PPI analysis was used to determine which voxels in the brain alter their relationship (connectivity) with a seed region of interest (the auditory cortex) in a given context, such as during music listening. After defining the contrasts of interest (e.g., *Original versus Tempo Modification* music and *Original versus Transposed* (key modification) music), BOLD signals were extracted from each seed region of interest (Left and Right Primary Auditory cortex, anatomically defined) for each participant (see Fig. 1).

These BOLD signals were used for putting together the PPI design matrix that contains the seed region's time course, the task time course, and the interaction term. The latter is the element-by-element product of the seed time course (physiological variable) with the task time course (psychological variable), which is a vector coding for a specific task (e.g. *Original music vs Tempo*), convolved with the HRF.

Next, two standard psychophysiological (PPI) analyses were carried out (one for each seed region, respectively) for each subject using the Generalized PPI toolbox that also supports standard PPI analysis (McLaren et al., 2012), in order to detect task-specific changes in the relationship between the seed regions and different brain areas (Friston et al., 1997). A task-specific increase in the relationship between brain regions suggests an increase in the exchange of information.

Subject-specific contrast images using the contrast (0 1 0), where the second column in the design matrix represented the psychophysiological interaction (PPI) term, were then entered into second-level analyses to identify clusters of voxels for which the PPI effect was significantly present.

In more detail, two sample t-tests, one for each seed region (right and left primary auditory cortex anatomically defined), were performed for each pair of groups (*Preterm-Music versus Preterm-Control, Preterm-Music versus Full-Term and Preterm-Control versus Full-Term*).

Multiple comparisons correction at cluster level

For corrections of multiple testing at 0.05 FWE of each statistical map, the individual voxel threshold was set at $p < 0.005$ and the corresponding threshold of cluster size was set based on the Random Field Theory (RFT).

RFT corrections attempt to control the FWE rate by assuming that the data follow certain specified patterns of spatial variance so that the distributions of statistics mimic a smoothly varying random field. RFT corrections work by calculating the smoothness of the data in a given statistic image and estimating how unlikely it is that cluster with particular statistic levels would appear by chance in data of that local smoothness. Finally, RFT methods are computationally extremely

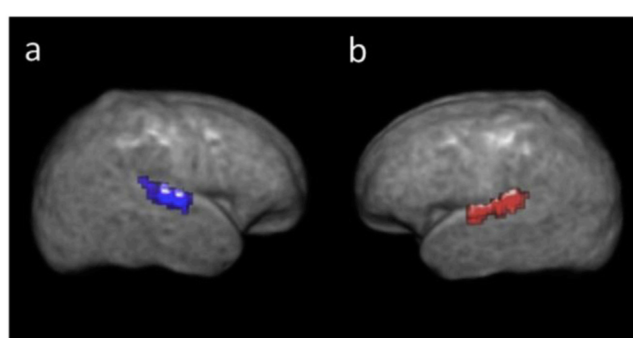

Fig. 1. Seeds (regions of interest) anatomically defined on T2 template: (a) Right and (b) Left Primary Auditory Cortex.

efficient and offered by SPM.

In more detail, the corresponding thresholds defined by the RFT corrections were: FWEc: 171 for the one-sample *t*-test and FWEc: 257, FWEc: 207 and FWEc: 474 for Music vs Non-music group for right primary auditory cortex (A1), Music vs Full-Term group for left A1 and Music vs Full-Term group for right A1, respectively. Therefore, all the identified clusters were significant at cluster level with $p < 0.05$ FWE (for more details see Appendix C.).

Results

The present results explore the effective connectivity of the primary auditory cortex (seed regions) with the entire newborn brain; i.e., how is connectivity modulated by music processing studied by different types of musical conditions (Original music, Tempo modification, Key modulation, Background music, see below) in preterm infants at term equivalent age and full-term infants.

A group of preterm infants had listened to the Original music for several weeks during their NICU stay prior to term age and another group of preterm infants received a caregiver blinded intervention with headphones but without music.

Brain network based music processing as a function of music exposure: We examined between-group differences across the following experimental conditions: Original-music, Tempo-Modification music (same melody played 40% faster) and Transposed-music (same melody key transposed: B/Eb).

