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SHORT REPORT

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Attenuated brain responses to speech sounds in moderate preterm infants at term age

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Abstract
Recent findings have revealed that very preterm neonates already show the typical brain responses to place of articulation changes in stop consonants, but data on their sensitivity to other types of phonetic changes remain scarce. Here, we examined the impact of 7–8 weeks of extra-uterine life on the automatic processing of syllables in 20 healthy moderate preterm infants (mean gestational age at birth 33 weeks) matched in maturational age with 20 full-term neonates, thus differing in their previous auditory experience. This design allows elucidating the contribution of extra-uterine auditory experience in the immature brain on the encoding of linguistically relevant speech features. Specifically, we collected brain responses to natural CV syllables differing in three dimensions using a multi-feature mismatch paradigm, with the syllable/ba/ as the standard and three deviants: a pitch change, a vowel change to/bo/ and a consonant voice-onset time (VOT) change to/pa/. No significant between-group differences were found for pitch and consonant VOT deviants. However, moderate preterm infants showed attenuated responses to vowel deviants compared to full terms. These results suggest that moderate preterm infants' limited experience with low-pass filtered speech prenatally can hinder vowel change detection and that exposure to natural speech after birth does not seem to contribute to improve this capacity. These data are in line with recent evidence suggesting a sequential development of a hierarchical functional architecture of speech processing that is highly sensitive to early auditory experience.

KEYWORDS
EEG, MMN, preterms, speech processing, voice-onset time, vowel quality

1 | INTRODUCTION

According to the World Health Organization, almost 15 million babies were born preterm all around the world in 2010 (Blencowe et al., 2012). Preterm birth can impact language and cognitive development. Around 25%–30% of very preterm infants (i.e. born between 28- and 32-week gestational age [wGA]) show delays in language acquisition that can be observed already in their 2nd year of life (Sansavini et al., 2010). Premature infants are also at risk for cognitive delays with immaturity levels at birth being linked to cognitive outcomes at school age (Bhutta, Cleves, Casey, Cradock, & Anand, 2002). In the speech perception domain, developmental timing differences between healthy full-terms (FT) and preterms have also been reported in early language discrimination skills, word segmentation and lexical stress differentiation in very preterm infants (Peña, Pittaluga, & Mehler, 2010; Bosch, 2011 and Herold, Höhle, Walch, Weber, & Obladen, 2008 respectively).

Previous results on the impact of preterm birth on the brain responses to different types of speech sounds are still scarce and not clear-cut. While a few days after birth, very preterm neonates exhibit discriminative brain responses for a phonetic change in place of articulation of a consonant (ba vs. ga) (Key, Lambert, Aschner, & Maitre, 2012; Mahmoudzadeh et al., 2013; Mahmoudzadeh, Wallois, Kongolo, Goudjil, & Dehaene-Lambertz, 2017). Later in development, very preterm infants, tested between 3 and 9 months of age, may present delayed brain responses to a different place of articulation consonant contrast (ba vs. da) (Paquette et al., 2015; Peña, Werker, & Dehaene-Lambertz, 2012). The latter results are more in line with previous neuroimaging studies showing an atypical organization of the language network in preterm infants (Baldoli et al., 2015; Liu et al., 2010; Mürner-Lavanchy et al., 2014). However, these studies exclusively focused on very preterm infants, born at or before 32 wkGA, and very little is known about moderate preterm neonates born between 32- and 36-wGA and their capacity to discriminate different types of speech contrasts.

The perception of a voicing contrast in stop consonants relies on a fine-grained temporal analysis which is related to changes in the voice-onset time parameter (VOT), i.e., the interval between the noise burst produced at consonant release and the onset of the waveform periodicity associated with vocal cord vibration (Lisker & Abramson, 1967). On the other hand, the perception of a vowel change is based on spectral differences conveyed by the distribution of the frequencies of the first few formants (Hillenbrand & Gayvert, 1993). Because the womb strongly degrades and filters the fine-grained temporal information necessary to identify the stop consonants contained in the speech signal (Griffiths, Brown, Gerhardt, Abrams, & Morris, 1994; Lecanuet & Schaal, 1996), preterm babies may benefit from the early and rich stimulation received from the outside world to successfully detect a consonant change (Key et al., 2012; Therien, Worwa, Mattia, & DeRegnier, 2004). But at the same time, an early experience with the broad spectrum of frequencies of speech and especially the high-frequency noise in the neonatal units may have a negative impact on the functioning of the speech network (Lahav & Skoe, 2014). In other words, exposure to low-pass filtered sounds and speech during intrauterine life, as typically experienced by full-term infants, plays not only a protective role for hearing development but it may also constrain the auditory system in favor of prosody-based information reflected by the sequential acquisition of specific prosodic and phonetic speech features (Ragó, Honbolygó, Róna, Beke, & Csépe, 2014). Preterm birth may, thus, disrupt the developmental timing in the processing of different speech properties relevant to language learning.

