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ELECTROPHYSIOLOGICAL RESPONSES TO SPEECH STIMULI IN CHILDREN WITH OTITIS MEDIA

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Abstract

Background: Otitis media in childhood may result in changes in auditory information processing and speech perception. Once a failure in decoding information has been detected, an evaluation can be performed by auditory evoked potential as FFR.

Material and Methods: 60 children and adolescents aged 8 to 14 years were included in the study. The subjects were assigned into two groups: a control group (CG) consisted of 30 typically developing children with normal hearing; and an experimental group (EG) of 30 children, also with normal hearing at the time of assessment, but who had a history of secretory otitis media in their first 6 years of life and who had undergone myringotomy with placement of bilateral ventilation tubes. Each group was sub-divided into two age subgroups: 8–10 and 11–14 years. All children completed audiological evaluation (audiometry, speech audiometry, and immitance audiometry) and electrophysiological assessment.

Results: The subjects who participated in the study presented behavioral thresholds and click-ABR within normal limits ($p > 0.05$). No differences were observed in the FFR responses from different age groups (8–10 years and 11–14 years). Significant differences in FFR were observed in the latency values ($p < 0.05$) when compared to control group, although amplitude values did not show significant differences between groups ($p > 0.05$).

Conclusion: Children suffering from secretory otitis media in their first 6 years of life and who have undergone myringotomy for bilateral ventilation tube placement exhibit changes in their electrophysiological responses to speech.

Keywords Frequency-following response; otitis media, speech perception, electrophysiology

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RESPUESTAS ELECTROFISIOLÓGICAS A ESTÍMULOS ACÚSTICOS TRANSITORIOS EN NIÑOS CON OTITIS MEDIA

Resumen

Introducción: Otitis media en la infancia puede originar cambios en el procesamiento de la información auditiva y la percepción del habla. Una vez detectados los problemas en la descodificación de la información, se puede realizar una evaluación a través de la prueba de Potenciales Evocados Auditivos de Tronco Cerebral (PEATC) a estímulos acústicos transitorios.

Materiales y métodos: En el estudio participaron 60 niños y adolescentes en la franja de edad de entre 8 y 14 años. Los sujetos se dividieron en dos grupos: un grupo control (CG) formado por 30 niños de desarrollo típico y un grupo experimental (EG) formado por 30 niños que presentaron audición normal a la hora de la exploración pero con antecedentes de otitis media secretora en los primeros seis años de vida y que se habían sometido a una miringotomía con colocación bilateral de tubos de ventilación. Cada grupo se dividió en dos subgrupos de edad: de 8-10 años y de 11-14 años. Todos los niños se sometieron a exploración audiológica (audiometría, audiometría del habla, impedanciometría) y a evaluación electrofisiológica.

Resultados: Los participantes del estudio presentaron umbrales conductuales y umbrales determinados por el PEATC a click normales (p> 0,05). No se observaron diferencias en las respuestas PEATC a estímulos acústicos transitorios entre los distintos grupos de edad (8-10 años y 11-14 años). Diferencias importantes en el PEATC a estímulos acústicos transitorios se observaron en los valores de latencia (p< 0,05), comparando con el grupo control con audición normal. Los valores de amplitud no presentaron diferencias importantes entre los grupos (p> 0,05).

Conclusiones: Niños que sufrieron otitis media secretora en los primeros seis años de vida y se sometieron a una miringotomía bilateral con el fin de colocar tubos de ventilación presentan alteraciones en las respuestas electrofisiológicas relacionadas con la percepción del habla.

Palabras clave: frecuencia de la respuesta, otitis media, percepción del habla electrofisiología

ЭЛЕКТРОФИЗИОЛОГИЧЕСКИЕ ОТВЕТЫ НА РАЗДРАЖИТЕЛИ, НАПОМИНАЮЩИЕ РЕЧЬ, У ДЕТЕЙ СО СРЕДНИМ ОТИТОМ

Резюме

Введение: Средний отит в детстве может вызывать изменения в обработке слуховой информации и восприятии речи. После обнаружения проблем в декодировании информации оценку можно провести с помощью слуховых вызванных потенциалов ствола мозга (ABR) на раздражители, напоминающие речь.

