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Research paper

Electrophysiological auditory response to acoustically modified syllables in preterm and full-term infants



María Elizabeth Mónica Carlier ^{a,*}, Thalía Harmony ^a,
Omar Mendoza-Montoya ^b, Jose L. Marroquin ^c, Donna Jackson-Maldonado ^d,
Josefina Ricardo-Garcell ^a

^a Unidad de Investigación en Neurodesarrollo "Augusto Fernández Guardiola", Departamento de Neurobiología Conductual y Cognitiva, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus Juriquilla. Boulevard Juriquilla 3001, Querétaro, 76230, Mexico

^b Freie Universität Berlin, Department of Mathematics and Computer Science, Arnimallee 7, 008, 14195, Berlin, Germany

^c Departamento de Ciencias de la Computación, Centro de Investigación en Matemáticas (CIMAT), Jalisco S/N, Col. Valenciana CP. 36240, Guanajuato, Gto, Mexico

^d Facultad de Lenguas y Letras, Universidad Autónoma de Querétaro (UAQ), Centro Universitario, Cerro de las Campanas, Santiago de Querétaro, Qro, C.P. 76210, Mexico

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ABSTRACT

This study explored the effect of extending the duration of the syllable formant transition on auditory habituation in full-term and preterm infants at 12 months, as measured by decreases in amplitude for syllable repetition using EEG time–frequency analyses. EEG recordings for four repetitions of the syllable (/ta/) under two different conditions (non-modified and modified) were collected for one group of 13 full-term and two groups of preterm infants differing in language production performance; 15 infants had high scores (HS), and 14 had low scores (LS). Full-term and HS preterm infants showed significant decreases in amplitude for syllable repetition in both conditions. LS preterm infants showed a decrease only in the modified syllable condition, suggesting a facilitation effect of modified syllables in the LS preterm group.

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1. Introduction

Preterm infants have a higher risk of developing cognitive disorders than healthy, full-term infants (e.g., [Ortiz-Mantilla, Choudhury, Leevers, & Benasich, 2008](#)), and these cognitive disorders often manifest as language development problems ([Kurtzberg, Hilpert, Kreuzer, & Vaughan, 1984](#); [Sansavini et al., 2011](#)). Studies using indirect measures of processing speed, such as paired comparison and habituation, show that preterm infants process visual (e.g., [Rose, Feldman, Jankowski, & Caro, 2002](#)) and auditory information (e.g., [Peña, Pittaluga, & Farkas, 2010](#); [Ramon-Casas, Bosch, Iriondo, & Krauel, 2013](#)) more slowly than full-term infants.

* Corresponding author.

E-mail addresses: carliermonica@gmail.com (M.E.M. Carlier), thaliah@unam.mx (T. Harmony), omar.mendoza@fu-berlin.de (O. Mendoza-Montoya), jlm@ciamat.mx (J.L. Marroquin), djacksonqro@gmail.com (D. Jackson-Maldonado), oojrg@yahoo.com (J. Ricardo-Garcell).

Harmony et al. (2009) suggested impaired auditory cortical processing in infants at risk for cerebral damage with normal hearing. These authors found differences in oscillatory brain activity during the processing of linguistic (syllables) and non-linguistic stimuli (tones) between full term and at-risk infants at 6 weeks of age. A further study conducted by *Avecilla-Ramírez et al. (2011)* suggested that altered cortical sound processing in at-risk infants is related to impaired language acquisition in subsequent child development.

In particular, *Avecilla-Ramírez et al. (2011)* showed that the time–frequency EEG measures of 6-week-old infants during the processing of repeated syllables and tones could discriminate between infants with different risk levels for language development who later, at 14 months of age, scored high or low on a standard language inventory. The researchers suggested that an alteration in the low scoring infants' sensory memory could affect the habituation effect.

The habituation process has been studied as an indirect measure of processing speed. In fact, a significant relationship has been found between habituation, auditory temporal processing, and recognition memory, suggesting that these measures of information processing are based on a similar mechanism: processing speed (*Benasich & Tallal, 1996*). In particular, the researchers found that 6-month-old full-term infants who could process rapidly (lower auditory temporal processing thresholds) also habituated more efficiently (fewer trials to reach habituation and steeper habituation slopes) and discriminated better (higher scores for novel image recognition memory).

Processing speed plays an important role in speech temporal perception for phoneme representation (*Eimas, Siqueland, Jusczyk, & Vigorito, 1971; Pisoni, 1973*). The auditory signal unfolds over time; therefore, the process of decoding input sounds to link them to meaningful objects requires integrating sensory information over time at multiple scales (*Poehpel, 2003*). In speech perception, this temporal integration must occur in at least two distinct time scales that are related to syllable-level (approximately 200 ms or 5 Hz) or phonemic level (approximately 25 ms or 40 Hz) information (*Doelling, Arnal, Ghitz, & Poehpel, 2014*). This multi-time resolution analysis and integration could be performed in the auditory cortex using neuronal oscillations to parse the stimulus into meaningful chunks that are appropriate for subsequent decoding, enhancing perception and intelligibility (*Doelling et al., 2014; Ghitz, 2011*). Similar results have been shown in studies of the oscillatory brain activity in healthy full-term infants.

Ortiz-Mantilla, Hämäläinen, Musacchia, and Benasich (2013) reported amplitude increases at 4–6 Hz (theta) and phase synchronization at 2–4 Hz (delta/theta) in 6-month-old full-term infants during syllable processing. *Bosseler et al. (2013)* also showed amplitude increases over baseline in theta in 6-month- and 12-month-old full-term infants. *Zhang et al. (2011)* investigated neural coding of formant-exaggerated speech in 6–12-month-old full-term infants and reported increases in the EEG amplitude in delta, at the frontal-central-parietal electrode, and in the theta band, at the frontal-central electrode, in response to vowels pronounced using formant-exaggerated speech, which is known as motherese, compared to speech addressed to adults.