To better characterize the influence of an early exposure to the broad spectrum of frequencies of the language on the automatic processing of syllables in infants born moderately preterm, we recorded the brain responses to changes in three different speech dimensions in 20 healthy FT and 20 healthy moderate preterm infants (PTm) tested at term age. Importantly, compared to FT, preterm infants had had a different auditory experience in the 7–8 weeks before testing. We used a largely validated multi-feature mismatch negativity (MMN) paradigm (Näätänen, Pakarinen, Rinne, & Takegata, 2004; Partanen, Pakarinen, Kujala, & Huotilainen, 2013) with the syllable/ba/ as standard and three deviants on the following dimensions: pitch (F0 change), vowel quality (spectral change in formant frequency values) and VOT difference (a consonant change based on the voicing dimension). This paradigm allowed us collecting the mismatch response (MMR) indicating cortical processes of automatic memory-based auditory change detection or prediction error (Friston, 2005; Gagnepain, Henson, & Davis, 2012; Näätänen, Paavilainen, Rinne, & Alho, 2007). The MMR can be elicited by low-level (acoustic) changes in pitch, duration, VOT or vowel type in neonates and children (Cheour et al., 1998; Chobert, François, Habib, & Besson, 2012; Chobert, François, Velay, & Besson, 2012; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Partanen et al., 2013; Rivera-Gaxiola, Silva-Pereyra, & Kuhl, 2005). Importantly, the MMR can be also obtained in multi-feature MMN paradigms involving different types of deviants with different probabilities of occurrences or containing abstract rules determining regularities between non-consecutive linguistic and non-linguistic stimuli (François et al., 2017; Mueller, Friederici, & Männel, 2012), so the MMR can also reflect the ability to generate higher-order predictions (Näätänen et al., 2004; Vidal, Brusini, Bonfieni, Mehler, & Bekinschtein, 2019). The analysis and comparison of brain responses to VOT and vowel changes should reveal which speech dimension is most affected by differences in the nature of the speech stimulation experienced in the months preceding the testing (i.e. low-pass filtered speech vs. broad-spectrum natural speech in the outside world). Considering previous studies on the perception of a place of articulation consonant contrast (ba/ga) and a male/female voice change in very early preterms, showing clear neural discrimination of the phonetic contrast but attenuated neural responses to voice changes (Mahmoudzadeh et al., 2013, 2017), we expected PTm infants evaluated at term age to show equivalent (or attenuated) MMR to pitch and vowel changes when compared to FTs. For VOT deviants, two possible outcomes were possible. If the early exposure to the broad spectrum of frequencies before term age has a positive impact leading to better processing of fine-grained temporal

Research Highlights

- We collected brain responses to natural CV syllables differing in three different dimensions (pitch, vowel, and consonant changes) using a multi-feature mismatch paradigm.
- Full-term and healthy moderate preterm infants were tested at 40 weeks gestational age, thus differing in the nature of previously experienced linguistic stimuli.
- We showed that in the preterm group 7–8 weeks of extra-uterine exposure to language can impact speech processing mainly affecting vowel change detection.
- These results favour the view of a functional architecture of speech processing involving a dual processing stream for fast and steady-state features of syllables.

cues, then we could expect PTm infants to exhibit an enhanced MMR to VOT deviants as compared to FT neonates. Alternatively, if this early exposure has a negative impact, PTms should exhibit an attenuated MMR as compared to FTs.

