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Neural Correlates of Voice Perception in Newborns and the Influence of Preterm Birth

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Abstract

Maternal voice is a highly relevant stimulus for newborns. Adult voice processing occurs in specific brain regions. Voice-specific brain areas in newborns and the relevance of an early vocal exposure on these networks have not been defined. This study investigates voice perception in newborns and the impact of prematurity on the cerebral processes. Functional magnetic resonance imaging (fMRI) and high-density electroencephalography (EEG) were used to explore the brain responses to maternal and stranger female voices in full-term newborns and preterm infants at term-equivalent age (TEA). fMRI results and the EEG oddball paradigm showed enhanced processing for voices in preterms at TEA than in full-term infants. Preterm infants showed additional cortical regions involved in voice processing in fMRI and a late mismatch response for maternal voice, considered as a first trace of a recognition process based on memory representation. Full-term newborns showed increased cerebral activity to the stranger voice. Results from fMRI, oddball, and standard auditory EEG paradigms highlighted important change detection responses to novelty after birth. These findings suggest that the main components of the adult voice-processing networks emerge early in development. Moreover, an early postnatal exposure to voices in premature infants might enhance their capacity to process voices.

Key words: brain development, EEG, MRI, prematurity, voices

Introduction

The human voice is one of the most prominent sound stimuli in the auditory environment and conveys social cues of high importance, such as identity, affective, and speech information (Belin et al. 2004). Voice-selective brain regions were found in similar brain areas in adults along the upper bank of the superior temporal sulcus (STS) (Belin et al. 2000) and, in monkeys, in the superior temporal plane (Petkov et al. 2008; Perrodin et al. 2011). Other brain regions respond specifically to vocal sounds in humans and primates, such as the inferior prefrontal cortex (Fecteau et al. 2005; Romanski et al. 2005), the insular cortex (Remedios et al. 2009) and the amygdala to decode the affective quality of voice in human adults (Fecteau et al. 2007). Voice processing seems to be evolutionarily conserved; however, only

little is known regarding its functional cerebral network in newborns. A clear evidence of the fetus ability to process auditory stimuli at the cortical level has been demonstrated by functional magnetic resonance imaging (fMRI) experiment at 33 gestational weeks (GW) (Jardri et al. 2008). Using fetal fMRI in vivo, Jadri et al. have observed an activation of the auditory cortex of the temporal lobe in response to stimulation by pure tones. Postnatal electrophysiological studies could record cortical auditory evoked responses to pure tones as early as 24–25 GW (Graziani et al. 1968) and to syllables at 28–32 GW (Mahmoudzadeh et al. 2017).

Infants seem to be particularly sensitive to human voices. A few fMRI and NIRS studies in infants aged between 1 and 7 months (Dehaene-Lambertz et al. 2002; Grossmann et al. 2010; Blasi et al. 2011; Shultz et al. 2014) have highlighted an early specialization in the voice-sensitive temporal regions (e.g., anterior and posterior STS). Former behavioral and electrophysiological studies have demonstrated that full-term newborns (FTs) prefer voices to nonvocal auditory stimuli during the first days of life (Ecklund-Flores and Turkewitz 1996; Cheng et al. 2012). FTs react with higher suck frequency to a native language (Moon et al. 1993) and have an innate preference for mother's voice (DeCasper and Fifer 1980). The mother's voice, one of the first sounds encountered during fetal life, is a socially salient vocal stimulus, relevant for the emotional and social development of the infant and foundations for language development.

Preterm birth occurs when the fetal brain is maturing rapidly and therefore at high risk of cerebral lesions. It is generally argued that premature birth leads to negative effects on the developing brain, especially due to pathological processes such as hypoxia-ischemia, infection, and inflammation but also repetitive harmful stimuli present in intensive care units (noise, absence of night–day cycle, and painful procedures) and administrated drugs. However, a few studies stipulate that enriched neonatal sensory stimulation such as developmental care based on behavioral individuality of each infant (Als et al. 2004) can improve early structural and behavioral brain development in preterm infants (PTs) (Draper et al. 2017). Furthermore, Caskey et al. demonstrated the positive impact of adult language during the neonatal intensive care unit stay on vocalizations (Caskey et al. 2011) and on cognitive and language outcomes of PTs at 7–18 months corrected age (Caskey et al. 2014).

Neonatal neuroimaging studies on voice processing are scarce and the actual literature demonstrates a lack of knowledge of the precise localization of voice-specific brain processing areas in neonates and the impact of early vocal exposure on these networks. This current study explores the cerebral responsiveness to mother's and stranger's female voice stimulation in PTs at term-equivalent age (TEA) and in FTs in their first days of life with two independent neuroimaging techniques: 3 T fMRI and high-density electroencephalography (EEG) recording from 128 channels. A standard auditory paradigm and an auditory oddball paradigm were used to assess primary and secondary auditory processing. The ultimate aim of this study is to determine if PTs may benefit at TEA of their prolonged extrauterine auditory exposure. The rationale driving this aim lies in controversial conclusions on a positive versus deleterious role of an early extrauterine sensorial stimulation in infants born prematurely. We hypothesized that following a premature birth, PTs at TEA may have an enhanced processing of the mother's and the stranger's voices due to their protracted auditory experience ex-utero.

Materials and Methods

Subjects

All 49 infants included in this study were born at the University Hospital of Geneva and from French-speaking mothers. The FT group was composed of infants born between 37 and 42 weeks of gestation and was tested during the first week of life. No FT exhibited signs of neurological disorders or hearing impairments at birth. The PT group was composed of healthy infants born before 33 complete weeks of gestation and tested between 39 and 42 weeks of gestation. All PT infants stayed in a private room from birth to stabilization stage (up to 32–34 GW), then in a semiprivate room. Our exclusion criteria were children with severe neurologic complications such as brain lesions including periventricular leukomalacia and intraventricular hemorrhage and those with impaired hearing or other developmental impairment. The study was approved by the institutional ethical review board at University Hospital of Geneva. All parents gave their written informed consent prior to infant's participation to the studies.

Subjects in MRI Experiment

A total of 39 infants participated in the fMRI study: 19 FTs (mean gestational age, 40 weeks, standard deviation [SD] = 1.1 weeks) tested between their 2nd and 6th day of life (mean age at MRI scan: 40.4 weeks, SD = 1 week) and 20 PTs (mean gestational age at birth = 28.7 weeks, SD = 2.5 weeks) tested at TEA (mean age at TEA = 40.3 weeks, SD = 0.7 weeks). Demographic data concerning the studied population are shown in Supplementary Tables 1 and 2.

Nine infants were excluded from the study or not included in subsequent analyses, due to 1) excessive motion (2 FTs), 2) because of a lack of activation (absent BOLD response) to the overall sound versus rest contrast in auditory regions at the level of significance of $P < 0.05$ (1 FT and 5 PTs), and 3) severe development impairment of unclear etiology (1 FT). All subsequent fMRI analyses were performed on 30 infants (15 FTs and 15 PTs).

Subjects in EEG Experiment

A total of 23 babies participated in the EEG study: 11 FTs (mean gestational age = 39.9 weeks, SD = 1.2 weeks) tested between their 2nd and 5th day of life and 12 PTs (mean gestational age at birth = 29.1 weeks, SD = 2.1 weeks) tested at TEA (mean age at TEA = 41 weeks, SD = 0.9 weeks). No participant was excluded for the standard auditory paradigm; one infant in each group was excluded for the oddball paradigm due to excessive movement artifacts.

