

Early Exposure to Environment Sounds and the Development of Cortical Auditory Evoked Potentials of Preterm Infants During the First Three Months of Life

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Research note

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Abstract

Objective

Prenatal experience influences the course of development of sensory pathways. Preterm infants are exposed earlier than their term counterparts to unattenuated sounds from the external environment during the sensitive period of organization of auditory cortical circuitry. In the current study, we evaluated how gestational age (GA) correlates with the latency of the P1 component of the cortical auditory evoked potential of two experimental groups measured at one or three months of age. Our sample consisted of 23 infants delivered at GA ranging from 31.28-41.42 weeks and separated into two groups evaluated transversally at one or three months of corrected age (CA).

Results

In the group evaluated at one-month CA, the latency of the component P1 was similar in both term and late-preterm infants (GA>32 weeks). However, in the group evaluated at three months CA, P1 latency was significant smaller in preterms. These preliminary results suggest an acceleration of the development of auditory cortical pathways in preterms, probably due to their early exposure to socially relevant auditory stimuli from the external environment.

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Introduction

The remarkable adaptability of the human brain results from the interplay of both evolutionary and developmental mechanisms. Genetically determined developmental programs set up the stage for cortical circuits to be sculpted by experience and learning, especially during periods of heightened synaptic plasticity called sensitive periods (Barkat, Polley, & Hensch, 2011; de Araújo Costa Folha et al., 2017; Hensch, 2005).

Though animal-based research has contributed the most for our understanding about the perinatal organization of sensory systems, preterm birth presents an opportunity to advance our knowledge of this issue in humans. Preterm birth is characterized by delivery before 37 weeks of GA (Abbott, 2015; Goldenberg, Culhane, Iams, & Romero, 2008) and The World Health Organization (WHO) proposes the following sub-categories for preterms, based on GA at birth: extremely preterm (<28 weeks), very preterm (28 to <32 weeks), and moderate to late preterm (32 to <37 weeks) (Walle, Reschke, & Knothe, 2017). Most preterm births (>70%) are late-preterm (34 to <37 weeks) (Blencowe et al., 2012) and happen during a period when the cortical volume increases by 50% (Adams-Chapman, 2006; Loftin et al., 2010).

The cortical auditory evoked potential (CAEP) is characterized by waveforms with positive and negative deflections occurring between 0-300 ms after sound onset in adults. Both the amplitude and latency of these components change during maturation of auditory cortical circuits. The earliest components are

called P1 and N1 and are already present in newborns (Cunningham, Nicol, Zecker, & Kraus, 2000; Melo, Biaggio, Rechia, & Sleifer, 2016). Latency of the P1 component shows a steady decrease until it stabilizes in adulthood (D. R. Moore, 2002; Valerie L Shafer, Yan, & Datta, 2011; V. L. Shafer, Yu, & Wagner, 2015; Sharma, Gilley, Dorman, & Baldwin, 2007) and has been proposed as a biomarker for the maturation of central auditory (Eggermont & Ponton, 2003; Sharma et al., 2005) and visual pathways (Jandó et al., 2012; Mikó-Baráth et al., 2014).

In the present study, we present preliminary results about the latency of P1's CAEP component in a sample composed of moderate to late preterms recruited in a public hospital in the City of Natal, state of Rio Grande do Norte, Brazil.

Methods

The participants were 23 newborns (GA: 31.28-41.42 weeks) recruited at the Maternity School of the Federal University of Rio Grande do Norte according to the following inclusion criteria: no signs of hearing problems during routine maternity screening, normal Auditory Brainstem Responses (ABR) with click and normal threshold for ABR tone burst at 500 Hz, 1000Hz and 4000 Hz in both ears, normal Distortion Product Otoacoustic Emissions (DPOAE) and tympanometry result with curve type A in both ears. For this study, infants were considered preterm if delivery occurred at GA < 37 weeks. Table 1 shows demographic characteristics and birth outcomes of mothers and infants.

For the CAEP recording, subjects were accommodated either on a car seat or in their caregivers' lap within a sound attenuated room. All tests were performed while infants were in stage 4 of the Neonatal Behavioral Assessment Scale (alert, awake state) (Brazelton & Nugent, 1995). We used ER-3A insert phones (Etymotic Research, Inc.) for sound delivery to the right ear and the CAEP recordings were performed with a Smart EP USB Jr system with two channels (Intelligent Hearing Systems, Inc.) and disposable surface electrodes. The CAEP was recorded on channel A, while channel B was used to register eye movements for off-line artifact removal. The CAEP was recorded at midline (Cz) and referenced to the right mastoid. The ground electrode was placed at the left mastoid. All electrode impedances were balanced and were less than 3kΩ.