Материал и методы: В исследовании приняло участие 60 детей и подростков в возрасте 8-14 лет. Исследуемых разделили на две группы: контрольную группу (CG), состоящую из типично развивающихся детей с правильным слухом, и экспериментальную группу (EG), состоящую из 30 детей с анамнезом, касающимся секреторного среднего отита в течение первых шести лет жизни, у которых была проведена операция парацентеза (мирингoтомии) с двусторонним размещением вентиляционных дренажных трубок, и с правильным слухом во время проведения оценки. Каждая группа была разделена на две подгруппы по возрасту: соответственно 8-10 и 11-14 лет. Все дети прошли аудиологическую оценку (аудиометрию, аудиометрию речи, импедансную аудиометрию) и электрофизиологическую оценку.

Результаты: Участники исследования имели поведенческие пороги и для ABR, вызванных треском, в пределах нормы (p> 0,05). Не наблюдалось различий в ответах ABR на раздражители, напоминающие речь, между разными возрастными группами (8-10 лет и 11-14 лет). Существенные различия в ABR на раздражители, напоминающие речь, наблюдались в значениях латенции (p< 0,05) по сравнению с контрольной группой с правильным слухом. Значения амплитуды, в свою очередь, не показали существенных различий между группами (p> 0,05).

Выводы: Дети, страдающие секреторным средним отитом в первые шесть лет жизни и прошедшие операцию парацентеза (мирингoтомии) с целью двустороннего размещения вентиляционных дренажных трубок, проявляют изменения в электрофизиологических ответах, связанных с восприятием речи.

Ключевые слова: частотно-ведомый отклик, средний отит, перцепция речи, электрофизиология

ODPOWIEDZI ELEKTROFIZJOLOGICZNE NA BODŹCE PRZYPOMINAJĄCE MOWĘ U DZIECI Z ZAPALENIEM UCHA ŚRODKOWEGO

Streszczenie

Wprowadzenie: Zapalenie ucha środkowego w dzieciństwie może powodować zmiany w przetwarzaniu informacji słuchowej oraz percepcji mowy. Po wykryciu problemów w dekodowaniu informacji, oceny można dokonać za pomocą słuchowych potencjałów wywołanych pnia mózgu (ABR) na bodźce przypominające mowę.

Materiał i metody: W badaniu wzięło udział 60 dzieci i młodzieży w przedziale wiekowym 8-14 lat. Badanych podzielono na dwie grupy: grupę kontrolną (CG) składającą się z 30 typowo rozwijających się dzieci z prawidłowym słuchem oraz grupę eksperymentalną (EG) składającą się z 30 dzieci z wywiadem dotyczącym wysiękowego zapalenia ucha środkowego w ciągu pierwszych sześciu lat życia, u których przeprowadzono operacje paracentezy (myringotomii) z obustronnym umieszczeniem dreników wentylacyjnych i z prawidłowym słuchem w czasie przeprowadzania oceny. Każdą grupę podzielono na dwie podgrupy wiekowe, odpowiednio grupy 8-10 lat oraz 11-14. Wszystkie dzieci zostały poddane ocenie audiologicznej (audiometrii, audiometrii mowy, audiometrii impedancyjnej) oraz ocenie elektrofizjologicznej.

Wyniki: Uczestnicy badania, mieli progi behawioralne i dla ABR wywołanych trzaskiem w granicach normy (p> 0,05). Nie zaobserwowano różnic w odpowiedziach ABR na bodźce przypominające mowę między różnymi grupami wiekowymi (8-10 lat do 11-14 lat). Istotne różnice w ABR na bodźce przypominające mowę obserwowano w wartościach latencji (p< 0,05) w porównaniu z grupą kontrolną ze słuchem prawidłowym. Natomiast wartości amplitudy nie wykazywały istotnych różnic między grupami (p> 0,05).