All included PTs in EEG study also participated in the MRI part, but only 1 FT took part in both experiments. The 10 remaining FTs of the EEG study are thus not identical to those included in the MRI part. This is explained by the difficulty for the mothers of healthy FTs to join both studies during their short stay (maximum 3 days) at the postnatal ward.

Study Design and Sound Recording

The MRI and EEG acquisitions were performed during natural sleep or quiet rest without any sedation. All infants were fed immediately before testing to increase the likelihood of getting asleep through the entire procedure. Each neuroimaging technique brings its strengths: the fMRI provides a high spatial

resolution to localize the brain activations and the EEG allows a high temporal resolution of these cerebral processes.

Brain fMRI and high-density EEG recordings were performed on FTs and PTs at TEA while listening to their mother's voice and the voice of an unknown mother. Each voice was played forward and backward (time-reversed).

In this study, the stimuli were natural human voice auditory stimuli, spoken by the mother of each newborn and a stranger's female voice. The stranger's voice varied for each infant and was the maternal voice from another included infant in order to control for any "motherese" effects. Motherese speech consists in a special form of speech used by caretakers talking to infants. This infant-directed speech provides a unique acoustic signature, as it is slower and contains exaggerated pitch contours (Kuhl 1997).

Prior to fMRI or EEG acquisition, the voices were recorded in a soundproof room (background noise <25 dBA sound recording parameters: Wave PCM signed 16-bit, 44 100 Hz, 705 kbps, mono) and acquired and edited with the Goldwave Inc. software program. Sentences were normalized to have the same intensity level. The amplitude envelope of each sound was kept intact in order to keep the specificity of each voice and the natural rising envelope of the sound to ensure the voice to remain as natural and identifiable as possible. The same manipulations were done in backward sentences which are only time-reversed using MATLAB software program (MathWorks Inc.). Backward speech is a good acoustic control condition, because it keeps global characteristics of the sound (spectral contents, intensity, acoustic complexity, and duration) but is unintelligible and breaks the prosodic structure of the sentence in preserving the familiarity of the speaker.

Information pertaining to the three experiments design can be appreciated in Supplementary Figure 1.

fMRI Experiments

Auditory Stimuli

The four auditory stimuli were the own mother's and stranger's (another mother's) voices played forward and backward. The stimulus consisted of free speech from each mother lasting approximately 5 min. The mothers were told to speak as if they were speaking to their child, to respect as close as possible the "motherese" effect. The 5-min sound recorded was cut, edited to 10 fragments of 24 s (Goldwave Inc. software program) and presented to each infant using a MR-compatible headphone (MR Confon GmbH, Magdeburg, Germany) during MRI acquisition.

The 5 auditory conditions (4 auditory stimuli and one rest condition) were presented in a block paradigm during 24 s and each condition was repeated 5 times per run in a pseudorandomized order.

The level of sound presentation during MRI acquisition was adjusted to a comfortable level but to be easily understandable above the residual scanning noise by an adult.

MRI Procedure

When infants were fed and quiet, they were swaddled in a blanket and headphones placed on the ears. Infants were set up in a vacuum pillow that was longer than their body to surround the head and prevent movements. The well-being and behavior of infants were monitored during the experiment with pulse oximetry, camera, and microphone. A nurse stayed during the entire MRI acquisition. Scanning was interrupted immediately if the infants became restless.

MR images were acquired on a Siemens 3 Tesla scanner (Siemens Magnetom Trio, Erlangen, Germany) using 32-channel head coil. Two runs of 310 functional images were acquired during auditory stimulation using a single-shot T_2*-weighted gradient-echo Echo-Planar Imaging (EPI) sequence for each run (TR = 2000 ms, TE = 30 ms, 30 slices, voxel size = $1.56 \times 1.56 \times 3$ mm^3). A T_2-weighted structural image was acquired for anatomical reference (TR = 4990 ms, TE = 160 ms, 113 coronal slices, voxel size = $0.78 \times 0.78 \times 1.2$ mm^3) and was reviewed by a pediatric neuro-radiologist to exclude any pathology.

MRI Preprocessing

The preprocessing of the functional images was performed with SPM8 (Wellcome Department of Imaging Neuroscience, at University College London) and included 1) realignment, 2) slice timing, 3) rigid-body coregistration of functional images on a T_2 structural image, 4) normalization of subject's anatomical T_2 image ($1 \times 1 \times 1$mm^3) and EPI ($2 \times 2 \times 2$ mm^3) to a T_2 template of the newborn brain, and 5) spatial smoothing (FWHM 6 mm).

To provide the best brain template as possible to study our cohort, we created a template from anatomical T_2 images of 10 PTs at TEA and 10 FTs.

To accommodate the high level of motion in babies, images with framewise displacement superior to 1 mm as well as one previous and two following images were excluded (Power et al. 2012). Sessions without motion superior to 1 mm and including a minimum of one repetition of each condition were used for the analysis.

fMRI Analysis

Functional time-series were analyzed voxel by voxel with a general linear model (GLM). The six realignment parameters and their Volterra expansion (Friston et al. 1996) were reduced using singular value decomposition (SVD). The number of components (NC) first SVD components explaining at least 99% of the variance, or the first six SVD components if NC > 6, were included into the GLM model as covariate regressors. This SVD reduction allows the consideration of the 24 realignment parameters to remove any residual motion-related variance without decreasing the degrees of freedom too much while ensuring the orthogonality of the model. The block design was convolved by the canonical hemodynamic response function (HRF) for each auditory stimulation and used as a regressor. Low-frequency noise and signal drift were removed using a discrete cosine transform basis set with a filter cut-off period of 256 s.

The overall Sound versus Rest contrast was inspected in each newborn, at the individual level, for both negative and positive BOLD signal. We only included subjects to further analyses in which the result showed a significant activation in primary auditory regions (in the left and/or right superior temporal gyrus), at least at the level of significance of $P < 0.05$ uncorrected.

fMRI Group Analysis

To identify brain regions that showed differential activity levels in response to mother's and stranger's voice stimulation, several analyses were performed at the group level to evaluate the functional cerebral development for voice processing and the effect of a premature birth. The threshold of significance was set at $P < 0.005$ with an extent threshold of 10 voxels.

First, the effect of specific vocal stimulation, namely the processing of the mother's voice and a stranger's voice, was

investigated using a one sample *t*-test (random-effect analysis) for each condition and in each group separately. Second, we conducted a group comparison, using a two-sample *t*-test, for each condition to compare the effect of postnatal experience on mother's and stranger's voice processing between groups. Then, to evaluate the ability to differentiate a familiar from an unfamiliar voice and to study the effects of prematurity on voice discrimination processes, we first compared the mother's voice versus the stranger's voice using a one sample *t*-test in each group, followed by a group comparison.

To investigate the effect of voice processing, the main effect of voice was used by considering the Forward and Backward condition together. It is of interest that the results of the Forward condition only were similar to the main effect but that they did not reach significance in the contrasts, possibly due to the low number of repetitions.

High-Density EEG

Stimuli and Paradigm

Standard auditory paradigm. The stimulus consisted in the French sentence "pleure pas" ("do not cry" in English), played forward and backward (time-reversed). Several "pleure pas" stimuli were spoken by the mothers and recorded prior to the event-related potential (ERP) study. The sound envelope of each recording was visually inspected. The best physical match between the own infant's mother and another mother was retained to obtain, respectively, the mother's and stranger's voice stimuli for each subject.

All sound files (Forward and Backward) were edited (Goldwave Inc. software program) to start at the same timing (17 ms before onset of the sound), to have an identical and fixed length of 1250 ms in which all sound envelopes were lasting on average 716 ms (SD = 136 ms) and were normalized to the same intensity level.