2 | METHODS

2.1 | Participants

A total of 40 healthy babies were enrolled in this experiment with 20 healthy full-term neonates (12 males; mean gestational age [GA] at birth = 39.6 weeks GA [38.2–41.4]; mean birth weight = 3,122 g [2,210–4,420]; Apgar-5 >9; mean postnatal age at test = 2.8 days ± 0.7; mean maturational age at test (gestational age at birth + postnatal age) = 40.1 weeks [38.2–42]) and 20 healthy moderate preterm neonates (19 males; mean GA = 33 wGA [32.2–35.6]; mean birth weight = 1,837 g [1,520–2,400]; Apgar-5 >9; mean postnatal age at test = 51 days ± 15 and mean maturational age at test = 40.1 weeks [39–42.3]; see Figure 1 for an illustration of the design). The mean postnatal age (t_{19} = 22.57; p < .0001, two-tailed), the mean GA at birth (t_{19} = 18.90; p < .0001, two-tailed) and the mean birth weight (t_{19} = 9.303; p < .0001, two-tailed) were significantly different between the two groups. Importantly, however, the mean maturational age at test was not significantly different between the two groups (t_{19} = 0.27; p = .78, two-tailed). All the newborns were recruited and tested at the maternity ward. Parents were informed and signed a consent form at the beginning of the experimental session. The hospital ethics committee approved our procedures and protocols (CEIC-PIC-69-13). All neonates had normal hearing from the universal screening test (automated auditory brainstem response) and normal examination made by a neonatologist at the delivery ward.

2.2 | Stimuli

Stimuli were natural syllables with a Consonant-Vowel (CV) structure recorded from a female Spanish speaker. The standard stimulus/ba/ had a fundamental frequency (F0) of 180 Hz, vowel duration of 213 ms and a VOT of −130 ms with a total duration of the stimulus of 340 ms (see Figure 1). For pitch deviant, the vowel identity and the VOT were the same as for the standard but the F0 of the vowel was increased by 50% using the software Audition (270 Hz). For vowel deviant, we recorded a/bo/ syllable and used Praat to excise the vowel and replace the original vowel/a/ in such a way that vowel duration and VOT were the same as for the Standard. Therefore, the onset of vowel change occurred at 127 ms after syllable onset. The VOT deviant/pa/ had a F0 of 180 Hz, a vowel duration of 213 ms for a total syllabic duration of 233 ms and a VOT of −20 ms.

2.3 | Procedure

The entire recording session took place directly in the room of the hospital and at least one of the parents was present during the session. Infants were tested while sleeping on their cribs. Stimuli were played at a 75-dB volume through a loudspeaker placed at about 1 m from the infant's crib in a single block that lasted 12.2 min. A total of 704

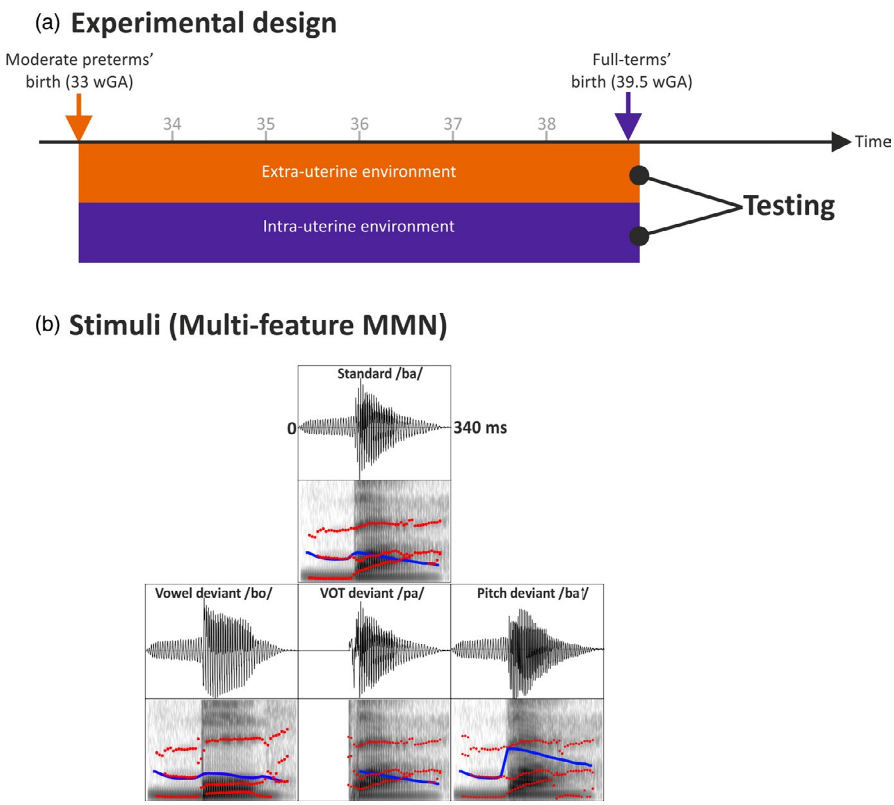

FIGURE 1 (a) Experimental design used in the present study. (b) Illustration of the four CV syllables used in the multi-feature MMN paradigm with both the sound wave and spectrogram. The red dots depict the four first formants and the purple trace depicts the fundamental frequency of each stimulus with the CV syllable/ba/ used as a standard, the/ba↑/ used as deviant in pitch, the/bo/ used as deviant in vowel quality and the/pa/ used as deviant in VOT. The four syllables had a duration of 340 ms. The onset of vowel change occurred at 127 ms after syllable onset