Limitations in decoding temporal cues to discriminate phonemes can be detected in infants (*Trehub & Henderson, 1996*); they are predictive of later language difficulties (*Benasich & Tallal, 2002; Choudhury & Benasich, 2011*) and are associated with poor language learning at school age (*Merzenich, Jenkins, Jonson, Schreiner, Mille, Tallal, et al., 1996; Tallal, Miller, Bedi, Byrna, Wang, Nagarajan, et al., 1996*). One approach for ameliorating such impairment in school-aged children is to use acoustically modified syllables to lengthen the transition and enhance the contrast between phonemes, implementing a digital signal processing algorithm to modify the fast amplitude envelope modulations of the speech signal (*Nagarajan, Wang, Merzenich, Shreiner, Johnston, Jenkins, et al., 1998*).

The amplitude envelope of the speech signal provides information about syllables (syllabic rhythm) or serves as the basis for entrainment between speakers and listeners (*Giraud & Poehpel, 2012*). One hypothesis is that the delta–theta brain oscillations are realigned with the critical bands of the envelope of the speech signal, which is the crucial property that carries the temporal and syllabic information about the signal (*Doelling et al., 2014*).

The use of modified speech as a therapeutic treatment to improve the discrimination of phonemes in school-aged children with limited processing speed has generated a vigorous debate in the academic community. Some studies supporting the procedure are the work of *Heim, Friedman, Keil, and Benasich (2010)* and *Choudhury and Benasich (2011)*. Among those studies with contrasting results are *Studdert-Kennedy and Mody (1995)* and *Strong, Torgerson, Torgerson, and Hulme (2011)*.

As preterm birth is a risk for impaired cognitive development and preterm infants often perform poorly in tasks thought to depend on processing speed (e.g., *Escobar, Littenberg, & Petitti, 1991*), modified speech that prolongs the duration of the syllable formant transition could facilitate speech processing in preterm infants at risk for language development problems.

The purpose of this study is to examine whether exposure to acoustically modified syllables that prolong the duration of the syllable formant transition facilitates perceptual processing of syllables in preterm infants. The facilitation effect was measured by examining auditory habituation through the time–frequency analysis of the EEG recordings during the processing of repeated syllables from three groups of 12-month-old-infants: full term, preterm with high language production scores and preterm with low language production scores. For preterm infants, the corrected age was considered. The auditory habituation task is particularly suitable for our purpose because it is a measure that is present from the first months of life (*González-Frankerberger et al., 2008; Ramon-Casas et al. 2013; Rose et al., 2002*) and is an indirect measure of processing speed. We hypothesized that the extension of the syllable formant transitions would facilitate auditory habituation in preterm infants who are at risk for language development problems.

2. Method

2.1. Ethics statement

The ethics committee of the Instituto de Neurobiología, Universidad Nacional Autónoma de México approved this study, which also complies with the Ethical Principles for Medical Research Involving Human Subjects established by the Declaration of Helsinki. Informed written parental consent for participation was obtained for all infants, anonymity was maintained, and all files were safeguarded.

2.2. Participants

We studied a total of 42 infants from middle class and working class Mexican families residing in Queretaro, a mid-sized city located in central Mexico. All infants were monolingual Spanish speakers. Twenty-nine (9 girls) infants were preterm, and 13 (7 girls) were full term. The preterm and full term infant samples for this study were selected from a large research project at Unidad de Investigación en Neurodesarrollo (Neurodevelopment Research Unit) of the UNAM-Institute of Neurobiology. Prior to the experiment, the following examinations were performed on the infants to establish that they met specific inclusionary criteria:

2.2.1. Clinical examination by an expert pediatric neurologist

For the preterm infants, the inclusion criteria encompassed mild to moderate abnormal neurological signs, and for the full-term infants, the inclusion criteria encompassed normal neurological signs, according to the Amiel-Tison's neurological assessment criteria (Amiel-Tison, 2002). For both groups, the exclusion criteria included severely abnormal neurological signs, according to the Amiel-Tison's criteria, such as clinical epilepsy, genetic syndromes, muscular pathology, and metabolic syndromes.

2.2.2. Magnetic resonance imaging examination (MRI)

Scans were obtained using a 1.0-T Philips Intera in axial planes. A licensed pediatric radiologist reviewed all of the MRI scans. All preterm infants had dilated ventricles that may be a sequel of diffuse PVL. For both preterm groups, the exclusion criteria were: cystic PVL, cerebral hemorrhages, brain infarcts, or brain malformations.

2.2.3. Clinical electroencephalograms (EEGs)

Data were analyzed by a clinical neurophysiologist. For both preterm groups, the inclusion criteria comprised normal EEG or non-ictal paroxysmal activity, and the exclusion criteria included epileptiform activity or periods of marked background attenuations (i.e., amplitude of less than 5 μ V).

2.2.4. Visual evoked potentials (VEPs)

VEPs were obtained to ensure visual system integrity. For both groups, the inclusion criterion was normal VEPs.

2.2.5. Brain stem auditory evoked potentials (BAEPs) and auditory steady state (ASS) responses

For both groups, the inclusion criteria included normal BAEPs and ASS responses. The exclusion criterion was hypoacusia.

2.3. Stimuli

The phonetic stimuli consisted of a consonant-vowel syllable, /ta/, that is naturally produced by a female adult whose mother tongue was Spanish. The same syllable was acoustically modified to prolong the duration of the formant transition and to create a more salient version of the rapidly changing elements in the acoustic waveform of speech. The acoustical modification was performed using Praat, a free computer software package for speech analysis designed by Boersma and Weenink (2013), following procedures similar to those proposed by Nagarajan et al. (1998). We prolonged the signal by 50% and applied an emphasis algorithm available in Praat to enhance the contrast between phonemes. See Fig. 1.