The sounds were pseudorandomly presented for 100 trials in each condition while brain activity was recorded. The interval between stimuli varied randomly from 1500 to 2500 ms.

Auditory oddball paradigm. The oddball paradigm has been used for investigating voice discrimination abilities (Titova and Näätänen 2001) and auditory sensory memory during the neonatal period (Cheour et al. 2000). Irrespective of the conscious state, a mismatch response (MMR) reflects a brain's automatic change-detection response elicited by deviant auditory stimuli in an auditory stream of similar stimuli, called the oddball paradigm (Näätänen and Alho 1995; Cheour et al. 2002; Martynova et al. 2003). The MMR is defined by a cortical ERP component topographically distributed mainly over the fronto-central regions in adults, but also recorded in central and parietal sites in infant (Cheour et al. 1998). It is obtained by subtracting ERPs elicited by standard stimuli from those evoked by deviant stimuli (Näätänen and Alho 1995). A MMR is elicited by the deviant stimulus based on memory representation of the frequent stimuli (Näätänen et al. 2005). It was demonstrated that the familiarity of the deviant stimulus can modulate the MMR (Beauchemin et al. 2006; Sambeth et al. 2006; Beauchemin et al. 2010; Zinke et al. 2018). This paradigm can serve to study the influences of memory processes in auditory stimulation.

The auditory stimulus for passive listening was the speech syllable "ta" pronounced either by the biological mother's voice or a stranger's voice. The sound envelope of each recording was lasting on average 188 ms (SD = 68 ms) and has received similar processing as in the standard auditory paradigm; thus, voice intensity and duration were matched between all voices used. Two oddball paradigms were tested. In the first oddball paradigm, the speech syllable "ta" was said by the natural voice of a stranger's mother voice as deviant and by the biological mother as frequent stimulus. The second oddball paradigm was the opposite: the syllable "ta" pronounced by the biological mother as deviant stimulus and by the stranger mother as frequent stimulus. The frequent stimuli occurred at a probability of 80%. The interstimulus interval was fixed at 800 ms. The sounds were presented in a pseudorandomized sequence of the two blocs of 200 stimulations, for 160 trials in the standard condition and 40 in the deviant condition. Any deviant stimulus was always preceded by at least 2 frequent stimuli to ensure that a neural trace for the standard stimulus had formed.

In both the standard auditory paradigm and the auditory oddball paradigm, the sequence of stimuli was generated by the E-Prime Psychology Software on a computer located in an adjacent room. The recording was made in a soundproof Faraday cage at the University Hospital of Geneva.

The infant was lying in the arms of his or her mother who was seated on a comfortable chair. A nurse was present during the entire EEG recording in the adjacent room. The sounds were delivered at 65 dB sound pressure level to infants through two loudspeakers positioned in front of the babies at one-meter distance.

EEG Data Acquisition and Preprocessing

The EEG was acquired with a 128-channel Hydrocel Geodesic Sensor Net® (Electrical Geodesics Inc., Eugene, OR, USA), using a sampling rate of 1000 Hz and a recording reference at the vertex (Cz electrode). Impedances were kept below 30 kΩ during recording.

The ERPs were preprocessed using the free academic Cartool 3.52 software by Denis Brunet (https://sites.google.com/site/cartoolcommunity/ Geneva, Switzerland), (Brunet et al. 2011). Data were band-pass filtered between 1 and 30 Hz (standard auditory paradigm) and between 0.5 and 20 Hz (oddball paradigm) and rereferenced to the common average reference (standard auditory paradigm) and to the mean of the mastoids (oddball paradigm). Epochs contaminated by eye and motion artifacts were rejected by visual inspection. The data were then averaged for each condition and each subject from −100 ms before to 1000 ms after the onset of the sound, including a baseline correction from −100 to 0 ms. For subsequent analyses, peripheral channels located on the cheeks and in the nape were excluded leading to a reduction from 128 to 109 channels. Moreover, bad channels were interpolated using the 3D-spline interpolation method.

ERPs

Standard auditory paradigm. In contrast to the fMRI part, we analyzed for each voice (i.e., Mother_forward and Stranger_forward) only the ERP elicited by the condition played forward. The backward condition was planned for supplementary analyses that are not included here. The temporal resolution of the EEG would result in different onset latencies of the evoked response of the time-reversed sounds, leading to temporal blurring if compared with the forward condition.

At first, the ERPs were subjected to an explanatory analysis using time-frame wise paired *t*-tests to determine the time periods where ERP amplitude differences occurred between voice

identity conditions. The *t*-tests were computed over all electrodes in each group of newborns, with a significance level of $P < 0.05$ and a temporal criterion of at least 10 ms of subsequent significant values. The results of this statistical analysis are also displayed as "*t*-test map" to show the electrodes with significant amplitude differences.

We also performed a topographic analysis of variance (TANOVA), which is a nonparametric randomization test, based on the computation of the global dissimilarity between maps at two successive time points (Murray et al. 2008; Michel and Murray 2012).

Auditory oddball paradigm. The ERP for the 4 conditions (mother's voice as frequent and deviant stimulus, stranger's voice as frequent and deviant stimulus) were computed separately for PT and FT infants. Amplitude differences between the ERP elicited by the deviant stimulus and the frequent stimulus from each oddball were compared for each time point and electrode with a two-tailed unpaired *t*-test using a significance level of $P < 0.05$ and a temporal criterion of at least 10 ms. The results of this statistical analysis are also displayed as "*t*-test map" to show electrodes with significant amplitude differences.

Results

Voice Processing in Newborns (fMRI)

Cortical Response to Vocal Stimulation in PT and FT Newborns

Both the mother's and the stranger's voice elicited activation of the middle and posterior superior temporal gyrus (STG) in the FT and the PT group. In addition, the left motor cortex was found to be activated (Fig. 1A,B, upper part) in FTs for stranger's voice.

The PT group showed for both voices significant activation of the entire posterior STS and gyrus to mid-STS/STG and anterior STG, the anterior part of the cingulate cortex (ACC), and the left orbito-frontal cortex (OFC). Both amygdalae were more activated for the stranger's voice in this group (Fig. 1C,D, middle part). A direct comparison between PT and FT groups (Fig. 1E,F, lower part) revealed more cerebral activations for each voice in PT than in the FT group. Concerning the PTs, the mother's voice elicited greater activation of the right dorsolateral prefrontal cortex (DLPFC), left OFC, sensory-motor areas, left superior parietal and the right inferior parietal lobule (Fig. 1E); the stranger's voice elicited a greater activation of the right DLPC, the right superior frontal cortex, the left OFC, and the precuneus (Fig. 1F).

Voice Discrimination in PT and FT Newborns

In FT babies, the stranger's voice elicited more cerebral activations than the mother's voice in the bilateral anterior part of the STG, the bilateral insula, the middle cingulate cortex (MCC), the bilateral hippocampus, and the sensory-motor cortex (Fig. 2).

In the PT group, this contrast (stranger > mother) gave a difference in activations of the posterior cingulate cortex (PCC) only. The opposite contrast (mother > stranger) did not show any significant difference in activations, neither in FT, nor in PT babies.