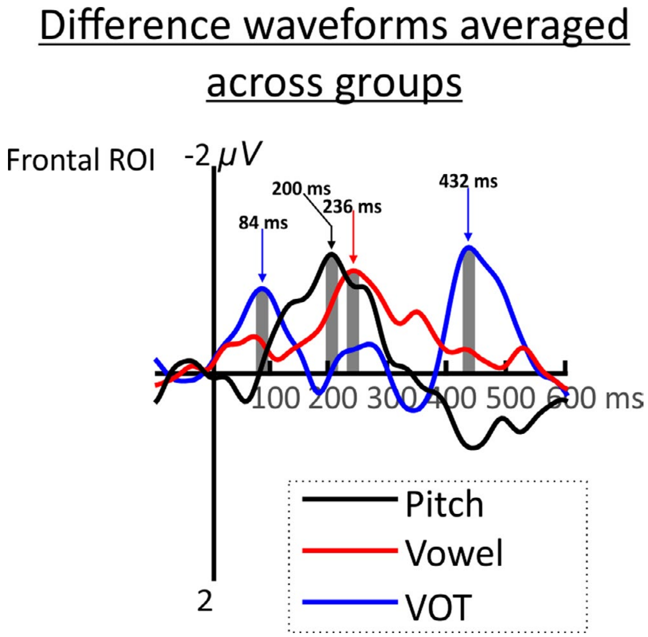

FIGURE 2 All infants (N = 40) grand-average difference waveforms (deviant—standard) over the frontal ROI (averaged of five frontal electrodes, see Methods) for the three conditions (Black: Pitch, Red: Vowel and Blue: VOT deviants). The grey areas show the peak-centred 20 ms time windows selected for between-group comparisons

stimuli were used with three deviants (72 for each of the three deviant types; 10% probability for each deviant). Pitch, vowel quality and VOT deviants were randomly presented within the auditory sequence with a Sound Onset Asynchrony of 600 ms synchronized with vowel onset.

2.4 | EEG data acquisition and processing

The EEG was recorded from 16 scalp electrodes (Biosemi ActiveTwo system, Amsterdam University) located at standard positions (International 10/20 system sites: Fp1, Fp2, F3, F4, T7, C3, C4, T8, P3, P4, O1, O2, Fz, Cz, Pz and Oz). The EEG was amplified by Biosemi amplifiers with a band pass of 0–102.4 Hz and was digitized at 250 Hz. The EEG data were re-referenced offline to the algebraic average of the mastoids. Those data were offline filtered from 1 to 20 Hz, and epochs containing external artefacts exceeding ±150 μV were removed, as done in previous studies in infants (Kostilainen et al., 2018; Kushnerenko et al., 2007; Martynova, Kirjavainen, & Cheour, 2003; Paquette et al., 2015). EEG data were split into epochs from −100 to 600 ms from stimulus onset and baseline corrected. The first 10 standards were systematically removed from the analyses.

2.5 | EEG data analysis

Based on previous literature showing a frontal distribution of the MMN (Mahmoudzadeh et al., 2017; Suppiej et al., 2010), we analysed the averaged brain responses over a frontal region of interest (ROI) that included five frontal electrodes (Fp1/2, F3/Fz/F4). This was done to increase the signal-to-noise ratio and to simplify the analyses.

We first performed point-by-point t tests comparing deviants and standards for each condition and in each group. As a second step, and to study group differences of habituation/adaptation in response to standards, we performed point-by-point t tests comparing responses to standards across groups. The corresponding significant temporal clusters were corrected for multiple comparisons using the Bonferroni-Holm FDR correction method to avoid false positives (Benjamini & Hochberg, 1995).

Finally, we studied differential MMN responses across groups by comparing the mean amplitude in 20 ms time windows centred on the peak difference waveforms (deviant minus standard) obtained in each condition as done in previous studies (Háden et al., 2009; Otte et al., 2013; Zhang et al., 2011). The peaks were visually identified as the most negative or positive peak in the all infants grand-average (collapsing the two groups of infants) difference waveform in each condition (Pitch: 200 ms, Vowel: 236 ms, VOT: 84 and 432 ms, see Figure 2). The mean amplitudes were compared using t tests for independent samples.