Auditory responses were recorded in response to a /da/ speech stimulus with an intensity of 70 dB HL, with an inter stimulus interval of 526 ms. For each stimulus and ear, a minimum of 150 stimuli were presented and the resulting signal, within an analysis window of -100 ms pre-stimulus and 500 ms post-stimulus, was averaged at both 70 dB and 0 dB after band-pass filtering from 1 to 30 Hz. Gain in both channels was 100.000. Latency of the P1 component was confirmed independently by two experienced judges.

Statistical analysis

Only 2-sided tests and nonparametric statistical tests were used due to non-normal distribution of variables and/or sample size. Sample characteristics were compared for preterm versus term infants

using Pearson's chi-square test or Fisher's exact test. Results are expressed as mean \pm standard deviation. Data from preterms and terms were compared with two-tailed Mann-Whitney rank sum U test. The relationship between GA and P1 latency was assessed with the Spearman correlation (r). Significance level was set at 0.05.

Results

P1 latency is not correlated with GA at both one ($r_s = 0.44, p = 0.183$) and three ($r_s = 0.49, p = 0.109$) months CA. We computed linear regression lines to fit the P1 latency data (Figure 1) and though the slopes of regression lines were not significantly different from each other ($p = 0.63$) (5.57 ± 7.21 v. 9.56 ± 4.44), their elevations are significantly different from each other ($p < 0.001$) (99.63 ± 262.30 v. -144.30 ± 160.50), indicating a general decrease in P1 latency between measurements at one and three months CA (Figure 1).

We separated the infants evaluated at the two distinct periods into two groups: preterm and term. According to Table 1, the demographic characteristics and birth outcomes of the two groups are similar, except for birthweight, which is lower in preterms ($p < 0.05$). Our sample is composed mostly of moderate to late preterms (GA 32 to <37 weeks), which represent about 10% of all births (CDC, 2017). Their prematurity ranged from 0.15-5.72 weeks (average 2.78 ± 1.58 weeks). For the infants evaluated at 1-month CA, the average latency of the P1 component was not significantly different between terms (309.40 ± 78.32 ms) and preterms (295.30 ± 47.66 ms) ($U = 10, p = 0.4242$) (Figure 2). However, for the group evaluated at 3 months CA, average P1 latency was 240.80 ± 57.67 ms for terms and 171.1 ± 26.44 ms for preterms, respectively (Figure 2), and significantly lower for the latter ($U = 5, p < 0.05$).

Discussion

The last trimester of gestation is marked by rapid cortical growth due to neurogenesis and the beginning of myelination and synaptogenesis (Kostovic & Jovanov-Milosevic, 2006; Malik et al., 2013). However, the rate of cortical maturation is not synchronous across cortical regions, with primary sensory areas developing faster than non-primary and association areas (Ball et al., 2013; Monson et al., 2018). In the auditory system, for instance, changes in cortical microstructure have largely stabilized in the primary auditory cortex by 28 weeks of gestation, while non-primary auditory areas are still immature at 42 weeks (Monson et al., 2018).

Our results confirm the findings from Didoné and coworkers (2014) showing that at one-month CA the latency of the P1 component is similar in both term and moderate-to-late-preterm infants (see Figure 2). However, we also showed that for three months old infants, P1 latency is shorter in moderate-to-late preterms than in terms (see Figure 2). Previous works had already shown that P1 has a latency of around 250 ms in one month old infants and steadily decreases towards adult levels (approximately 100 ms) (J. K. Moore & Linthicum, 2007; Sharma, Dorman, & Spahr, 2002). The smaller latency of the P1 latency of preterms seen in the three-month old group probably reflects the accelerating effect of early exposure to

the extrauterine environment on the maturation of the primary auditory cortex. Though we did not determine the specific characteristics of the environment the infants in our sample were exposed, it is fair to assume that there was a regular amount of speech stimulation available to them (Vouloumanos & Werker, 2007). Besides, in our sample, preterms were evaluated more closely by our medical team and probably also got special attention from caretakers at home, since preterm parents are susceptible to the Vulnerable Child Syndrome (VCS), whereby children who were at one point in their lives at risk of death continue to be perceived as being more vulnerable (Green & Solnit, 1964; Horwitz et al., 2015).