Voice Processing in Newborns (ERPs)

Standard Auditory Responses

Figure 3B illustrates the ERPs waveforms for the mother's and the stranger's voice for both neonate groups. In the FT group (left side), we observed significant differences between the two voices for ERP amplitudes (Fig. 3D) and changes in topography (TANOVA, Fig. 3C). The time course of ERP amplitude differences was assessed by a paired *t*-test over all 109 electrodes and at each time point (Fig. 3D). Significant differences in amplitude appeared at different time periods over several electrodes, from 170 ms after stimulus onset until the end of the period. The *t*-test maps are depicted at three different time windows (170, 530, and 960 ms) showing the localization of the significant electrodes. The TANOVA (Fig. 3C) also revealed significant differences in two-time windows, between 467 and 540 ms and between 910 and 960 ms.

In PT infants, only few amplitude differences were observed between the 2 voices (Fig. 3D, right side), and no significant difference in change in topography (TANOVA, Fig. 3C, right side) was found. The *t*-test maps are illustrated at two time periods, 130 and 660 ms, showing the localization of significant electrodes.

Auditory Oddball Responses

The number of accepted EEG trials after rejection of artifacts was for deviant and frequent stimuli, respectively: 26 ± 12 (range 16–37), 106 ± 44 (range 66–141) in the first oddball and 28 ± 9 (range 20–36) and 108 ± 38 (range 74–145) in the second oddball paradigm.

In the first oddball paradigm, both groups of newborns (Fig. 4, upper part) responded to deviant-stranger's voice stimuli (red line) with a higher positive voltage amplitude than those elicited by frequent-mother's voice stimuli (black line); therefore, the resulting difference (the MMR, green line) was positive. Unpaired *t*-test between both ERP over each 109 electrodes found a significant amplitude difference over the fronto-central electrodes in the early time window of 30–290 ms in FT group, corresponding to an early MMR (an early preattentional component). On the other hand, the PT group demonstrated statistically significant differences in more frontal electrodes from 290 to 420 ms between both voices. This later MMR shows a strong positivity for the stranger-deviant stimuli corresponding to a putative precursor of adults' P300a.

In the second oddball paradigm (Fig. 4, lower part), the FT group showed an early mismatch negativity response in the right centro-temporo-parietal areas that was statistically significant during the time window of 150–230 ms. The response to the deviant mother's voice (black line) elicited a smaller response than the frequent stranger's voice (red line), so that the resulting subtraction resulted in a negative MMR. We did not find any late MMR in the FT group. In the PTs, the deviant mother's voice elicited a statistically significant different response than the frequent stranger's voice from 670 to 860 ms over the centro-parietal electrodes. The resulting late positive MMR resembles a putative precursor of adults' P300b.

Discussion

This study was conducted to reveal brain processing of familiar and unfamiliar voices in newborns with different prior exposure to vocal auditory environment. The PT infants studied at TEA, compared with FT newborns in their first days of life, have the great particularity to cumulate several weeks of extrauterine auditory vocal experience in early development. Firstly, the study identifies and localizes cerebral mechanisms underlying voice processing in the newborn by using two independent

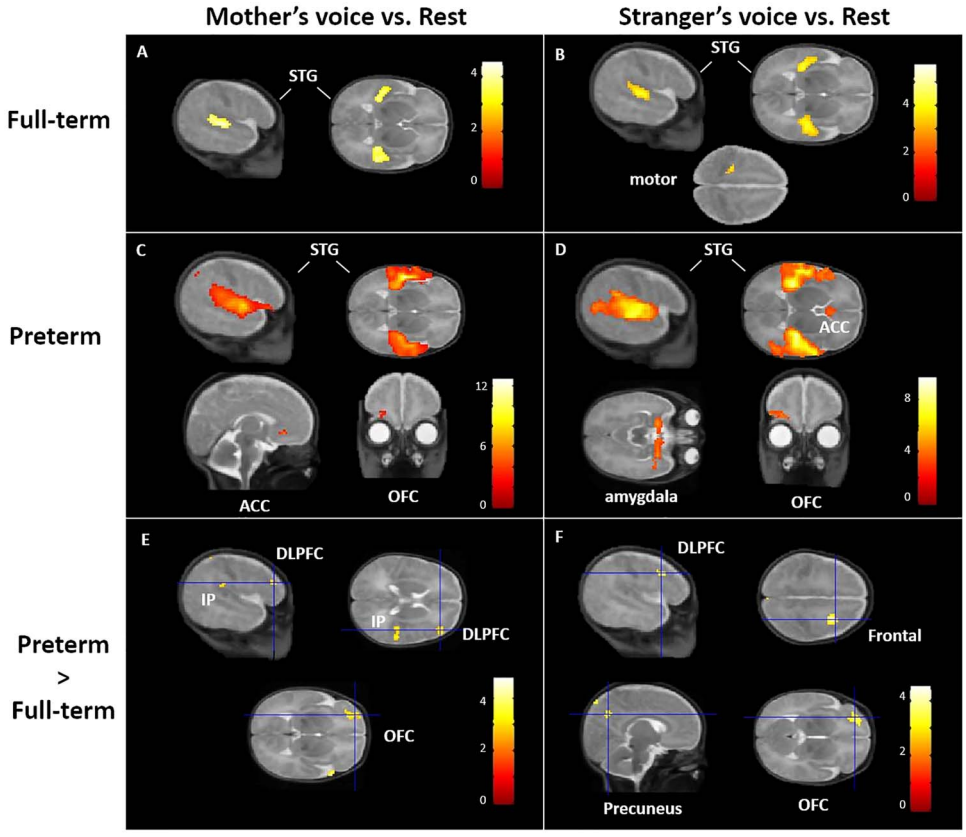

Figure 1. Upper and middle part: one sample *t*-test on the group of full-term (upper part, $n = 15$) and PTs (middle part, $n = 15$). (*A*) Activation of the bilateral superior temporal gyrus (STG) following the mother's voice stimulation in the group of full-term infants. (*B*) Activation of the bilateral STG and the left motor cortex following the stranger's voice stimulation in the group of full-term infants. (*C*) Activation of the bilateral STG, the anterior part of the cingulate cortex (ACC), and the left orbito-frontal cortex (OFC) following the mother's voice stimulation in the group of PTs. (*D*) Activation of the bilateral STG, the ACC, the bilateral amygdala, and the left OFC following the stranger's voice stimulation in the group of PTs. Lower part: Two sample *t*-test on both groups of newborns. (*E*) In the preterm group, greater activations of the right inferior parietal cortex, the right dorsolateral prefrontal cortex (DLPFC) and the left OFC following the mother's voice stimulation than in the full-term group. (*F*) In the preterm group, greater activations of the right DLPFC, the right frontal cortex, the precuneus and the left OFC following the stranger's voice stimulation than in the full-term group. Activations are overlaid on the T_2-weighted newborn's template with a display threshold: $P < 0.005$, uncorrected. Color bars indicate *t*-values.

methods, fMRI and high-density EEG. Both neuroimaging techniques showed converging results in FT and PT infants studied at the same postmenstrual age assessing important aspects of voice processing such as voice novelty detection, voice discrimination, and recognition of familiar and unfamiliar voices.

Brain Activation to Vocal Stimulation

Voice stimuli activated the bilateral auditory cortex along the STG in both neonate groups. These results confirmed that cerebral auditory activation was successfully recorded in newborns and were consistent with previous reports of brain activation following auditory stimulation in infancy (Dehaene-Lambertz et al. 2002; Blasi et al. 2011), as well as in the rare fMRI studies performed during the neonatal period (Perani et al. 2011; Baldoli et al. 2015).