3 | RESULTS

Average ERPs to standard and deviant stimuli are shown separately for the two groups in Figure 3. As can be seen, most of the deviants elicited MMRs in the two groups, thus confirming the usability of the multi-feature MMN paradigm in neonates (Partanen et al., 2013). In FT, pitch and vowel deviants elicited negative frontal brain responses peaking around 200 ms. However, the VOT deviant, based on a fast temporal cue, elicited a different pattern of response with an early negativity followed by a late negativity between 400 and 500 ms (Čeponienė et al., 2004; Dehaene-Lambertz & Dehaene, 1994; Kushnerenko, Ceponiene, Balan, Fellman, & Näätänen, 2002). Results of the point-by-point t tests revealed significant differences between standard and deviants between 180 and 200 ms for pitch deviants and between 200 and 272 ms for vowel deviants. However, despite visible effects on the waveforms in the VOT condition, no significant effects were found.

In PTm, the patterns of response for pitch deviants were very similar to those observed in FT, however, results of the point-by-point analysis failed to reveal significant differences between standards and deviants, probably due to a high interindividual variability in this group. For vowel deviants, no significant difference between standard and deviants was found. However, for VOT deviants, a significant difference was observed between 400 and 480 ms with a larger negativity for deviants than for standards.

To study habituation/adaptation processes, we compared ERPs to standards between the two groups. Interestingly, PTm presented a larger late positivity compared to FTs. Results of point-by-point t tests revealed significant differences between 324 and 484 ms (see