Original music versus Tempo-Modification

A stronger connectivity between the right primary auditory cortex and right thalamus ($p < 0.009$ FWE at cluster level), left middle cingulate cortex (MCC) ($p < 0.01$ FWE at cluster level) as well as with the left caudate nucleus ($p < 0.01$ FWE at cluster level) was observed during *Original* > *Tempo modified* music condition for the Preterm-Music group compared to the Preterm-Control group.

When comparing the Preterm-Music group to the Full-term group, during the Original > Tempo-Modification condition, the connectivity between the left primary auditory cortex region and the left superior temporal gyrus (STG) ($p < 0.03$ FWE at cluster level) and the left MCC ($p < 0.01$ FWE at cluster level) was stronger for the Preterm-Music group. In the same way, the connectivity between the right primary auditory cortex and left MCC and putamen ($p < 0.001$ FWE at cluster level) was increased (See Fig. 2) for the Preterm Music-group.

To further explore this stronger connectivity when listening to the Original music compared to the Tempo modified music condition, we explored the PPI data for each group separately. We found significant PPI effects (*Original* > *Tempo-Modification* condition) for the Preterm-Music, but not for the Preterm-Control and Full-term infants. In more detail, during the *Original* > *Tempo-modified* condition, the connectivity between the left primary auditory cortex and left MCC ($p < 0.007$ FWE at cluster level), right caudate nucleus and putamen ($p < 0.01$ FWE at cluster level) was increased in Preterm-Music group (See Fig. 3). A similar trend was observed between the right auditory cortex and left MCC, right caudate nucleus and putamen but failed to pass the statistical significance test based on the corrected p-values ($p = 0.275$ FWE) (See Fig. 3.).

The connectivity between the primary auditory cortices and the rest of the brain for the *Tempo-Modification* > *Original music* conditions was not increased in any comparison (e.g., Preterm-Music compared to Preterm-Control or to Full-term). Furthermore, Preterm-Control and Full-term groups did not show increased connectivity between the primary auditory cortices and the rest of the brain in any condition when compared to the Preterm-Music group.