Wnioski: Dzieci cierpiące na wysiękowe zapalenie ucha środkowego w pierwszych sześciu latach życia i poddane operacji paracentezy (myringotomii), w celu obustronnego umieszczenia dreników wentylacyjnych, wykazują zmiany w elektrofizjologicznych odpowiedziach związanych z percepcją mowy.

Słowa kluczowe: częstotliwość po odpowiedzi, zapalenie ucha środkowego, percepcja mowy, elektrofizjologia

1. Introduction

Inadequate auditory stimulation in childhood can lead to long-term alterations in structures of the central auditory nervous system (1). Recent studies show that even a brief period of auditory isolation can dramatically change the synaptic properties at both the cellular and cortical levels (2). These changes can be monitored using auditory evoked potentials (AEPs). Among the different types of AEPs, FFR protocols are considered a reliable procedure for evaluating auditory pathways (3)

FFR allows the identification of fine-grained auditory processing deficits associated with real-world communication skills. This procedure can be used for the early identification of auditory processing impairments in: (i) very young children; and (ii) individuals with normal hearing. Moreover, it can also be used to assess hearing across different clinical populations (4, 5). One protocol, widely used clinically, uses the computer-synthesized syllable /da/ as the AEP-eliciting stimulus. The use of synthesized speech keeps the acoustic stimulus parameters constant and ensures the quality of the stimulus during

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the assessment period (6). The response to the acoustic stimulus /da/, designed by Dr Nina Kraus of Northwestern University, consists of two parts: (i) the consonant /d/ (transient portion or response onset); and (ii) the short vowel /a/ portion (sustained portion or frequency following response). The AEPs elicited by this syllable present a waveform characterized by seven peaks (named waves V, A, C, D, E, F, and O), in which the only positive peak is wave V. Waves V and A reflect the onset response, wave C the transition region, waves D, E, and F the periodic region or frequency following response, and wave O the offset response (7-9).

The majority of studies which have used FFR have assessed adult normal subjects. Very few have assessed subjects with hearing deficits and/or across different age groups. Yet FFR can assess the functional integrity of the auditory system in young children, and can provide useful indices of hearing deficits, such as otitis media, which have high incidence in childhood.

Otitis media is one of the most common childhood diseases, affecting about 2/3 of children in the first 5 years of life (10, 11). This period is very important for the development of oral and written language skills. Otitis media can cause functional sequelae in the middle ear, inducing temporary mild to moderate hearing loss (1, 12). Concomitantly, the accumulation of fluid in the middle ear may interfere with speech perception, distort the perception of acoustic signals, and reduce the speed and accuracy of verbal encoding (13). If a hearing deficit occurs early in life during the period critical for language development, limitations in the acquisition of speech and language might appear. In this context, a young subject could present various communication problems, cognitive and psychosocial impairments, auditory processing deficits, and difficulties in acquiring literacy skills (14, 15).

Treatment for middle ear effusion can be clinical or surgical. To treat short-term cases, a conservative clinical approach, such as insufflation of the auditory tube associated with decongestant medication, can be attempted. However, in cases of recurrent and long-term otitis media, this type of treatment is generally not effective, so surgery is an alternative. Myringotomy is the standard surgical procedure, which restores hearing acuity almost immediately. Ventilation tubes are placed intra-operatively into the tympanic membrane and promote aeration of the tympanic cavity (16). However, even after middle ear function is restored, alterations in the encoding of acoustic signals may still remain (17).

FFR appears to be a promising tool in the early identification of changes in the coding of sounds in subcortical regions which may be related to otitis media. So far, there are no data in the literature of studies using FFR to assess the hearing status of children with a history of otitis media. The aim of this study was to investigate whether FFR could identify changes in the electrophysiological responses in children who suffered from secretory otitis media in their first 6 years of life, and who had undergone bilateral myringotomy surgery with insertion of ventilation tubes.