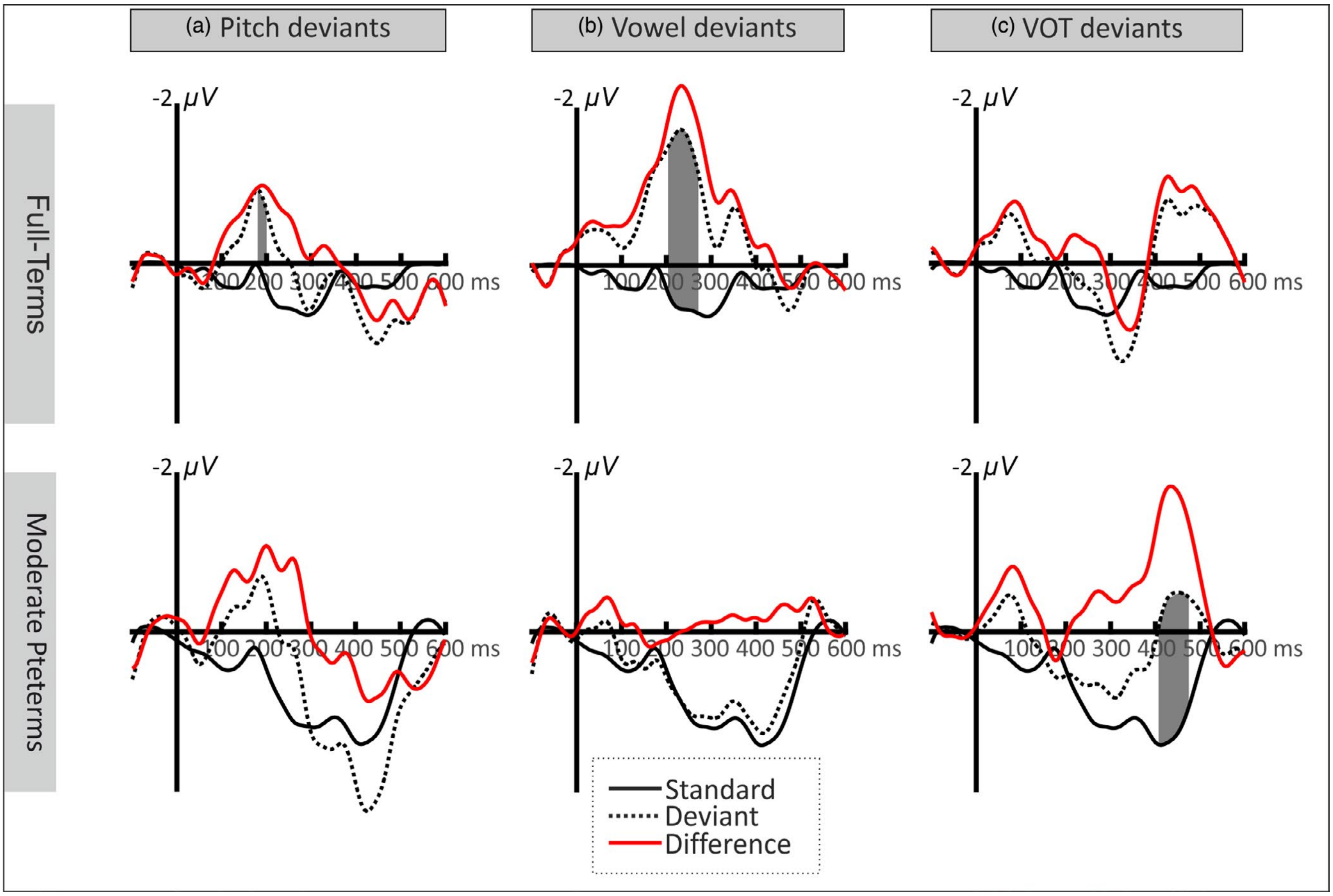

FIGURE 3 Grand-average ERPs over the frontal ROI (averaged of five frontal electrodes, see Methods) to standards (black), deviants (dotted lines) and to the difference waveform (deviant—standard, red) separately for the two groups of infants (top: Full terms; bottom: Moderate preterms) and for each deviant condition (a: pitch; b: vowel; c: VOT). The grey areas show point-by-point significant differences between standard and deviant ($p < .05$, FDR corrected at the cluster level)

Figure 4), suggesting that our group of PTm may present impaired habituation/adaptation processes.

Finally, we studied the differential MMRs across groups by directly comparing the difference waveforms separately for each condition (see Figure 5). For pitch deviants, the comparison of the two groups in the 20 ms time window failed to reach significance (FT: −1.1 μV; PTm: −1.1 μV; $t[38] = 0.09$; $p = .93$). For vowel changes, we found a significantly larger MMR in FT (−2 μV) than in PTm (0.04 μV; $t[38] = -2.34$; $p = .02$). For VOT deviants, the comparisons of the two groups were not significant neither for the early (FT: −0.73 μV; PTm: −0.88 μV; $t[38] = 0.27$; $p = .78$) nor for the late negativity (FT: −0.74 μV; PTm: −1.63 μV; $t[38] = 1.09$; $p = .28$).

4 | DISCUSSION

The present study brings new evidence on the role that early experience with natural language has on the processing of speech sounds. We compared 20 healthy moderate preterm infants matched in maturational age with 20 full-term neonates, thus differing in their previous auditory experience. We used a multi-feature MMN paradigm with deviants on three dimensions: pitch (F0), vowel quality (change in formant frequency values) and consonant VOT difference. We found an impact of 7–8 weeks of exposure to natural speech after moderately preterm birth on brain sensitivity to a vowel quality change. These results have strong implications for refining our knowledge on the early functional development of the auditory pathway supporting speech processing and on the impact of experience-dependent mechanisms during early development.

Regarding the response to a pitch change, no significant between-group differences were found even though only FTs presented a significant MMR (see Figure 3). This result suggests a high interindividual variability in the processing of pitch changes in both groups. Indeed, both groups may have presented a relatively small response, but in the case of FTs, due to random effects, the group average passes the statistical threshold while for the PTm group it does not. Such high variability could be due to inaccurate time locking of the inferior colliculus activity or to non-optimally functioning connections between the brainstem and the auditory cortex.

Contrary to the negative MMR elicited by the pitch and vowel deviants, the brain responses to VOT deviants elicited an early frontal negativity followed by a late negativity (see Figures 2 and 5). This pattern of brain responses is in line with previous results from older infants but also from newborns who show similar brain responses to consonant changes (Dehaene-Lambertz & Baillet, 1998; Dehaene-Lambertz & Dehaene, 1994; Dehaene-Lambertz & Peña, 2001; Maitre, Lambert, Aschner, & Key, 2013), as well as to white noise deviants in a sequence of harmonic tones (Kushnerenko, Van den Bergh, & Winkler, 2013; Kushnerenko et al., 2007). However, no between group differences and no differences at the level of the early negativity were observed, pointing to difficult avenues in the study of VOT changes in newborns.