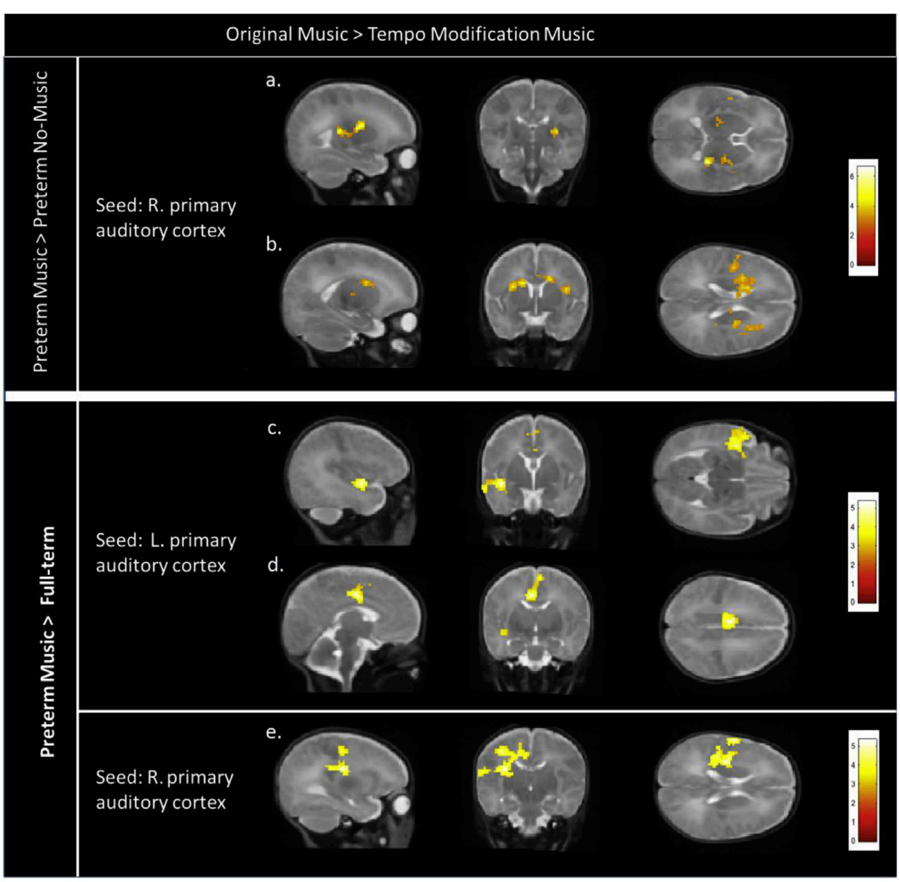

Fig. 2. Each row shows in a sagittal, coronal, and axial plane, results of the PPI analysis for Original > Tempo-Modification conditions ($p < 0.05$ FWE at cluster level): **(a–b)** Enhanced connectivity in Preterm-Music compared to Preterm-Control group between right primary auditory cortex (seed) and (a) the right thalamus and (b) the left caudate nucleus and middle cingulate cortex (MCC; $p < 0.01$ FWE at cluster level). **(c–d)** Enhanced connectivity in Preterm-Music compared to Full-Term group between left primary auditory cortex (seed) and (c) the left superior temporal gyrus and (d) the MCC. (**e**) Enhanced connectivity in Preterm-Music compared to Full-Term group between right primary auditory cortex (seed) and (e) the left MCC cortex and left putamen.

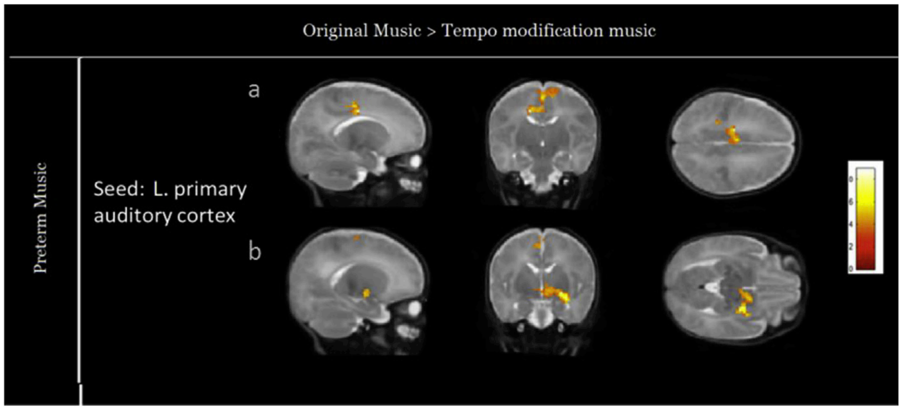

Fig. 3. PPI results for Original > Tempo-Modification conditions ($p < 0.05$ FWE at cluster level): enhanced connectivity in Preterm-Music infant between left primary auditory cortex (seed) and (a) the left MCC and (b) the right caudate nucleus and putamen. No significant activations were found for Preterm-Control and Full-Term groups.

Original music versus key-transposition (absolute pitch)

Finally, we compared the connectivity between left and right primary auditory cortex and the rest of the newborn brain during *Original versus Key-Transposed* music conditions. In this case, no difference was found in any group (one sample *t*-test) and no difference was found between groups (two-sample *t*-test).

Background music versus silence

We did not observe any difference between background condition and silence condition. We suppose that this absence of difference may be linked to the lower sound level of the background stimuli and that babies did not hear the background stimuli due to the high noise level in the MRI. The background only results are thus not presented in a figure.

Discussion

The aim of the current study was to explore cortico-subcortical music processing in the newborn and assess if early music exposure during NICU stay modulates brain processing of music in preterm infants at term equivalent age so that they can recognize the melody, differentiate its tempo and its absolute pitch at term equivalent age.

We hypothesized that music intervention would change effective connectivity between primary auditory cortex and brain regions implicated in music temporal processing (e.g. basal ganglia) when listening to known or Tempo modified music (*Original versus Tempo-Modification*). Thus, we used music played 40% faster (Tempo-Modification music) meaning we modified its tempo, but not the melody. Preterm-Control and Full-term infants (both groups without previous music exposure) did not modify connectivity of their auditory cortices for either Original or Tempo-Modification conditions. It has previously been observed by EEG recordings that full-term newborns may detect sudden rhythm change (Winkler et al., 2009) and modification of temporal relations within a train of sounds (Háden et al., 2015). Nevertheless, in our study the entire stimulus was presented faster meaning there is no violation or temporal difference within the music piece. Thus, this absence of difference in processing between the two tempi in our two control groups may be explained by the fact that they processed the unknown musical structure independently of the different tempi because they were not exposed to previous specific tempo.