Other studies had already investigated the effect of early extrauterine exposure on the maturation of auditory cortical pathways using CAEP. For instance, a study using the amplitude of P1 showed that extreme/very preterms had smaller P1 responses than terms at five years of age (Mikkola et al., 2007). Hövel and coworkers (2014; 2015) also showed that the P1 latency was longer in preterms than near-term and term children at five years of age. However, the preterms in both studies were classified as extreme/very-preterm and also had poor cognitive scores (Hövel et al., 2014; Hövel et al., 2015). Thus, the from those studies may have been influenced by concurrent clinical conditions associated with extreme prematurity (Suppiej et al., 2015).

At present, we can only speculate on the neural changes associated with the accelerating effects of early exposure to the extrauterine environment. One possibility is an increase in the effectiveness of thalamocortical connectivity with the primary auditory cortex (Barkat et al., 2011). A similar effect on thalamocortical connectivity was reported for the somatosensory modality in very preterm infants (GA<33 weeks) following the premature exposure to activities such as breastfeeding and bottle-feeding (Toulmin et al., 2015).

Pasman and coworkers (1992) showed that at 40 weeks of gestation the latencies of CAEP components N1 and P2 are significantly shorter in preterm infants, whereas at three months the latencies of these components are shorter in term infants. The authors speculate that this may be due to the slower maturation of cortical auditory pathways and the presence of middle ear effusion in preterms. This result is the opposite we observed in the present work and we suppose this difference is due both to the choice of auditory stimuli and the biomarker for physiological maturation. In the study by Pasman and coworkers (1992) the stimulus was a click, while we used speech stimuli (the phoneme /da/). Also, as pointed before, the latency of the P1 component is the gold standard for evaluating the maturation of cortical auditory pathways (Ceponiene, Rinne, & Naatanen, 2002; Cunningham et al., 2000; Kihara et al., 2010; Kushnerenko et al., 2002; Ohlrich & Barnet, 1972; Ponton, Eggermont, Kwong, & Don, 2000; V. L. Shafer et al., 2015; Silva, Magliaro, Carvalho, & Matas, 2017; Wunderlich & Cone-Wesson, 2006).

Our results are corroborated by findings in studies of auditory recognition memory (deRegnier, Wewerka, Georgieff, Mattia, & Nelson, 2002), binocular vision (Jandó et al., 2012), and language comprehension (Gonzalez-Gomez & Nazzi, 2012), which show advantages of healthy preterms over terms in these abilities. However, our results differ from visual evoked potential (VEP) measures of visual system development in preterms (Sayeur et al., 2015; Tremblay et al., 2014). These studies show that preterm

birth affects the development of visual pathways, as measured with both the latency and amplitude of the P1 component (Sayeur et al., 2015; Tremblay et al., 2014). The preterm group in both studies, however, was composed of very preterm infants, which may have been SGA at birth.

Conclusion

The present results reinforce the notion that early exposure to structured and socially relevant extrauterine environments contributes to the adaptive maturation of sensory pathways. This understanding is of practical importance because preterm birth is on the rise worldwide and the affected individuals would benefit from measures that help them overcome their developmental odds. For instance, many preterms need to remain hospitalized in the neonatal intensive care unit (NICU), isolated from their parents and subject to continuous loud noises or visual deprivation (Wachman & Lahav, 2011). These conditions can be detrimental to the maturation of cortical sensory circuits.

Limitations

The main limitation in the present work is the small sample number. Also, it is known that there are intrinsic and extrinsic variables that interfere in the cortical maturation rate and, consequently, in the latency values of CAEP components. In the present study, only the extrinsic variables (environmental exposure) were considered.

Abbreviations

ABR: auditory brainstem response

CA: corrected age

CAEP: cortical auditory evoked potential

DPOAE: Distortion Product Otoacoustic Emissions

GA: gestational age

NICU: neonatal intensive care unit

SGA: small for gestational age

VCS: vulnerable child syndrome

VEP: visual evoked potential

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte (#340.110) and written informed parental consent was obtained on behalf of all participants.

Consent for publication

Not applicable.

Availability of data and materials

The anonymized data collected are available under request

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

HGC, KFA, SAB, and AP analyzed and interpreted the patient data. HGP, ADSN, BKSC, KFA, SAB, and AP collected patient data. All authors read and approved the final manuscript.