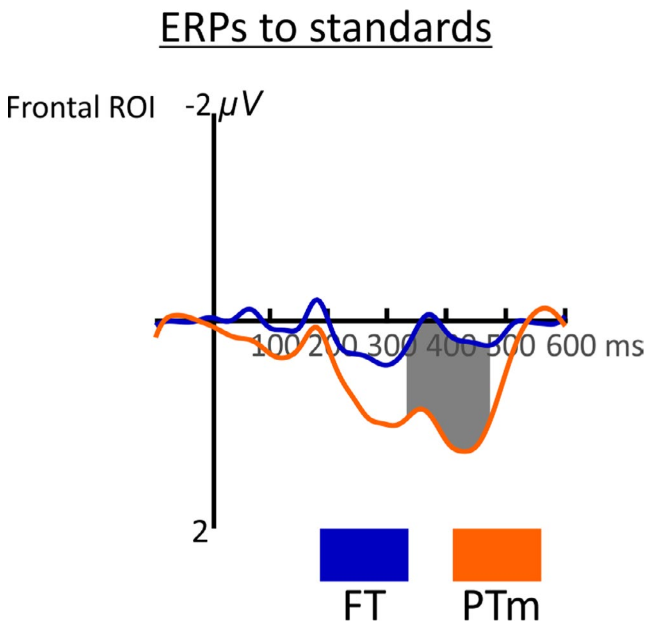

FIGURE 4 Grand-average ERPs to standards for the two groups of infants over the frontal ROI (blue: full terms, orange: moderate preterms). The grey areas show significant point-by-point differences between the two groups ($p < .05$, FDR corrected at the cluster level)

Mahmoudzadeh et al. (2017) tested very preterm neonates few days after birth using a two-deviant syllable discrimination task involving a voice change (male vs. female) and a change in place of articulation (/ba/ vs./ga/). Results showed clear MMRs for consonant changes but no response for the deviants that relied on steady-state differences as those required for voice processing (Zatorre & Belin, 2001). Here, preterms were assessed at term age (i.e. postnatal age corrected for gestation) and had been exposed to natural language for 7–8 weeks on average, time during which they could hear the broad spectrum of speech frequencies and prosody. Compared to FTs, the group of PTm showed attenuated MMRs to a vowel change. This result extends previous behavioural and electrophysiological evidence for differences in preterms' vowel processing compared to healthy FTs (Figueras & Bosch, 2010; Jansson-Verkasalo et al., 2010). However, the results in the VOT condition were not clear-cut enough to claim that the two groups were differing only in the processing of vowels. Premature birth may thus alter the functional maturation of the speech network by at least impacting the processing of steady-state features of speech. The present results support the idea that normal development facilitates the maturation of brain functions in a manner that is optimal for the still-developing human sensory system (Ragó et al., 2014; Werker & Hensch, 2015).

Interestingly, despite no group differences in the difference waveforms, the comparison of standards and VOT deviants showed significant differences at the level of the late negativity in the PTm group only. This may suggest enhanced predictive sound sequence processing mechanisms fostered by early exposure to the extra-uterine environment. The ability to generate predictions of upcoming stimuli at different hierarchical levels to enhance their processing is an important aspect of the human auditory system