In contrast the Preterm-Music group, showed stronger connectivity between the left primary auditory cortex and right dorsal striatum (caudate nucleus and putamen) during Original music (compared to Tempo-modification) (Fig. 3 b.). Furthermore, between group comparisons indicated a higher connectivity in Preterm-Music newborns between right primary auditory cortex and left caudate nucleus (Preterm-Music > Preterm-Control; Fig. 2 b.) and between primary auditory cortices and left putamen and superior temporal gyrus (Preterm-Music > Full-term; Fig. 2 ***c. & e.***) when listening to Original music (compared to Tempo-modification). These findings are in line with an important corpus of literature about the role of the basal ganglia and its connectivity with cortical areas in temporal structure processing (for a review see: Péron et al., 2013), an enhanced functional connectivity between putamen and superior temporal gyrus observed in adults during perception of beat rhythms compared to non-beat rhythms (Grahn and Rowe, 2009) and brain lesions in the striatum having been found to impair tempo detection (Schwartze et al., 2011). Taken all together, our results indicate that Preterm-Music infants, unlike Preterm-Control and Full-term newborns, processed the Original music differently from the Tempo-modified music, and that specific cortical and subcortical networks are involved in the detection of tempo variation at early age. However, increased activity was seen only for the Original music (compared to Tempo-Modification) and not for Tempo modification music (compared to Original). Thus, the increased functional connectivity observed during Original music compared to Tempo-modification music in preterm infants with the music intervention might reflect either an increased cortico-subcortical processing of known temporal features or to specific tempo recognition. These findings can also be interpreted in the context of the infants' abilities to extract regularities during specific dynamic pattern exposures (here music) creating thus a kind of early perceptual habit as defined by Graybiel (2008). Furthermore, extensive research has shown that noise levels in NICUs are often higher than general recommendations (White et al., 2013; Lahav, 2015) This loud noise has a negative effect on the stability of the cardio-respiratory system, behavior and sleep of the preterm infants (Aly and Ahmed, 2016; Joshi and Tada, 2017) and is presumed to have long lasting effects in preterm infants language and behavioral development (Lahav and Skoe, 2014). Our results support the view that preterm infants can learn from their auditory environment and that preterm infants could have memory also for auditory dis-stimulation and thus warrant for ambient noise reduction in NICU.

By comparing connectivity between primary auditory cortices and the rest of the brain during *Original versus Key-Transposed* music conditions we have tested if (ii) music intervention can increase functional connectivity between primary auditory cortex and regions implicated in absolute pitch processing. We did not find differences in connectivity within or between groups. Prior studies using ERP's reported that pitch processing is already present in full-term newborns (Haden et al., 2009), and that newborn process differently music with key shifts inside the music piece (Perani et al., 2010). However, in these previous studies, key modulations were presented either as deviant or as alteration of the melody. In contrast, in our study, the entire music excerpt was transposed to a different key and melody was preserved. Thus, Preterm-Control and Full-term infants process equally both Original and Key-Transposed music conditions, which might be due to preserved melody.

Lastly, preterm newborns with music intervention did not show any difference in Original and Key-Transposed music processing either. Therefore, our findings suggest that music exposure did not enhance cortical processing of absolute pitch. However, the lack of difference in cortical processing in Preterm-Music group could also be explained by a learning of the melody (relative pitch information) they heard during music intervention independently of absolute pitch information. In line with this finding, Plantinga and Trainor (2005) showed that key transposition do not affect melody recognition in 6 month-old infants.