The syllable/ta/was used for two reasons. First, it had already been used in a previous study to examine the processing of repeated syllables by AVECILLA-RAMÍREZ et al., 2011. Second, the contrast between dental consonants (such as/t/) is likely to be one of the first contrasts acquired in normal development in children whose first language is Spanish (ACEVEDO, 1993).

The syllable/ta/is formed by the consonant/t/, which has a dental articulation point, an occlusive articulation mode, and deaf loudness, and the vowel/a/, which has a central position and a low and open high. The sound intensity was adjusted so that it was perceived to 78 dB in the infants' ears.

Two similar paradigms, one with non-modified syllables and the other with modified syllables were designed. Both paradigms were adapted from the one in AVECILLA-RAMÍREZ et al. (2011). The stimuli were presented in trains (total 100 trains) of four syllables with an interval of 890 ms from syllable onset to onset and a 2 s inter-block interval. Each participant heard both paradigms and the presentation was counterbalanced between subjects.

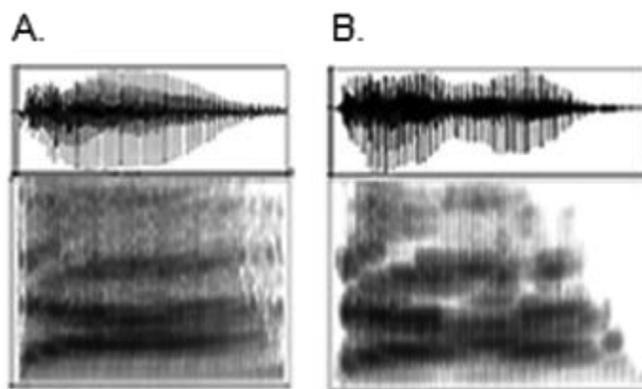


Fig. 1. Waveforms and spectrograms for the syllable/ta/. Time is represented on the abscissa and amplitude and frequency (0 Hz–5000 Hz) on the ordinate. The darkness of the trace indicates the amount of energy in the signal at that particular frequency and time. A. Syllable in the non-modified condition, total duration of 260 ms, and formant transition duration of 45 ms. B. Syllable in the modified condition, total duration of 380 ms, and formant transition duration of 90 ms. In both conditions, the syllables were matched for intensity (78 dB).

2.4. Recording

The EEG recording was performed by placing an infant Electro-Cap fitted with electrodes of the 10/20 international system: Fp1, Fp2, F3, F4, F7, F8, C3, C4, Fz, Cz, Pz, T3, T4, T5, T6, P3, P4, O1, and O2. The references were short-circuited in the earlobes. The sampling time was 5 ms (one sample every 5 ms), and the filter band was set between 0.2 Hz and 30 Hz. Editing for motion artefacts was performed off-line, and infants with less than 25 artefact-free trials were rejected. The initial sample was 47 infants, but only 42 infants achieved the artefact-free trial criterion. The amplitude changes relative to the pre-stimulus were determined by windows comprising 1000 ms for the pre stimulus and 3560 ms for the post stimulus.

The infants were recorded while they were asleep at 12 months. Corrected age was considered for preterm infants. The infant's heads were clean and dry. Once the Electro-Cap was placed, parents or caregivers fed them until they fell asleep. Registration took place in a sound-proof room under stable temperature and dim light. The mother held the infant during the session and two speakers were placed 100 cm from each of the baby's ears. The study lasted for approximately 1 h.

2.5. Assessment of language abilities

The Spanish version of the McArthur-Bates Communicative Development Inventories (SMBCDI), First Words and Gestures, was used to assess language production when the infants were 12 months old. This is a parent report instrument that is standardized for the Mexican population (Jackson-Maldonado et al., 2003) and that consists of vocabulary comprehension and production scales and a gesture section.

The questionnaire is completed by parents, and then, speech therapists make a direct observation to verify the information provided by the parents to avoid inaccuracies in responses due to a parent's inability to comprehend the questionnaire instructions. Control of this factor is important because some parents tend to overestimate or to underestimate the performance of their children.

Because it has been reported that not all preterm infants present cognitive disorders (Volpe, 2009) that affect language acquisition, we split the preterm infants into two groups using the median of the number of words produced as measured by the Spanish McArthur-Bates Communicative Development Inventories (SMBCDI) as a criterion. This test was applied at 12 months. Those preterm infants with scores below the median were classified as at-risk infants, and those with scores above or equal to the median were classified as infants at no risk for language development problems. The score of word production was chosen to split the preterm groups because it is one of the most objective subtests and ensures that the children have started to produce words for the purpose of communication. Details on the participants are shown in Table 1.

The average number of words produced was 14 (SD = 10, range = 6–36) in the full-term group, 20 (SD = 17, range = 7–58) in the HS preterm group, and 4 (SD = 1, range = 2–6) in the LS preterm group. As expected, no significant differences were observed between the productive lexicons of the full-term and HS preterm groups. Significant differences were observed between the productive lexicons of the full-term and LS preterm groups ($t = 3.9$; $p < 0.001$, $d = 25$) and between the HS preterm and LS preterm groups ($t = 3.4$; $p < 0.002$, $d = 27$). None of the participants had vocabularies below the 10th percentile, which can indicate an expressive lexical delay.

2.6. Data analysis

To evaluate oscillatory brain activity, we used the methodology of power changes with respect to the pre-stimulus in electroencephalographic signals proposed by Marroquin, Harmony, Rodríguez, and Valdés (2004). This technique involves

Table 1

Information on the infant sample. F= Female. M = Male. GE = Gestational Age. SCDI; Spanish McArthur Communicative Development Inventories.