2. Methods

2.1 **Ethics statement**

This study was approved by the State University of Campinas (UNICAMP), Ethics in Research Committee, Campinas, São Paulo, Brazil. Data was collected from October 2013 to January 2016 at the Laboratory of Audiology, Center for Studies and Research on Rehabilitation ‚Prof. Dr Gabriel Porto' of the Faculty of Medical Sciences (CEPRE-FCM/UNICAMP). Informed consent was obtained from all participants after explanation of the nature, purpose, and expected outcomes of the study.

2.2 **Participants**

Sixty children and adolescents aged from 8 to 14 years were included in the study. All participants were right-handed Brazilian-Portuguese native speakers. The subjects were assigned into two groups:

- *control group (CG)*: 30 typically developing children with normal hearing;
- *experimental group (EG)*: 30 children with a history of secretory otitis media in their first 6 years of life who had undergone a bilateral myringotomy with placement of ventilation tubes. They had normal hearing at the time of assessment.

2.2.1 Inclusion criteria

Inclusion criteria for both groups were defined as:

- a hearing thresholds below 20 dB HL (0.25 to 8 kHz);
- a type A tympanogram with the presence of ipsilateral and contralateral acoustic reflexes (0.5 to 4 kHz) in both ears (18, 19);
- a click Auditory Brainstem Response (ABR) with waves I, III, and V present and with an inter-peak interval I–III, III–V, and I–V within normal standards;
- no history of neurological disorders;
- no language or learning complaints.

The EG subjects also had to match the following criteria: (i) a history of otitis media in the first 6 years of life; and (ii) a documented absence of middle ear infection for a period of 12 months prior to the evaluation.

2.3 **Procedures**

2.3.1 Audiometry assessment

Behavioral thresholds were assessed at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. According to the Davis and Silverman classification (20), normal threshold values were considered as ≤ 20 dB HL. The hearing assessment was conducted with an Interacoustics AC 40 audiometer and with TDH 39 earphones calibrated according to ISO-389 and IEC-645 standards.

2.3.2 Electrophysiological evaluation

Electrophysiological evaluation was conducted with click- and FFR using stimuli delivered by a Biologic Navigator

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Pro (Natus, USA). All responses were recorded in a sound-attenuated and electrically shielded room in which subjects passively sat on a reclining chair in a comfortable position. For ABR recording, electrodes were dipped in conductive paste and then placed on the cleaned skin with the help of adhesive paste to produce a low-impedance contact.

Single-channel electrophysiological responses were collected with the electrodes fixed according to the 10-20 positioning system: the active electrode was positioned at the vertex (Cz), the reference electrodes at the ipsilateral mastoid, and the ground at the contralateral mastoid (21). During the recording session, impedance was maintained below 5 kΩ and inter-electrode impedance below 3 kΩ. Automatic switching of reference signals and amplifier ground, according to the stimulated ear, was activated on the equipment; the electrode from the left ear was connected to input 2, channel 1, and the electrode from the right ear was connected to the ground connection cable.

During ABR recordings, participants were asked to keep their eyes closed in order to avoid eye movement artifacts. In addition, the chair position was adjusted as needed for those who showed myogenic artifacts in order to control adequate recording conditions. The order of the ear tested was randomized across subjects.

2.3.2.1 Click-evoked ABR

Click-evoked ABR responses were elicited using the click stimulus provided by the Biologic Navigator Pro (Natus Medical). The stimulus was presented monaurally to the right and left ears through ER-3A insert earphones (Natus Medical) at a repetition rate of 19.3/s at 80 dB nHL (rarefaction polarity) in quiet. A time window of 10.66 ms and online filter setting of 0.1–3 kHz were used. Trials in which more than 10% of sweeps were rejected because of artifacts were repeated in order to obtain a reliable response with small artifact contamination. Two blocks of 2000 artifact-free sweeps were collected.

All analyses were conducted offline. The click-evoked ABR waves were visually identified and manually marked by two expert audiologists who were blinded about the age, sex, and group (CG or EG) of each participant. The waves I, III, and V and the inter-peak intervals I–III, III–V, and I–V were analyzed. For all identified waves, the latency in ms and amplitude in µV were determined. The amplitude was measured as the difference between the amplitude of the first peak of the wave and its subsequent reversal (the peak-to-peak amplitude).