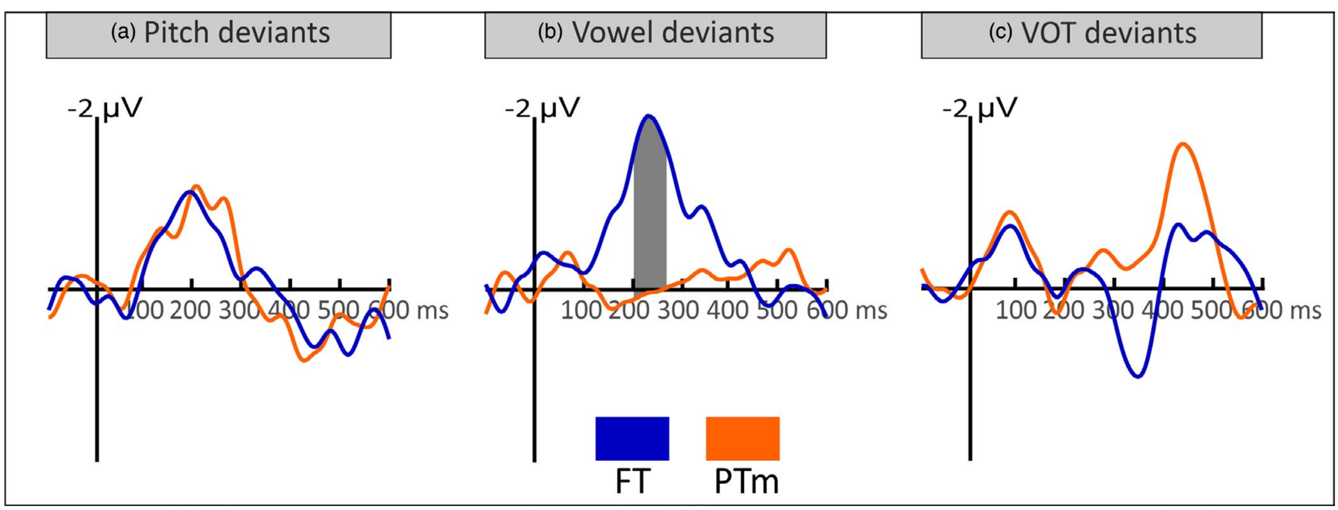

FIGURE 5 Grand-average difference waveforms (deviant—standard) for the two groups of infants (blue: full terms, orange: moderate preterms) over the frontal ROI separately for each condition (a: pitch, b: vowel, c: VOT). The grey areas show significant point-by-point significant differences between standard and deviant ($p < .05$, FDR corrected at the cluster level)

(Friston, 2005; Phillips et al., 2016; Wacongne et al., 2011). In the context of speech, predictive coding would lay on the generation of continuous sensory predictions based on the linguistic regularities of the environment (Bendixen, SanMiguel, & Schröger, 2012; Gagnepain et al., 2012) to facilitate not only speech perception and comprehension in adults (Arnal & Giraud, 2012; Bendixen, Scharinger, Strauss, & Obleser, 2014; Bendixen, Schröger, & Winkler, 2009; Grisoni, Mohr, & Pulvermüller, 2019) but also novel word learning in infants and toddlers (Benitez & Saffran, 2018; Ylinen, Bosseler, Junttila, & Huotilainen, 2017; Ylinen et al., 2016). The most common way to study auditory predictive coding abilities involves the Oddball paradigm which consists in the presentation of a sequence of repeated stimuli interleaved with deviants randomly presented. The ability to generate higher-order predictions is also largely studied with other types of Oddball paradigms such as the multi-feature MMN paradigm involving different types of deviants with different probability of occurrences or containing abstract rules determining regularities between non-consecutive stimuli (Näätänen et al., 2004; Vidal et al., 2019). Human healthy full-term neonates already possess functionally active auditory brain networks capable of predictive processes for speech and non-speech stimuli (François et al., 2017; Háden, Németh, Török, & Winkler, 2015). Previous studies have also revealed an influence of the context on the MMR to pure tone pitch changes suggesting that context-dependent auditory processing is present in healthy FTs (Háden, Németh, Török, Drávucz, & Winkler, 2013; Háden, Németh, Török, & Winkler, 2016). It also seems that very premature birth can negatively impact this type of predictive processing (Boldin, Geiger, & Emberson, 2018; Emberson, Boldin, Riccio, Guillet, & Aslin, 2017). However, it can also be considered that an early exposure to speech in the extra-uterine environment might positively impact the development of predictive context-dependent processing. Besides, it is important to keep in mind that the FT and PTm comparison of ERPs to standards revealed a larger late positivity in the PTm group (see Figure 4) and that this difference falls in the same latency range as the late negativity in the VOT condition. This larger positivity may reflect impaired habituation/adaptation to repeated stimuli. Further studies are needed to specify the role of early exposure on habituation/adaptation and predictive coding abilities with more controlled stimuli.

Our study presents some limitations related to the design and the stimuli used. First, we could only perform a single comparison based on matched maturational age but not based on chronological (postnatal) age. In order to better determine the effect of exposure to natural, non-filtered speech on the brain sensitivity to phonetic changes, at different postnatal ages, future studies should compare PTm and FT (a) when matched in postnatal age (i.e. both groups infants tested at 2 days after birth) or (b) when matched in the amount of exposure to non-filtered natural speech (i.e. both groups of infants tested after 7–8 weeks of postnatal exposure to the extra-uterine language environment). Second, we used natural speech stimuli which are less controlled than semi-synthetic or artificial syllables allowing a perfect control of the acoustic parameters. Further studies will have to address these issues to disentangle the role of pre-programmed as opposed to experience-dependent factors in development with more controlled stimuli. Finally, the relatively small number of infants included in the present study led us to perform our analyses on the averaged responses over a ROI; further studies with a better signal-to-noise ratio will allow specifying possible topographical differences between FTs and PTm infants.

In summary, our results suggest that 7–8 weeks of extra-uterine exposure to speech may have a negative impact on the processing of vowel quality changes in healthy moderate preterm infants tested at term age. These results favour the view of a functional architecture of the speech networks relying on a dual processing stream for fast and steady-state features of speech. Considering the interplay between early experience and built-in capacities, further studies using longitudinal designs will contribute to shed more light on the developmental changes occurring during the 1st year of life in moderate preterm infants.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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