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Table

Table 1

	Total Sample N=23	Preterm n=13	Term n=10	
		n(%)		p value
Maternal age ¹				
< 34 y.o. ²	8(66.67)	2(50.00)	6(75.00)	> 0.05
> 35 y.o.	4(33.33)	2(50.00)	2(25.00)	
Education ³				
Less than middle school	17(94.44)	10(100.00)	7(87.50)	> 0.05
More than middle school	1(5.56)	0(0.00)	1(12.50)	
Sex of child				
Male	10(43.48)	6(42.85)	4(44.44)	> 0.05
Female	13(56.52)	8(57.15)	5(55.56)	
Gestational age				
28 to <32 weeks	1(4.35) ⁴	1(7.14)	0(0.00)	
32 to < 37 weeks	13(56.52)	13(92.86)	0(0.00)	—
> 37 weeks	9(39.13)	0(0.00)	9(100.00)	
Birth weight ⁵				
< 1,500 g	0(0.00)	0(0.00)	0(0.00)	0.0147
1,500 to < 2,500 g	9(45.00)	8(61.54)	0(0.00)	
> 2,500 g	11(55.00)	5(38.46)	7(100.00)	
Family income (in minimum wages) ⁶				
< 1	7(46.67)	4(50.00)	3(42.86)	> 0.05
1 to 4	7(46.67)	4(50.00)	3(42.86)	
> 5	1(6.66)	0(0.00)	1(14.28)	
Socioeconomic Status ^{7,8}				
A	0(0.00)	0(0.00)	0(0.00)	> 0.05
B	3(15.00)	0(0.00)	3(37.50)	
C	3(15.00)	2(16.67)	1(12.50)	
D	9(45.00)	7(58.33)	2(25.00)	
E	5(25.00)	3(25.00)	2(25.00)	
NICU admission ⁹				
No	6(42.85)	3(50.00)	3(37.50)	> 0.05
Yes ¹⁰	8(57.15)	3(50.00)	5(62.50)	

¹ 11 missing values; ² y.o.: years old; ³ 5 missing values; ⁴ 31.28 weeks; ⁵ 3 missing values; ⁶ 8 missing values; ⁷ 3 missing values; ⁸ Brazil Economic Classification Criteria (www.abep.org/criterio-brasil); ⁹ 9 missing values; ¹⁰ all infants stayed in NICU for 2 days