2.3.2.2 FFR

FFR stimuli were elicited using a 40 ms synthetic speech syllable /da/ provided by the BioMARK software and recorded by the Biologic Navigator Pro (Natus Medical). The stimulus consists of the consonant /d/ (transient portion or onset) and the short vowel /a/ (sustained portion or frequency following response) (9, 22-29). This syllable has a stop burst, characterized by a harmonic and broadband frication, followed by a harmonically rich and spectrally dynamic formant transition. It is synthesized with a fundamental frequency (F0) which linearly rises from 103 to 125 Hz, with the voicing beginning at 5 ms and an onset noise-burst during the first 10 ms. Over the duration of the stimulus, the first formant (F1) increases from 220 to 720 Hz, while the second and third formants (F2 and F3) decrease from 1700 to 1240 Hz and 2580 to 2500 Hz, respectively. The fourth and fifth formants (F4 and F5) remain constant at 3600 and 4500 Hz.

The stimulus was presented monaurally to the right and left ears through the ER-3A insert earphones (Natus Medical), with a repetition rate of 10.9/s at 80 dB SPL (alternating

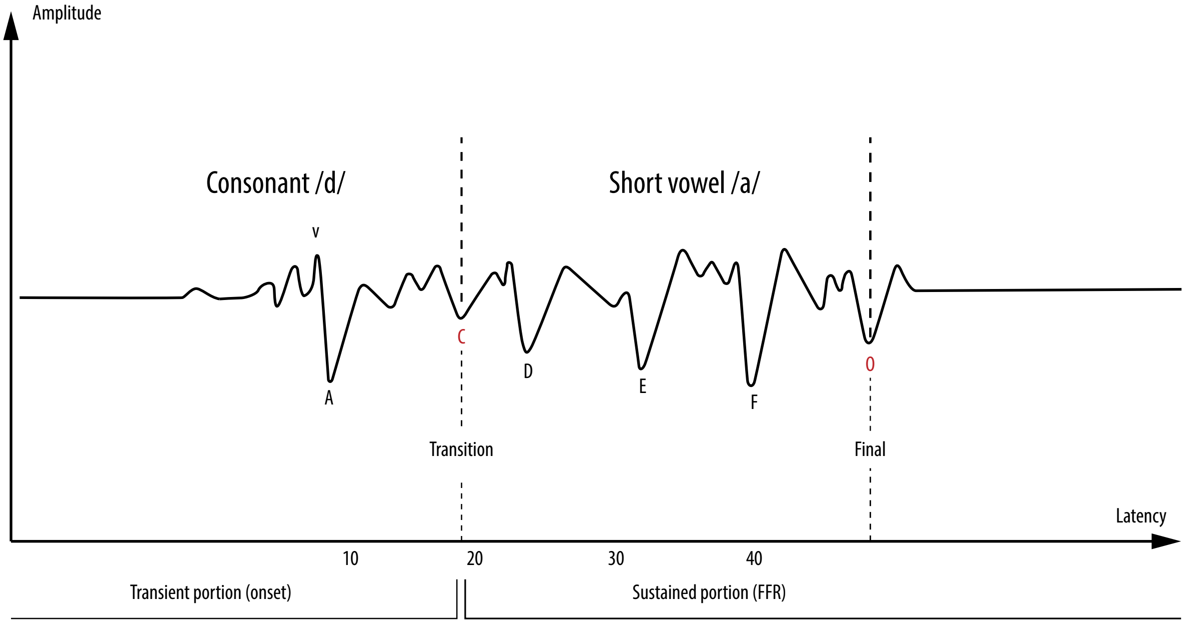

Figure 1. Example of a FFR response from a normal hearing subject elicited by the synthesized syllable /da/

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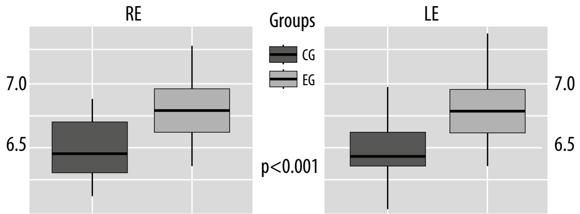