A final question that can be addressed is to what extent music processing presents familiarity concerning memory for listened music. As mentioned before, increased functional connectivity was found in favor of the Preterm-Music infants at group level (one sample *t*-test) when listening to known tempo (*Original* > *Tempo-Modification*) (Fig. 3 ***a. & b.***). Similarly, higher connectivity was found at second level analysis (two-sample t-tests) in Preterm-Music compared to either Preterm-Control (Fig. 2 ***a. & b. and*** Fig. 2 ***d. & e.***) or Full-term (Fig. 2 ***d. & e.***) when listening to Original music (compared to Tempo-modification). However, no difference of connectivity between the primary auditory cortices and the rest of the brain was observed under the *Tempo-Modification-Music* > *Original music* condition in the Preterm-Music group (compared either to Preterm-Control or to Full-term groups), suggesting that this effect does not rely on simple tempo detection ability but rather on memory for the tempo. Putamen and thalamus have been shown to be activated more for familiar than for unfamiliar music (Pereira et al., 2011). Moreover, dorsal striatum has been shown to activate more for beat prediction than beat detection (Grahn and Rowe, 2013). Thus, our findings are in line with previously published work in adults showing higher activity in putamen when listening to the known beat than to a new beat. Thus, putamen activity may be dependent on the familiarity of the perceived rhythm. In our study, faster tempo music activated the dorsal striatum less than the original music, indicating that Tempo-Modification rhythm may be perceived as less familiar by the Preterm-music infants. Also, activation of MCC and superior temporal areas for familiar music has been shown to be dependent on musical expertise (Groussard et al., 2010). It can thus be suggested that preterm-infants probably acquired specific tempo processing expertise during these weeks of music exposure. Furthermore, it is known that familiar music is perceived as more pleasant (Schellenberg et al., 2008). In adults, thalamus activity correlates to chills intensity when listening to pleasurable music (Blood and Zatorre, 2001). It has further been shown that consonant (Trost et al., 2014), pleasant (Koelsch and Skouras, 2014) and emotional arousing music (Trost et al., 2011) activates dorsal striatum. Thus, increased connectivity between auditory cortices and thalamus and dorsal striatum in Preterm-Music infants 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 this specific known music tempo induces a more arousing and pleasant state.

Conclusion and future implications

In conclusion, this study addresses important basic questions of music processing in preterm and full-term newborns relevant for designing music interventions for NICU patients. The study shows that music can have lasting learning effects on music processing with an increased effective connectivity between primary auditory cortex and brain regions implicated in tempo, familiarity and pleasant music processing. One can argue that, based on our results, preterm newborns are able to implicitly recognize a known musical temporal structure at a specific tempo and that listening to this known music evokes brain modulations of regions known to be involved in perceptual habits and related emotional aspects. Our findings bring new insights for supporting music exposure to preterm infants in the NICU. Rhythm processing has further been shown to be especially important for language processing and recognition. Here, we showed that early postnatal music intervention increases neural responses related to tempo processing and recognition in music. This might be relevant for language processing and recognition later in life. Based on these results, it is interesting to mention that future musical interventions in NICU should target tempo and rhythms aspects rather than absolute pitch processing because the sensitivity of these kinds of information at this stage of development seem more important compared to the one related to absolute pitch processing. However, additional studies are also needed to explore if the increased connectivity between regions implicated in tempo processing and recognition have an impact on the processing of other stimuli such as speech and singing. Lastly, we hope that longitudinal follow-up of these infants might reveal the impact of early music exposure on neurodevelopmental outcome.

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Appendices

Appendix A

Table A1

Demographic and perinatal characteristics of the populations. Differences between preterm with and without a musical intervention were calculated using the Mann-Whitney test or the Fisher test. We observed no differences between age at scan between the 3 groups (ANOVA, p 0.11). Socioeconomic status (Largo et al., 1989) was assessed based on maternal education and paternal occupation (range, 2–12, with 2 the highest score).