	Participants	Sex	GE	Words	Percentiles
Term	1	F	38	6	60
	2	F	39	6	60
	3	F	40	7	64
	4	F	39	8	65
	5	M	41	8	65
	6	F	38	10	70
	7	M	38	12	75
	8	F	39	12	75
	9	M	41	12	75
	10	M	38	18	81
	11	F	40	26	89
	12	M	39	31	93
	13	M	39	36	92
High score preterm	1	M	32	7	64
	2	M	35	7	64
	3	M	33	8	65
	4	F	35	8	65
	5	M	34	8	65
	6	F	26	8	65
	7	M	30	9	69
	8	F	35	10	70
	9	M	32	15	79
	10	M	33	18	81
	11	F	33	25	88
	12	M	36	32	91
	13	F	35	35	92
	14	M	35	56	99
	15	M	30	58	99
Low score preterm	1	F	27	2	50
	2	M	28	3	51
	3	M	34	4	53
	4	M	31	4	53
	5	M	28	4	53
	6	M	33	4	53
	7	F	36	4	53
	8	M	33	4	53
	9	M	32	4	53
	10	F	27	4	53
	11	M	35	5	54
	12	M	30	5	54
	13	F	30	6	55
	14	M	34	6	55

detecting changes in the amplitude, log-amplitude or power of the oscillatory cerebral activity against a baseline. The method is based on the time–frequency decomposition of the experimentally obtained EEG.

One method to represent a time-series in the time–frequency domain is short-time Fourier transform. This method transforms a signal at a given time of interest t_0 by multiplying the signal with a time window $w(t)$ centered at t_0 (i.e., $w(t - t_0)$) and by taking the Fourier transform of the resulting signal. Then, the local spectrum can be obtained, that is, the signal power at frequencies $2k\pi/N$, for $k = 0, \dots, N - 1$, where N is the total number of samples, and used to compute a time–frequency representation of the signal.

Alternatively, a bank of complex-valued band-pass filters (quadrature filters) can be constructed with tuning frequencies f_1, \dots, f_K , where the impulse response of the k^{th} filter is given by:

$$h_k = w(t)\exp[i f_k t] \text{ where } i = \sqrt{-1}.$$

If the tuning frequencies of the filters coincide with the Fourier frequencies $2k\pi/N$ for $k = 0, \dots, N - 1$, then both approaches coincide. However, the filter bank approach is more flexible because frequencies can be chosen that are easier to interpret, e.g., 1 Hz, 2 Hz, and so on, so this is the approach that we adopted for this study. The shape of the window function $w(t)$ determines the temporal resolution of the analysis, which is inversely proportional to the frequency resolution (the uncertainty principle). In continuous time, the Gaussian shape is the one that simultaneously maximizes both resolutions; when this shape is adopted, the filters are known as Gabor filters and are the ones that we chose to use in the current study.

One of the advantages of this approach is that because each time point has an associated frequency spectrum, defining a priori epochs that correspond to different events (e.g., each syllable or the complete syllable train) is unnecessary. Rather,

after the decomposition is performed, the power over regions of the time–frequency space can be averaged to perform the desired statistical analysis.

For data analysis, we consider changes in power in the brain activity against a baseline in the frontocentral region (electrodes C3, C4, Cz, F3, F4, Fz) because brain activity in this area is generated by the auditory cortex within the superior temporal plane and conducted to the surface by volume (Kurtzberg et al., 1984). We analyzed the delta and theta frequency bands because the reactivity of these bands to syllabic processing in infants and adults has been previously reported (e.g., Poeppel, 2003; Bastiaansen, Linden, Keurs, Dijkstra, & Hagoort, 2005; Doelling et al., 2014, Ortiz-Mantilla et al., 2013; Bosseler et al., 2013).

Changes in power with respect to the pre-stimulus were calculated over the time interval of 0 ms–4560 ms (1000 ms before stimulus presentation and 3560 ms after) for each subject in each experimental condition. These values were calculated from the time–frequency decomposition of the EEG signal. The objective was to estimate the local power in the signal to a set of frequency bands for each electrode.

As stated before, the time–frequency decomposition was accomplished by means of a set of band-pass Gabor filters applied to the EEG. These filters were tuned to frequencies ranging from 1 Hz to 8 Hz and had a bandwidth of approximately 5.0 Hz at a 3 db gain. The latency interval was considered with respect to the stimulus onset, t ; the frequency, f ; and the head electrode location, e . For more details about this method, see Marroquin et al. (2004).

The amount of spectral power change at a given time and frequency was color coded, with increases over the baseline level shown in increasingly warm (red) colors. A pre-stimulus segment was used as the baseline, and the values indicate the relative change after subtracting the baseline mean and dividing by the pre-stimulus standard deviation.

The mean value of the power increments corresponding to the first and second syllable (from onset to onset of each syllable, equivalent to a time interval of 890 ms) was then calculated for each frequency band studied, delta (1 Hz–3 Hz) and theta (4 Hz–8 Hz) in the frontocentral (electrodes C3, C4, Cz, F3, F4, Fz) region for each group for each condition. As the data do not have a Gaussian distribution, such means were evaluated with non-parametric methods to determine significant differences.

To determine whether there were differences among the three groups (Full-term, HS preterm, and LS preterm) the Kruskal Wallis test for independent samples was applied; to examine the contrasts between two groups, the Mann–Whitney test was applied. To examine differences between conditions in the same group, we used the related samples Wilcoxon Signed Rank test. The repetition effect (habituation) in each group was evaluated as the significant lower power of the EEG activity in response to the second syllable relative to the first using the related samples Wilcoxon Signed Rank test.

In the study of the oscillatory EEG responses, any change in oscillatory activity that is related to an experimental event is time-locked to the event, but not necessarily phase-locked to the event. The reason for this is that oscillations are ongoing phenomena present in the absence of any experimental task. As a result, the phase of the oscillations at the time of the occurrence of the event is variable (Bastiaansen & Hagoort, 2006). In particular there are two types of oscillations related to the event: phase-locked event-related EEG responses, known as evoked power, and non-phase-locked event-related EEG responses, known as induced power (Pfurtscheller & Lopes da Silva, 2005). Although both types of oscillatory responses (evoked and induced) may be meaningfully related to the event in question, averaging of a number of trials in which this response occurs (i.e. using the ERP approach) cancel out the non-phase-locked responses. The trial-by-trial power analysis includes both induced and evoked response data, and ERP waveform analysis includes primarily evoked response data; therefore, both methods do not necessarily agreed with each other.