Figure 2. Boxplots of latencies of wave V values from the EG and CG for the right and left ears

polarity) in quiet. Alternating polarities were used in order to cancel out neural responses from the cochlear microphonic and to reduce the effect of stimulus artifacts (30). A time window of 85.33 ms (including a 15-ms prestimulus time) and online filter setting of 0.1–2 kHz were used. Trials in which more than 10% of the sweeps were rejected as artifact were repeated in order to obtain a reliable response with small artifact contamination. Two blocks of 3000 artifact-free sweeps were collected and then averaged, resulting in a wave based on 6000 sweeps.

2.3.2.2.1. Method of analysis

All analyses were conducted offline. FFR waves were visually identified and manually marked by two expert audiologists who were blinded about the age, sex, and group (CG or EG) of each participant. Latency and amplitude values of the seven waves elicited by the syllable /da/ (V, A, C, D, E, F, and O) were based on the analysis criteria of previous published studies (4, 22, 23, 27-29, 31). Analyses focused on four major elements: (i) the onset stimulus portion (represented by waves V and A); (ii) the transition period between the consonant and vowel (wave C); (iii) the sustained portion (represented by waves D, E, and F); and (iv) the offset portion, represented by wave O (8, 9). An example of FFR response from a normal hearing subject is depicted in Figure 1.

The first step of the analysis was to identify the onset portion with latency values <10 ms. The onset portion consists of a positive peak (wave V) followed by a negative peak (wave A). After that, the subsequent waves (C, D, E, F, and O), which are negative peaks, were identified (7, 8, 32). The BioMARK software displays a normative wave, which helps the examiner identify and set the latencies of the waves according to the age of the subject. The data were collected twice in each ear in order to ensure good reproducibility of the recordings. After that, comparison of the left and right ears was performed.

2.3.3. Statistical analyses

ANOVA analyses were used to determine age and gender effects, and their interactions. The variables group, gender, and age were considered fixed effects with two levels each. The *F*-distribution was used to determine whether there was a significant difference among the groups or the interactions. The ANOVA *p*-values were adjusted for multiple comparisons using FDR (false discovery rate). In order to test the homogeneity of the sample, Pearson's chi-square test was applied. The level of significance was set at 5% ($p \leq 0.05$). Statistical analyses were performed using the R-project software (www.r-project.org).

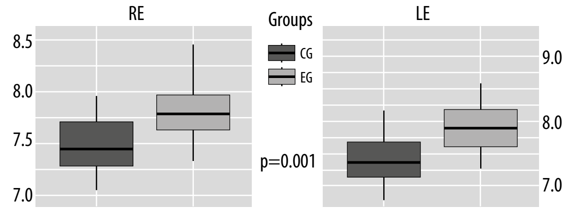

Figure 3. Boxplots of latencies of wave A values from the EG and CG for the right and left ears

3. Results

3.1. Sample characterization

Each group was sub-divided into two age subgroups (8–10 y and 11–14 y). Preliminary analysis showed no age or gender effects in the sample and so all data were pooled. Table 1 shows the sample data.

3.2. Audiometric thresholds

No significant differences were observed between groups for the tested audiometric frequencies ($p = 1.000$ for each frequency).

3.3 Latency of the click-ABR responses

Table 2 compares the latency values from the two groups of subjects. Significant differences were observed in the latencies of the waves I (left ear, $p = 0.039$) and V (right ear, $p = 0.016$; left ear, $p = 0.015$).

3.4 Amplitude of the click-ABR responses

Table 3 shows the ABR amplitude values (μV) between groups. Significant differences were observed in wave III (right ear, $p = 0.018$; left ear, $p = 0.031$) and wave V (left ear, $p = 0.013$).

3.5. Latency of FFR responses

Significant differences were observed in the latency between groups for wave V (right ear, $p = 0.001$; left ear, $p = 0.001$) and wave A (right ear, $p = 0.001$; left ear, $p = 0.001$). The data are summarized in Figures 2 and 3.