Moreover, the stranger's voice induced a response within the motor cortex of the FT infants a few days after birth. This response may represent an arousal effect with increased motor activity while they are hearing a novel voice. In the PT group at TEA both voices resulted, besides the auditory cortex, in the activation of the ACC and the left OFC; the unfamiliar voice only further activated amygdala bilaterally. In adults and older children, these brain areas are known to be involved in emotional and attentional processing of vocal stimuli. The ACC has been shown to be activated following emotional vocalizations in adults (Sander et al. 2007) and is known to regulate attentional and emotional processing (Bush et al. 2000). The OFC is involved in sensory integration with a role in the processing of affective stimuli (Kringelbach 2005) and contributes to the evaluation of emotional association (Wildgruber et al. 2005). A past fMRI study in 3- to 7-month-old infants found that OFC was activated by vocalization with emotional content (Blasi et al. 2011). The amygdala is involved in the emotional labeling of a vocal stimulus and responds to the hedonic value (positive and negative) of a stimulus in detecting biologically relevant stimuli in the environment (Sander et al. 2003; Fecteau et al. 2007). Consequently, the activation of bilateral amygdala by stranger's voice in our study might reflect that PT infants at TEA already distinguish familiar from unfamiliar voices and perceive a stranger's voice as a relevant stimulus in their auditory environment.

Both voice stimuli chosen in this study expressed the "motherese" effect. This infant-directed speech corresponds to an exaggerated acoustically and articulatory speech which conveys

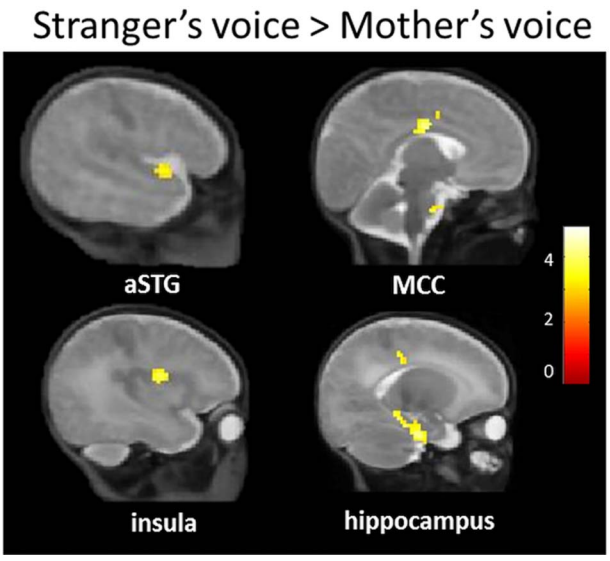

Figure 2. Voice discrimination. One sample *t*-test in the group of full-term infants ($n = 15$), showing greater activation of the right anterior part of the superior temporal gyrus (aSTG), the right insula, the right hippocampus and the middle cingulate cortex (MCC) for the stranger's voice than for the mother's voice. Activations are overlaid on the T_2-weighted newborn's template with a display threshold: $P < 0.005$, uncorrected. Color bars indicate *t*-values.

a positive prosody and an emotional aspect (Trainor et al. 2000; Soderstrom 2007). The present study suggests, that the prolonged extrauterine auditory exposure to different voices experienced by PT newborns at TEA have enhanced the emotional processing of voices as relevant stimuli in their environment. The neural processing of vocal emotional content seems to emerge early and need several weeks of extrauterine auditory experience to appear as this processing was not yet present in FT newborns in their first days of life.

Full-term and Preterm Infants at TEA

The direct group comparison was conducted to investigate the differences between groups in addition to the brain response to specific vocal stimuli. In comparison with FT infants, PTs at TEA showed enhanced cortical responses for voices. Their vocal responsiveness involved not only more brain areas, but brain areas such as the frontal lobe, shown to be activated in voice processing of older infants (Dehaene-Lambertz et al. 2002). We observed, in PT group at TEA but not in FT group, that both voices activated the right DLPFC and the left OFC; the mother's voice activated the right inferior parietal lobule; the stranger's voice, the right superior frontal cortex and the precuneus. As very PTs at TEA experience the same duration of ex-utero auditory stimulation than 3-month-old FTs, this more mature way of voice processing can be viewed as a direct effect of extrauterine voice exposure.

Previous fMRI studies of adults using vocal stimuli highlighted that frontal areas are sensitive to voice, such as the prefrontal area (Fecteau et al. 2005). The posterior inferior frontal region activation was present in a voice identification paradigm, when differences in newly learned voices were tested (Latinus et al. 2011). The DLPFC in particular and the inferior parietal cortex, which were both activated in the PTs at TEA, are known to be involved in affective prosody processing with a right hemispheric dominance (Wildgruber et al. 2002; Wildgruber et al. 2005). DLPFC and precuneus activations were also observed in one fMRI study, which tested a speech paradigm in 3-month-old infants (Dehaene-Lambertz et al. 2002). Our demonstration that only PTs at TEA activated comparable frontal regions during the processing of speech sequences indicates that PT infants, compared with FTs, involve higher-level cortical areas to process our vocal speech-stimuli. Although the frontal lobe is generally viewed as a late-maturing area and still too immature to be functional during the first months of life, recent imaging studies showed that this high-level area is already operative at 3 months of age (Dehaene-Lambertz et al. 2002; Dehaene-Lambertz et al. 2006; Benavides-Varela et al. 2012; Mahmoudzadeh et al. 2013; Cusack et al. 2016) or as shown by our results in PTs at TEA. However, degree of wakefulness was shown to be linked to activation in the frontal region (DLPFC) (Dehaene-Lambertz et al. 2002). We cannot exclude that our PTs were more awake, while the FTs were more asleep. Only a simultaneous EEG-fMRI recording could more precisely determine the awake state of the newborns during the fMRI scan.

Voice Discrimination

In line with past electrophysiological studies (deRegnier et al. 2002; Therien et al. 2004), our fMRI and EEG results of the standard auditory paradigm confirmed that FTs, compared with PTs at TEA, demonstrated a larger difference between the two voices. Confronted to both voices, FTs showed in our fMRI experiment a stronger activation for the stranger's voice in voice-specific cortical areas such as the anterior part of the bilateral STG and in areas involved in attentional and novelty processing, the bilateral insula, the MCC and the hippocampus. These findings were consistent with former fMRI studies of adults in which the anterior part of the STS was involved in speaker identity processing and was activated by the unfamiliar voice (Belin and Zatorre 2003; von Kriegstein et al. 2003; Kriegstein and Giraud 2004; Maguinness et al. 2018). Although the insula is involved in many functions, it has been implicated in voice and speech information processing in adults (Wong et al. 2002; Bamiou et al. 2003; Giraud 2004; Wong et al. 2004; McGettigan et al. 2013), as well as in monkeys (Remedios et al. 2009). The insula is possibly active in the temporal aspect of speech and complex sound processing (Ackermann et al. 2001; Bamiou et al. 2003), in detection of novelty in a paradigm involving unfamiliar bimodal (odor and music) stimuli (Plailly et al. 2007), and in detection of salient events (Menon and Uddin 2010). Furthermore, the MCC, which is connected to the insula (Mesulam and Mufson 1982), plays a role in environmental monitoring, in modulation of attention, and in control and pain process (Taylor et al. 2009) and see Bush et al. 2000 and Shackman et al. 2011 for Reviews. The hippocampus is also known to be activated in novelty detection to auditory stimuli (Knight 1996; Ranganath and Rainer 2003; Rutishauser et al. 2006). Consequently, these areas activated by the stranger's voice stimuli in our FT group may reveal unfamiliar voice detection and novelty. This hypothesis is also reinforced by concordant results obtained in our oddball paradigm experiment. FT newborns responded to stranger's voice as a deviant stimulus with a large early MMR, a response of novelty in itself.