	Full-term n = 9	Preterm music (PM) n = 9	Preterm control (PC) n = 9	PM *versus* PC *p value*
Gestational age at birth, weeks, mean (SD)		28.70 (±2.5)	28.70 (±2.0)	0.79
Birth Weight, gram, mean (SD)	3324.4 (±366.1)	1151.7 (±329.62)	1051.1 (±265.5)	0.65
Small for gestational age, n (%)	0	1/9 (11%)	2/9 (22%)	1
Birth Height, centimeter, mean (SD)	49.33 (±1)	37.9 (±3.4)	35.8 (±2.7)	0.65
Birth head circonference (cm), mean (SD)	34.22 (±1.30)	27 (±3.1)	25.6 (±2.4)	0.28
Female, n (%)	4/9 (44.44%)	4/9 (44.44%)	5/9 (55.56%)	1
Neonatal asphyxia, n (%)	0	0	0	N.A

(*continued on next page*)

Table A1 (*continued*)

	Full-term n = 9	Preterm music (PM) n = 9	Preterm control (PC) n = 9	PM *versus* PC *p value*
Bronco-pulmonary dysplasia, n (%)	0	3/9 (33%)	4/9 (44%)	1
Intraventricular haemorrhages (grade 1–2), n (%)	0	2/9 (22%)	3/9 (33%)	1
Early and late onset sepsis, n (%)	0	2/9 (22%)	3/9 (33%)	1
Number of music/no-music intervention, mean (SD)	NA	25.2 (±9.8)	25.9 (±5.6)	0.75
Gestational age at scan, weeks, mean (SD)	39.63 (±1.02)	40.25 (±0.51)	40.40 (±0.77)	0.53
Socio-economic score (range 2–12), mean (SD)	4.88 (±2.87)	6.4 (±3.7)	4.9 (±2.5)	0.36

Appendix B

Behavioral response to the music was assessed by a nurse specialized in developmental care using a behavioral assessment tool (Martinet et al., 2013) on 12 preterm newborns between 33 and 37 weeks of gestational age. Also, cardiorespiratory response and oxygen saturation level were taken during 10 min before, during and 10 min after the music intervention. We observed increased oxygen saturation level during and after music listening and no other modification of the cardiorespiratory system. Furthermore, nurses specialized in developmental care observed the babies listening (or not) to music and did not notice any discomfort behavior. We thus concluded that this music was adapted to preterm newborns.

Table B1
Heart rate, respiratory rate and oxygen saturation level in 12 preterm infants listening to the music created by A. Vollenweider. Each infant listened one time to the music and physiological responses were registered during 10 min before, during music listening and 10 min after. We used paired *t*-test to assess cardio-respiratory and oxygen saturation level responses to music.

	Before Mean	During Mean	After Mean	Paired *t*-test Before *versus* During (p-value unco.)	Paired *t*-test Before *versus* After (p-value unco.)	Paired *t*-test During *versus* After (p-value unco.)
Heart rate (beats/min)	158.74	161.29	161.37	0.453	0.354	0.971
Respiratory rate (breaths/min)	48.94	49.86	48.29	0.723	0.806	0.431
Oxygen saturation level (%)	97.15	97.73	97.83	0.062	0.056	0.651

Appendix C

Table C1
Two sample *t*-test: Significant activations for Preterm-Music > Preterm-Control group comparison (seed: right primary auditory cortex).

Preterm-Music > Preterm-Control, Original-Music > Tempo modification, Seed: Right primary auditory cortex			
Region	Number of voxels	T value	P value (FWE)
R Thalamus	272	6.64	0.009
L Caudate and MCC	257	5.13	0.013

Table C2
Two sample *t*-test: Significant activations for Preterm-Music > Full-Term control group comparison (seed: left primary auditory cortex).

Preterm- Music > Full-Term control, Original Music > Tempo modification, Seed: Left primary auditory cortex			
Region	Number of voxels	T value	P value (FWE)
L STG	207	5.30	0.035
MCC	267	5.32	0.01

Table C3
Two sample *t*-test: Significant activations for Preterm-Music > Full-Term control group comparison (seed: right primary auditory cortex).

Preterm-Music > Full-Term control, Original Music > Tempo modification, seed: Right primary auditory cortex			
Region	Number of voxels	T value	P value (FWE)
MCC	474	4.94	0.001

Table C4
One sample *t*-test: Significant activations for Preterm-Music group at group level (seed: Left primary auditory cortex).

Preterm-Music, Original Music > Tempo modification, Seed: Left primary auditory cortex			
Region	Number of voxels	T value	P value (FWE)
MCC	208	8.92	0.007
R Caudate and Putamen	171	7.98	0.01

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