In the present study, in addition to the trial by trial power analysis, averaged ERP waveforms were also calculated at the electrodes C3, C4, Cz, F3, F4, Fz. The ERP epoch length was 100 ms pre-stimulus baseline interval and 3560 ms post-stimulus interval. The N1 and P2 peaks of the first and second syllable were analyzed at these electrodes. The search windows for N1 and P2 were respectively at 0–120 ms for N1 and 120–250 ms for P2. Average peak amplitudes were quantified in each window. As the data do not have a Gaussian distribution, to determine significant differences between the first and the second syllable, non-parametric methods were used. The repetition effect (habituation) in each group was evaluated as the significant lower amplitude of the N1 and P2 average peaks in response to the second syllable relative to the first using the related samples Wilcoxon Signed Rank test.

3. Results

Time–frequency response maps to each condition per group are presented in Fig. 2. In general, by visual inspecting such maps, it is possible to observe amplitude increases relative to the pre-stimulus in the first syllable for all three groups in both conditions.

The repetition effect may be observed in Table 2. For the non-modified or non-exaggerated syllables, a typical auditory habituation effect (reduced amplitude from first syllable to second syllable in the 4-syllable train) was found for the term infants in the theta band and for the HS preterm infants in the delta and theta band, but not in the LS preterm group (Fig. 3A). For the exaggerated or modified syllables, all three infant groups showed the effect in the theta band, and the term group also showed the effect in the delta band (Fig. 3B). Fig. 2 presents these differences visually in time–frequency plots of each group in each condition.

Differences in power increases between groups in both conditions may be observed in Table 3. For the non-modified syllables, term infants showed lower power than the HS preterm group in the first syllable in the delta band. Term infants

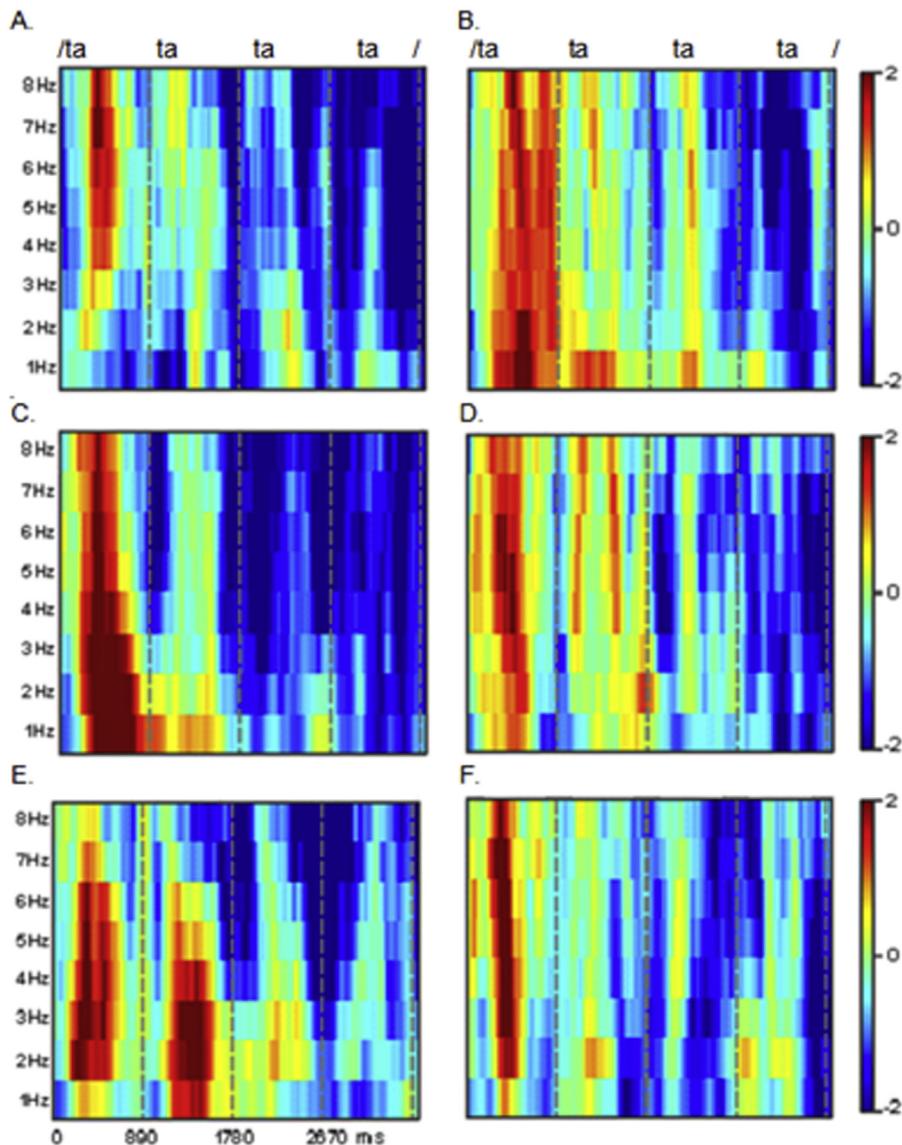


Fig. 2. Time–Frequency Representation of the infants' brain activity during processing of repeated syllables. On the X axis is the duration of the train of four syllables. On the Y axis is the frequency corresponding to the delta (1 Hz–3 Hz) and theta (4 Hz–8 Hz) bands. The vertical dotted lines represent the end of each syllable. The color palette represents changes of amplitude with respect to a prestimulus. A, C, and E depict the responses of the Term, HS preterm, LS preterm groups, respectively, in the non-modified syllable condition. B, D, and F represent the responses of the Term, HS preterm, and LS preterm groups, respectively, in the modified syllable condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

also showed lower power than the LS preterm group in the second syllable in the delta band (Fig. 3C). For the modified syllables, term infants had higher power than the other two groups in the first syllable in the delta band. In the theta band, the term and HS preterm groups showed greater power than the LS preterm group only for the first syllable (Fig. 3D).