In PTs at TEA, in contrast, we observed very few differences between both voices in our fMRI and EEG experiments. Only a stronger PCC activation for the stranger mother's voice compared with the mother's voice was seen in fMRI. We hypothesize

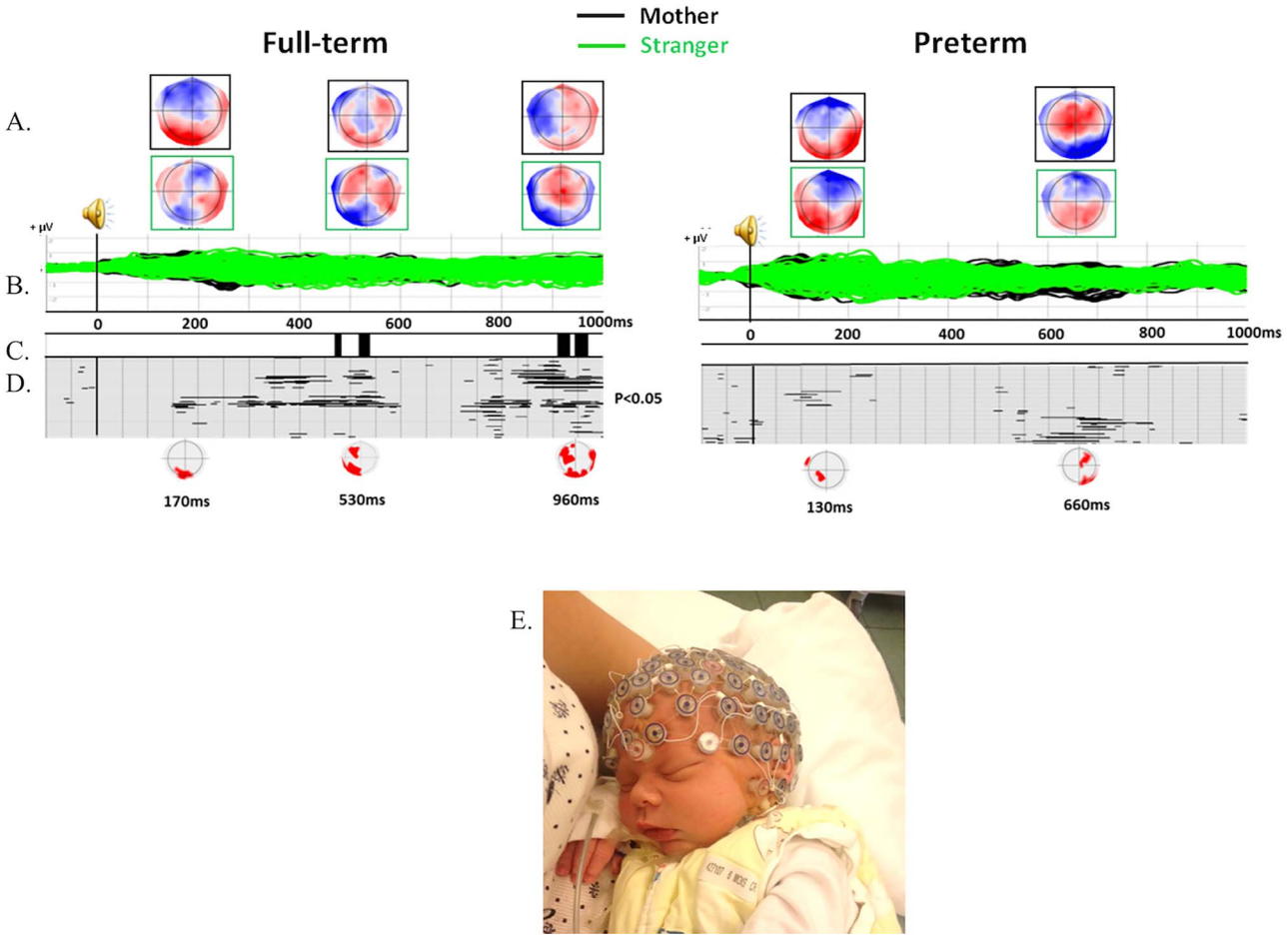

Figure 3. ERP responses to the mother's and stranger's voices. (*A*) Topographical maps for each condition at the following time points: 170, 530, and 960 ms (full-term group), and 130 and 660 ms (preterm group). (*B*) Superimposed ERPs waveforms of all 109 electrodes in each condition. (*C*) Topographic analysis of variance (TANOVA) between conditions with time windows of significant differences at $P < 0.05$. (*D*) Statistical *t*-tests on all electrodes across time. Their *t*-test maps showing significant amplitude differences at the electrode level at $P < 0.05$, for 10 consecutive milliseconds are shown below. (*E*) Full-term neonate with high-density EEG cap.

that our population of PTs at TEA might detect voices of a stranger mother as "familiar" given their extended extrauterine exposure to different female voices, which included a motherese effect. In further support of this hypothesis, past fMRI studies in adults demonstrated that PCC was involved in detecting the familiarity of heteromodal stimuli (faces and voices) (Shah et al. 2001) and the emotional content of the words (Maddock et al. 2003).

Standard Auditory Paradigm

As in our fMRI study, the ERP results showed different voice processing between FTs and PTs at the same postmenstrual age. The ERP analyses of the standard auditory paradigm illustrated an enhanced voice discrimination in the FT group, both in terms of voltage amplitude and topographic changes driven by the stranger's voice, whereas only small differences in voltage amplitude and no significant topographic differences were observed in the PT group.

During infancy, some studies on processing voice familiarity reported significant amplitude differences between the ERPs of the mother's and stranger's voices around 300 ms at 2 months of age (Mai et al. 2012) and from 350 ms at 4 months old (Purhonen et al. 2004). Regarding the electrophysiological correlates of voice processing, a fronto-temporal positivity to voices has been found as early as 150 ms when contrasting voices with nonvocal sounds in adults (Capilla et al. 2012) and in 4- to 5-year-old children (Rogier et al. 2010).

Significant amplitude differences were detected in both groups of newborns in our experiment. The first amplitude differences between both voices peaked very early, from 130 ms in PTs and from 170 ms in FT infants, and were consistent with previous findings, where first ERP amplitude differences were described around 200 ms between familiar and unfamiliar voices in adults (Beauchemin et al. 2006) and in newborns (Beauchemin et al. 2010). For the FT group, we found different time periods with clear amplitude differences along the whole epoch, more prominent over the left-sided electrodes, together with significant topographic differences (TANOVA) between both voices around 470–540 ms and 910–960 ms. A change in map topography of the electrical field is necessarily induced by a change of underlying brain generators, thus by distinct brain networks (Vaughan 1982; Srebro 1996; Murray et al. 2008). Therefore, when FT infants processed the voices, we observed a change of active source of neural population for each voice, which was confirmed and localized by our fMRI analysis and was specified also for the stranger's voice. For the PT group,