Figures

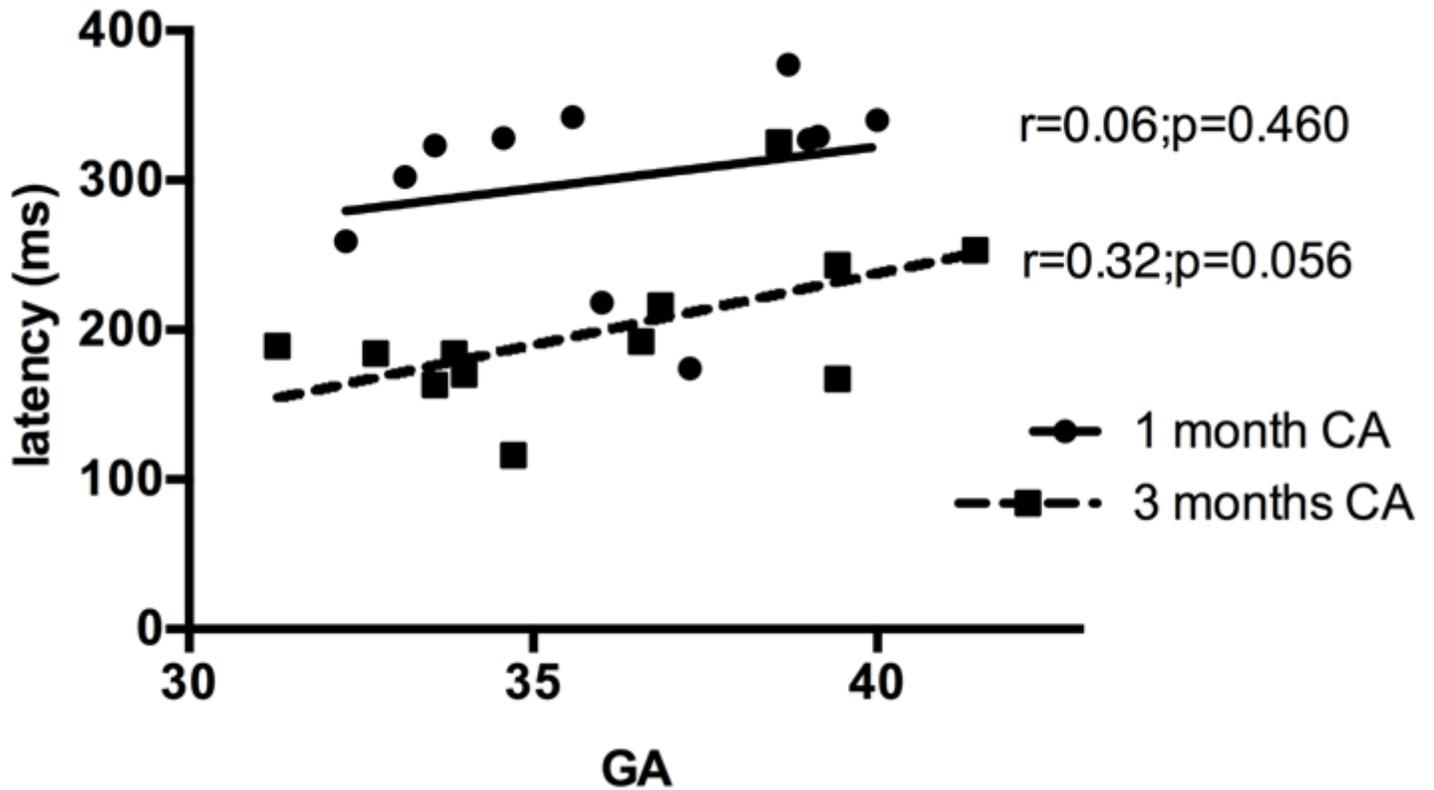


Figure 1

P1 latencies recorded at 1 and 3 months CA as a function of GA. Linear regression lines are superimposed on the raw data for the CAEP recordings at 1 and 3 months CA, respectively.

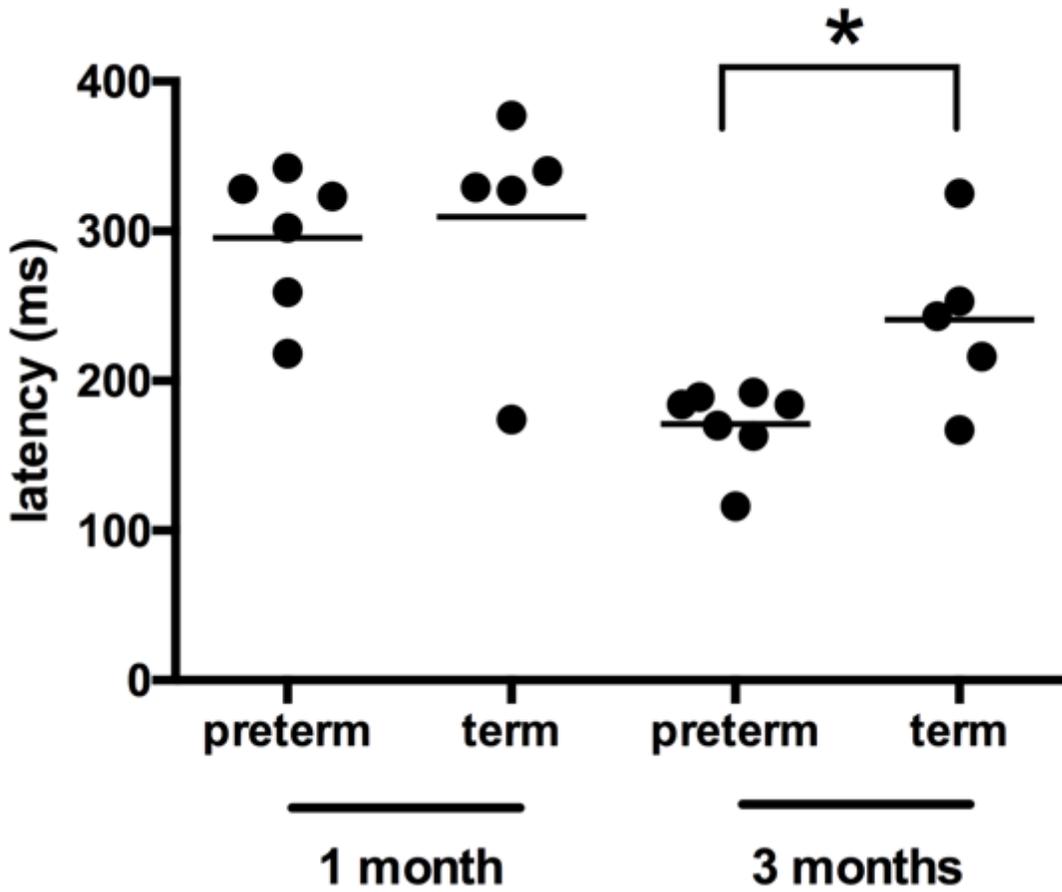


Figure 2

Latency of the P1 component of the CAEP of preterm (GA<37 weeks) and term (GA≥37 weeks) infants recorded at 1 or 3 months CA. Lines represent median. * p<0.05