Differences between conditions were only observed in the term and LS preterm groups. In the term group, the amplitude increases in the delta range in the first ($p < 0.002$) and second ($p < 0.028$) syllables were higher in the modified syllable condition than in the non-modified syllable condition (Fig. 3E). In the LS preterm group, the amplitude increases in the second syllable were higher in the delta ($p < 0.026$) and theta ($p < 0.030$) bands in the non-modified syllable condition than in the modified condition (Fig. 3F). In the HS preterm group, no differences were observed between the conditions.

Finally, because we observed that the LS preterm group in the modified syllable condition looks like the term group in the non-modified syllable condition, we compared the first and second syllables of these groups using the Mann–Whitney test, and no significant differences were found, confirming that the responses of these two groups were similar.

The averaged ERP waveforms are presented in Fig. 4. The Auditory habituation effect (lower amplitude of the N1 or P2 average peaks in response to the second syllable relative to the first) was found for the term infants in the modified syllable

Table 2

Repetition effect. T = Term. HS = High Score preterm group. LS = Low Score preterm group. S1: First syllable. S2: Second Syllable.

Condition	Group	S1 vs. S2 Sig.	
		Delta	Theta
Non-modified syllables	Term	p < 0.087	p < 0.013*
	HS preterm	p < 0.005*	p < 0.004*
	LS preterm	p < 0.397	p < 0.330
Modified syllables	Term	p < 0.002*	p < 0.003*
	HS preterm	p < 0.211	p < 0.011*
	LS preterm	p < 0.245	p < 0.002*

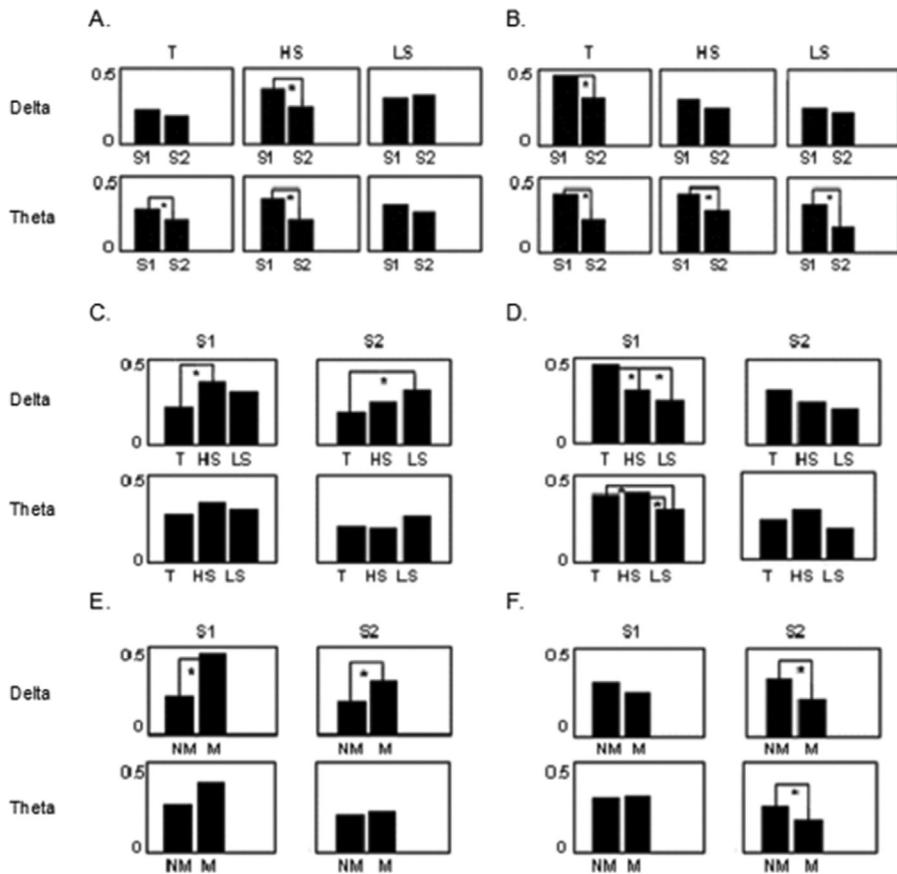


Fig. 3. A. Repetition effect for non-modified syllables. B. Repetition effect for modified syllables. C. Group differences in the non-modified syllables. D. Group differences in the modified syllables. E. Condition differences for the term group. F. Condition differences for the LS preterm group. S1: First Syllable and S2: Second Syllable. T: Term, HS: High Score Preterm. LS: Low Score Preterm. NM: Non-Modified Syllables. M: Modified Syllables. On the Y axis are the average values of the changes of amplitude with respect to the prestimulus. * = Significant differences.

Table 3

Differences between groups. T = Term group. HS = High Score preterm group. LS = Low Score preterm group. S1: First syllable. S2: Second Syllable.