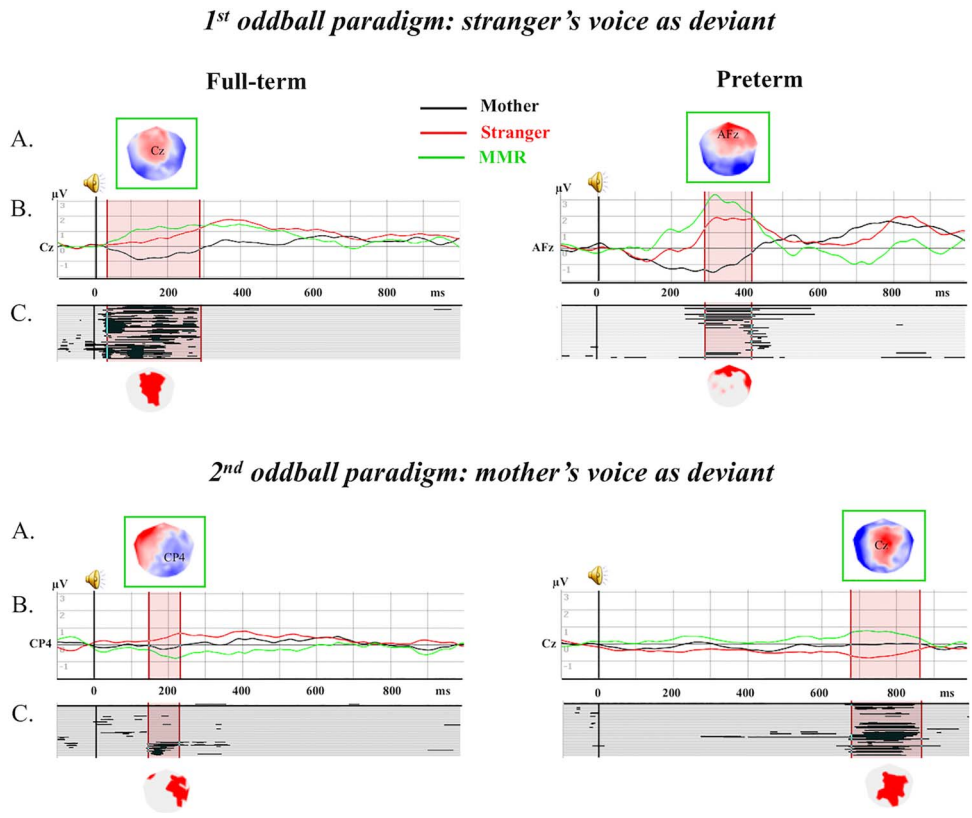

Figure 4. Electric response to both oddball experiments. The 1st oddball paradigm uses the stranger's voice as deviant and studies the detection and discrimination of unfamiliar voice. The 2nd oddball paradigm uses the mother's voice as deviant and explores the auditory memory recognition. (*A*) Topographical maps for mismatch response: red area shows a positive mismatch response and blue area a negative mismatch response. (*B*) Superimposed grand-average ERPs elicited by mother's voice (black); by stranger's voice (red). In green, the mismatch response, which is deviant-minus-frequent difference waves. Red frame highlights main periods of significant amplitude differences between deviant and frequent sounds. For clarity purposes only responses obtained over one electrode, which was statistically significant, is shown. (*C*) Results of *t*-tests of the amplitudes for each of the 109 electrodes and each time point between the ERPs to deviant and frequent voices. Their *t*-test maps show in red electrodes with significant amplitude differences at level of $P < 0.05$, for 10 consecutive milliseconds.

we measured a second later period with significant amplitude differences between 600 and 750 ms over the right-sided electrodes, but without significant topographic differences. Thus, it is highly possible that the absence of topographic modulations may indicate more similar brain networks across conditions as confirmed by the results of our fMRI experiment.

Oddball Paradigms

The oddball paradigm approach was not only complementary to fMRI and standard ERP studies on demonstrating the novelty detection and the effects of postnatal exposure but provided additional information about the voices' processing abilities in neonates. It enabled the study of auditory short-term and long-term memory processes. The MMR reflects the cerebral comparison process between the sensory memory traces of repeated-frequent sounds and the neural trace of a deviant change in an auditory stream of stimuli, called change detection process, which occurs in short-term memory (Cheour et al. 2000). Moreover, as the MMR is also modulated by the familiarity of the deviant stimulus, long-term memory processes can influence and bias change detection (Beauchemin et al. 2006; Beauchemin et al. 2010; Zinke et al. 2018).

Our results confirmed that infants at a mean age of 41 weeks could elicit a MMR to voice changes (Beauchemin et al. 2011). Past studies demonstrated no voice discrimination in very preterm (28–32 GW) (Mahmoudzadeh et al. 2017) and late PTs (35–38 GW) (deRegnier et al. 2002), while these PTs could already discriminate syllables or tones.

In our study, the first oddball paradigm with the stranger's voice as deviant tested the detection of novelty and discrimination of an unfamiliar voice and reflected cerebral processes occurring in short-term memory. The second oddball with the mother's voice as deviant tested memory trace of a familiar voice and was based on long-term memory processes.

The first oddball paradigm demonstrated that the deviant-stranger's voice elicited a positive MMR in both neonate groups and confirmed their ability to detect novel stimuli in the auditory environment. Instead of the usual negative MMR measured in adult studies, a positive MMR to deviant stimuli is common in pediatric literature (Dehaene-Lambertz 2000; Dehaene-Lambertz and Pena 2001; Friederici et al. 2002; Kushnerenko et al. 2002; Sambeth et al. 2006; Beauchemin et al. 2010). Similar to our fMRI and standard auditory EEG results, our first oddball paradigm showed that FT group showed larger differences between both tested voices than the PT group. We could demonstrate a particularly strong early positive MMR in FT group over the fronto-central electrodes to deviant-stranger's voice, which occurred shortly after the stimuli presentation (30–290 ms). On the other hand, we reported a later and more frontally positive MMR in PTs at TEA (after 290–420 ms poststimulus). Linking

previous studies performed in children and adults (Cheour et al. 2002; Kushnerenko et al. 2002; Sambeth et al. 2006), we considered this slightly later positive component for the deviant stimulus as a putative precursor of the P300a response. The P300a wave peaks over fronto-central scalp areas and reflects attentional orienting responses to novel stimulus (Picton 1992; Nelson et al. 1998; Escera et al. 2000; Kushnerenko et al. 2002). The P300a wave follows the MMR, as subsequent attentional process toward a deviant or novel sound would have first required any detection of a sound change. Transposed to our results in PT infants, the MMR to the deviant stimulus might have been overlapped by the subsequent positivity (the P300a wave), which might explain both the absence of an early MMR and its positive polarity (Kushnerenko et al. 2002). This hypothesis might suggest that PT infants at TEA are already able to detect the change of voice and to pay attention to a new stimulus.

The second oddball paradigm highlighted that PTs at TEA have developed the first signs of auditory memory for their mother's voice during their prolonged extrauterine auditory experience. Indeed, only PT infants at TEA demonstrated a late positive MMR to the deviant-mother's voice between 670 and 860 ms over the centro-parietal electrodes. This late response to the mother's voice as deviant stimuli could well represent the P300b subcomponent of attentional cognitive processes. Previous studies showed that P300b appeared over the centro-parietal areas and is related to subsequent memory, compared with P300a indexing involuntary attentional switch (Escera et al. 2000; Kushnerenko et al. 2002; Polich 2007; Riggins and Scott 2019). This late positive difference to infrequent highly familiar stimuli (deviant-mother's) reveals two important findings. First, PT infants at TEA are able to perform voice processing with higher-cognitive processing than FT infants of the same postmenstrual age. Second, PT infants at TEA have consolidated the long-term representation of the voice of their mother as proposed by the recent study of Zinke et al. in 3-month-old FT newborns (Zinke et al. 2018). Based on Zinke et al. findings, we have enough confidence to conclude that PT infants at TEA processed familiar voices according to their chronological age rather than their postmenstrual age.

In our sample of FT infants, we did not find an early or a late positive MMR for the deviant-mother's voice at midlines electrodes as measured by Beauchemin et al. in healthy newborns of less than 24 h of life (Beauchemin et al. 2010). The right-lateralized negative voice difference present around 200 ms poststimulation is not to be considered as a mismatch negativity component, as it does not occur over the midlines electrodes (Fz, Cz, Pz) as described in adult and pediatric literature to evaluate a MMR (Beauchemin et al. 2006; Näätänen et al. 2007; Beauchemin et al. 2010). However, the difference is negative because of the more positive amplitude response measured for the frequent-stranger's voice, which is again in line with our precedent results showing that FT react to novelty detection.

Detection of Novelty

In our study, both fMRI and ERPs results have shown that the FT newborns processed the voice of an unknown woman more strongly, in comparison with the maternal voice, an effect attributed to the detection of novelty. The detection of an unknown auditory signal might be perceived as a relevant and novel stimulus in the environment of the FT infants having heard mainly the voice of their mother at this age.

In early infancy, the involvement of the hippocampus in the encoding of novel stimuli (Nelson 1995) has been linked to an increased negative slow wave for an unfamiliar voice (deRegnier et al. 2000; deRegnier et al. 2002). In addition, other studies have reported intensified ERP components (P350, P600, P750) for the stranger's voice during the first months of life (Purhonen et al. 2004, 2005; Mai et al. 2012). Similarly, one fMRI study performed in adults showed an enhanced activation of areas, such as the right posterior STS and frontal regions for the unfamiliar voice (Kriegstein and Giraud 2004).

However, our results contrast with other findings described during infancy and childhood. Dehaene et al. (Dehaene-Lambertz et al. 2010) found an enhanced brain activation for the mother's voice compared with the stranger's voice in 2-month-old FT infants, but not a stronger activation for the stranger's voice. Similarly, Abrams et al. (2016) found in 5-year-old children, brain activations for the mother's voice only and not for the stranger's voice. These differences with our study can be attributed to an exposure effect. Indeed, stranger's voice might be perceived as less novel by children in the first months or even years than by neonates in the first days of life.

Although we found a stronger activation for the unknown voice, we cannot conclude that FT newborns did not demonstrate a preference for their mother's voice, as described in the behavioral literature (DeCasper et al. 1987; Ockleford et al. 1988). Doubtlessly, we cannot directly compare neuroimaging results with behavioral measures. However, both methods carry different and complementary information (Moon et al. 2015). The presence of a differential brain response confirms that the mother's and the stranger's voices are processed differently by the brain of newborns. The weaker processing for the maternal voice in the FTs may be interpreted as though the familiarity of a stimulus reduced the ERP amplitude of its response. Mai and al. suggested that one memory template was created for the mother's voice heard during the prenatal experience and would imply less resources to process it (Mai et al. 2012).

Effect of Postnatal Exposure

Our data suggest that PTs at TEA process both voices in a similar complex manner, reducing the measured differences in our fMRI and EEG results. PTs at TEA have been exposed to several human voices during their hospitalization and the input of these auditory stimuli may facilitate the processing and the brain responses to unfamiliar voices. Based on this observation, we hypothesize that the early postnatal exposition of PT infants to environmental sounds enhanced their processing capacities of both voices, mother's and stranger's voices. Effects of auditory experience on brain activity has already been demonstrated in fetuses. Partanen and al. demonstrated an enhanced brain activity to speech stimuli at birth in fetuses with a prenatal speech exposition (Partanen et al. 2013). Similarly, our group recently showed that a music exposure in PTs leads to learning of a familiar music (Lordier, Loukas, et al. 2019) and modified resting state neural networks at TEA (Lordier, Meskaldji, et al. 2019).

Our findings suggesting that PT infants at TEA processed voices more similarly to 3-month-old infants were congruent in three different experiments using 2 different neuroimaging techniques.

Although a MMR can be elicited as early as at 30 GW (Cheour-Luhtanen et al. 1996; Mahmoudzadeh et al. 2013), a discriminative response to voices was not found in all

neonatal studies, especially in PT infants tested at TEA (Fellman et al. 2004). However, it was demonstrated, that early sensory exposure could have a positive effect on brain development, such as the maturation of the auditory system (Nishida et al. 2008), a faster maturation of cerebral white matter (Gimenez et al. 2008) and a greater interhemispheric connectivity in the temporal and temporoparietal regions during speech processing (Naoi et al. 2013). Modulation of sensory development has been studied extensively in preclinical animal models. In a primate model of PT and FT infants, Bourgeois et al. showed a genetically controlled number of synapses in visual cortex but modified existing synapses by early sensorial extrauterine experience in the preterm primate (Bourgeois et al. 1989). Developing connectivity of thalamocortical fibers is the main structural substrate influenced by early extrauterine sensorial (auditory, visual, tactile or even pain) experience (Kostovic and Judas 2010). Before 26 GW thalamo-cortical afferents make transient synaptic connections in the subplate zone of sensory cortical areas (Kostovic and Judas 2010). A recent study in ferrets suggested that extrinsic auditory stimuli would be able to already activate neurons in the subplate compartment which would influence the organization of the future auditory cortex (Wess et al. 2017).

An important consideration in interpreting these data is the fact that the cohort came from private room care in the neonatal intensive care unit (NICU) and semiprivate room in the neonatal intermediate unit. A recent systematic review recommended a private NICU room design for several reasons such as less noise, less infections, reduced length of stay, morbidity, and mortality (O'Callaghan et al. 2019) and allows for family centered care. Pineda and al. however reported altered brain development on neuroimaging and electrophysiological studies at TEA and a lower language score at 2 years of age in PTs hospitalized in private rooms without family integrated care (Pineda et al. 2014). Less auditory exposure in private NICU rooms compared with open bay may drive this finding (Pineda et al. 2017). Our cohort could benefit from a mixture of private and semiprivate room design. Acute care mainly occurs early in the third trimester (28–32 GW), a vulnerable period for brain development to stressful nonphysiological extrauterine environment. During this vulnerable period, consisting, for auditory system, in the maturation of neural connections to the temporal lobe (Kostovic and Judas 2010) and starting organization of the tonotopic columns (Goldberg et al. 2020), NICU private-rooms might ensure protection for high-intensity electronic noise from machines and alarms (Pineda et al. 2017). Then, by 32 GW when the PTs start to differentiate sounds (Webb et al. 2015), during feed and growth stabilization stage (32–40 GW), the semiprivate rooms might offer increased time spent with distant language and increased number of intelligible words heard (Pineda et al. 2017).

Consequently, the quality, the amount, the timing, and the type of the early experience (Als et al. 2004) during the postnatal life of PTs (Lickliter 2000) seem to influence the structural and functional cerebral development.

Conclusion

To summarize, our study provides unambiguous evidence that human voice sensitivity emerged already in the first days of life with a functionally wide and complex range of brain regions enabling newborns to perceive vocal environment. While FT newborns shortly after birth have a great ability to detect novel unfamiliar voice stimuli, it is remarkable that PT infants at TEA treat voices with higher level cognitive processing compared with FT newborns of the same postmenstrual age. When listening to own mother's voice and stranger's mothers voice, PTs at TEA activate cortical areas involved in emotional and attentional processing of human vocalizations, as well as long-term memory representation of their mother's voice. Our results suggest that the prolonged ex-utero auditory stimulation of PT infants has a positive effect on the maturation of functional neural networks involved in voice processing.

Understanding the impact of this early ex-utero auditory stimulation will strengthen the necessity to control auditory stimuli and the sensory environment in NICUs. Further studies are needed to determine whether early voice exposure of PTs might promote neurodevelopment, in particular in language and behavioral skills.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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