Condition	Band	Syllable	Kruskal–Wallis Sig. ($\alpha = 0.05$)	Mann–Whitney U test	Sig. ($\alpha = 0.05$)
Non-Modified	delta	S1	p < 0.046*	T < HS T < LS	p < 0.019* p < 0.085
		S2	p < 0.036*	T < LS	p < 0.014*
	theta	S1	p < 0.389		
		S2	p < 0.171		
Modified	delta	S1	p < 0.009*	T > HS T > LS	p < 0.019* p < 0.005*
		S2	p < 0.217		
	theta	S1	p < 0.043*	T > LS HS > LS	p < 0.048* p < 0.020*
		S2	p < 0.106		

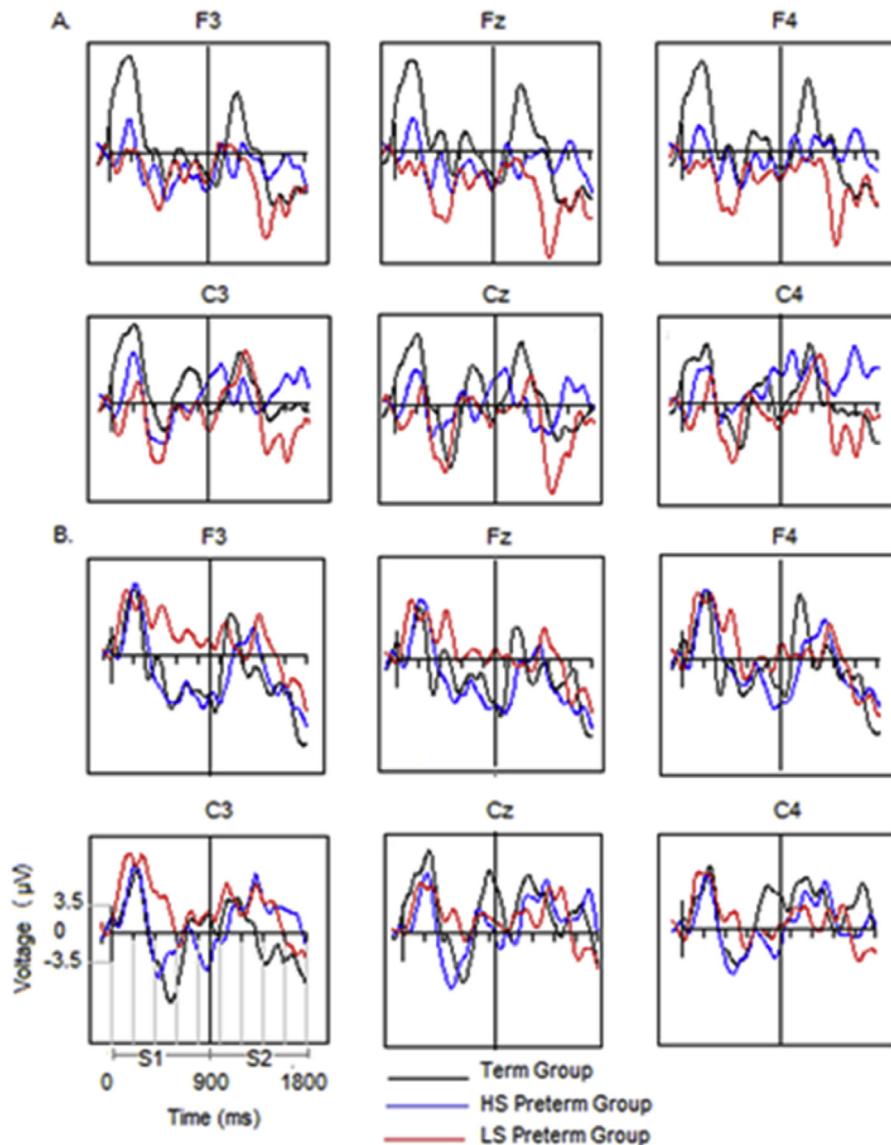


Fig. 4. Grand mean ERP waveforms of the infants' brain activity during processing of the first 2 repeated syllables of a train of 4. On the X axis is the duration of the two syllables. On the Y axis is the amplitude in μV . A depicts the responses in the frontocentral region (C3, C4, Cz, F3, F4, and Fz) of the Term, HS preterm, LS preterm groups respectively, in the non-modified syllable condition. B represents the responses of the Term, HS preterm, and LS preterm groups, respectively, in the modified syllable condition.

condition, in the N1 component in C3 ($p < 0.034$), and in the P2 component in F3 ($p < 0.028$). The habituation effect was also found in the HS preterm group, in the N1 component in C3 ($p < 0.035$) in the non-modified syllable condition, and in the P2 component in F3, F4, and Fz (respectively, $p < 0.027$, and $p < 0.047$, $p < 0.041$) in the modified syllable condition. No significant differences were observed between the first and second syllable in the ERP of the LS group.

4. Discussion

This study explores the effect of manipulating the phonetic elements of speech by extending the duration of the syllable formant transition and by then examining the effect of this manipulation on infants' auditory habituation using time–frequency analyses. For the non-exaggerated syllables, the typical auditory habituation effect (reduced amplitude from first syllable to second syllable in the 4-syllable sequence) in the theta band was found for the full-term and HS preterm infants, but not in the LS preterm group. For the exaggerated syllables, all three infant groups showed the effect in the theta band. These data supports our hypothesis that temporal exaggeration facilitates the processing of repeated syllable in the LS preterm group, which is at risk for language development problems.

Overall, for both non-modified and modified syllables, the responses of the three groups during the processing of syllables elicited amplitude increases with respect to the baseline in the first syllable in the delta and theta bands. This response had already been observed in studies on language in infants (Bosseler et al., 2013; Ortiz-Mantilla et al., 2013; Zhang et al., 2011) and is consistent with the adults' multi-time resolution analysis model of the speech signal (Doelling et al., 2014; Ghitza, 2011; Poeppel, 2003). Therefore, the results of this study support previous reports about the processing of syllables, not only in full term infants but also in preterm infants. To our knowledge, few studies of the local functional network involved in processing repeated syllables have been conducted.

The difference between the conditions in the LS preterm group highlights the difficulty in processing non-extended syllables in at-risk infants. In the LS preterm group, the amplitude increases for the modified syllables were lower than those for the non-modified syllables, while the opposite occurred in the term group. This difference in the term group can be explained by the longer duration of the modified syllables because longer stimuli elicit greater EEG amplitude responses than shorter stimuli (Grill-Spector, Henson, & Martin, 2006; Zhang et al., 2011). Thus, the LS preterm response is atypical. In addition, the differences between the term and the LS preterm group in the second syllable of the train confirm a possible deficit in the LS preterm group. This difference in the second syllable of a train of repeated syllables has also been noted by *Avecilla-Ramirez et al.* (2011) and *Peña et al.* (2010), indicating differences in the habituation effect between term and at-risk preterm infants.

Avecilla-Ramírez et al. (2011) suggested that the absence of habituation in preterm infants with periventricular leukomalacia could be related to alterations in sensory memory that hinder sensory learning (Moore, Halliday, & Amitay, 2009). In the current study, we suggest that the absence of habituation may also be related to a deficit in the processing speed. Such a limitation in processing speed in terms of the memory system may cause a representation of a noisy or degraded phoneme repertory and of a defective processor or noisy model in the brain that limits memory operations in the use of language (Merzenich, 2008). However, more research is needed in this direction.

The differences between term and HS preterm groups most likely have to do with differences in the neuronal mechanisms that are involved in processing repeated syllables. This result is consistent with *Peña et al.* (2010), who described that the term and preterm infants in their study reached auditory habituation at one year old, but with differences in the use of neural networks involved in memory. The presence of the habituation effect in the HS preterm infants and its absence in the LS preterm group in response to the non-modified syllables confirms the theory that not all preterm infants will develop cognitive problems (Volpe, 2009).

However, from the data generated in the current study, we cannot be certain whether the deficit in habituation during the processing of syllabic information in at-risk infants is merely a linguistic or more general problem. Considering the results of other studies that failed to show habituation to visual stimuli in infants at risk for brain damage (*Gonzalez-Franquenberger et al.*, 2008), the deficit may be general rather than merely linguistic. Tallal and collaborators (Tallal et al., 1996) reported a general temporal processing deficit in school-aged children with specific language impairments, further supporting the idea that the deficit of at-risk infants is general. More research is needed in this direction.

Notably, we tested habituation in sleeping infants and compared our results with studies that tested awake infants (*Peña et al.*, 2010) in addition to those that tested sleeping infants (*Avecilla-Ramirez et al.*, 2011; *Gonzalez-Frankenberger et al.*, 2008). The habituation effect can be recorded by EEG in sleeping subjects, as long as the inter-stimulus interval, ISI, is short (Firth, 1973), which is true in our case. *Avecilla-Ramirez et al.* (2011) found intra-block auditory habituation in 6-week-old sleeping infants using ISIs of 500 ms. *Gonzalez-Frankenberger et al.* (2008) found a visual inter-block habituation effect in 3-month-old sleeping term infants using an inter-block interval of 15 s. Consistent with these two prior studies, we found habituation in sleeping full term infants and at-risk infants using a short inter-stimulus interval.

Similarly, we opted to use time frequency analysis of the EEG recording instead of just ERPs because we were interested in studying habituation between stimuli presented rapidly (short ISIs). Some studies have suggested that a failure to detect the habituation effect can occur due to the averaging process necessary for filtering ERPs out of the background EEG, particularly when examining habituation in a block of stimuli separated by short ISIs (*González-Frankenberger et al.*, 2008; *Verbaten, Roelofs, & Sjouw*, 1986).

In fact in this study, we failed to detect habituation in the Term group in the non-modified syllable condition, using ERPs. However, we found the habituation effect in the term group, in the modified syllable condition, in the N1 component in C3 and in the P2 component in F3. We also found the habituation effect in the HS preterm group, in the non-modified syllable condition, in the N1 component in C3, and in the in the modified syllable condition in the P2 component in F3, F4, and Fz. We did not find the habituation effect using ERPs in the LS preterm group. On the other hand, we found the habituation effect in all at-not-risk groups in both conditions using time–frequency analysis. This difference must obey to the different types of information analyzed in each method, evoked power in the ERP and evoked and induced power in the time–frequency analysis. *Peña et al.* (2010) reported habituation in infants using ERPs, but this study differ from the present study in many ways. The infants were register awake, they used an EEG register of 64 electrodes, and their samples were greater (about 26 infants) than ours.

Recently, *Koerner and Zhang* (2015) showed that the adult's auditory ERP responses (N1 and P2) to speech stimuli were correlated with the inter-trial phase coherence measures in the delta, theta, and alpha bands. According to this study, in adults, the alpha band also appears to be an important indicator for speech processing in addition to the delta and theta bands. In the present study we showed that in infants, the repetition effect in delta and theta band are an important indicator for speech processing. We did not find significant habituation effects associated with alpha band power, mainly because this

band is not present in infants at one year old as in adults. The absence of habituation in the alpha band might indicate the immaturity of the system. Probably at older ages the repetition effect will be present also in the alpha band as a result of infants' neurodevelopment and these changes will be observed in the EEG power distribution over the low-range EEG frequencies.

Finally, the absence of the habituation effect to repeated stimuli may have no functional significance early in life in infants at risk of brain damage, but could have repercussions later, when the children are faced with learning under demanding cognitive conditions. Several studies have indicated that preterm infants show cognitive problems when they reach school age (Sansavini et al., 2011; Yliherva, Olsen, & Jarvelin, 2001). Therefore, the repetition effect, or its absence in the EEG measures, are highly applicable to early detection and intervention in at-risk infant populations.

5. Conclusions

The data from the current study suggest that modifying syllables by extending the duration of the formant transitions facilitates the processing of syllables in preterm infants who are at risk for language impairment. Although the results are derived specifically from premature infants with low language scores, they could be extended in the future to other at-risk infant populations, such as infants with a family member diagnosed with language disability.

The EEG measures of the presence or absence of the habituation effect (or repetition effect) could be applied to early detection of a language impairment; likewise, the modified syllables could be applied to early intervention, for example, by means of recorded stories with extended syllables, computer-based training in auditory perception, and computer-based early language stimulation programs.

Our study contributes to a better understanding of the processing of syllables in term and at-risk infants and reveals alternatives for early detection and early intervention.

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