For wave C, there was a statistically significant increase in latency (right ear, $p = 0.005$; left ear, $p = 0.025$) bilaterally

Table 1. Sample characterization: distribution of age and gender between the groups

Variable		**Group**		***p*-value***
		Control	**Experimental**	
Number		30	30	
Age	8–10	14	13	1.000
	11–14	16	17	
Gender	Male	15	16	1.000
	Female	15	14	

*Fisher's exact test for count data

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in EG subjects compared to CG (Figure 4). However, the EG group showed a larger number of outliers (dots in Fig. 4) compared to controls.

Statistical differences were also observed bilaterally in the latencies of wave D (right ear, $p = 0.001$; left ear, $p = 0.011$), wave E (right ear, $p = 0.005$; left ear, $p = 0.011$), and wave F (right ear, $p = 0.011$; left ear, $p = 0.025$). The mean latencies of the EG group were higher than those of the CG and showed higher variability (higher standard deviations). The data are summarized in Figure 5.

Significant differences between groups were also observed in the latency of wave O bilaterally (right ear, $p = 0.015$; left ear, $p = 0.025$), as shown in Figure 6. Outliers were identified in both groups (dots).

Figure 7 shows the latency values distribution of waves V, A, C, D, E, F, and O and between left and right ears in the two groups. Note that the latency values of wave C (transition), waves D, E, and F and wave O (offset) varies between the ears in the EG. It is possible to observe that in the CG there is a higher concentration of values, reflecting the cohesiveness of the group. In the experimental group, the latency values show a larger variation.

3.6. Amplitude of FFR responses

The FFR amplitude values did not present significant differences across groups and ears, for all seven waves. Outlier values were identified in the EG group.

4. Discussion

The data from this study suggest that children who suffered secretory otitis media in their first 6 years of age and who underwent bilateral surgery for insertion of ventilation tubes exhibited changes in their electrophysiological responses to speech stimuli compared to typically developing children.

Audiometric measurements, click-ABR response, and otitis media

The subjects who participated in the study had behavioral thresholds and click-ABR within normal limits. In terms of hearing thresholds, the data showed no differences between the groups. Although the click-ABR responses were within normal limits in both groups, there was a statistically significant difference between them. It was observed that the EG had increased latency of waves I and V compared to controls and had reduced wave III and V amplitudes. These observations corroborate previous data in the literature regarding children with learning impairments (33), who showed timing changes in brainstem responses.

ABR: age effects

In the present study, no differences were observed in FFR responses from different age groups (8–10 years and 11–14 years). The data is consistent with previous findings in the literature reporting no significant latency

Table 2. Comparison of click-ABR latency (in ms) between groups and for right and left ears

Source	Control				Experimental					
	Mean		**SD**		**Mean**		**SD**		***p*-value***	
	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
I	1.57	1.57	0.09	0.09	1.60	1.61	0.09	0.08	0.243	**0.039***
III	3.72	3.71	0.11	0.11	3.78	3.79	0.14	0.17	0.053	0.069
V	5.57	5.58	0.13	0.14	5.68	5.68	0.18	0.17	**0.016***	**0.015***
I-III	2.07	2.15	0.38	0.11	2.17	2.17	0.15	0.14	0.171	0.597
III-V	1.85	1.86	0.11	0.11	1.89	1.90	0.12	0.11	0.193	0.246
I-V	3.99	4.01	0.13	0.13	4.07	4.06	0.18	0.16	0.066	0.151

RE, right ear; LE, left ear; SD, standard deviation. Significant differences are indicated by an asterisk and bold numerals.

Table 3. Comparison of amplitude (µV) values between groups for right and left ears

Source	Control				Experimental					
	Mean		**SD**		**Mean**		**SD**		***p*-value***	
	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
I	0.18	0.20	0.09	0.09	0.19	0.19	0.09	0.08	0.893	0.746
III	0.30	0.31	0.11	0.10	0.24	0.25	0.07	0.10	**0.018***	**0.031***
V	0.23	0.23	0.10	0.08	0.18	0.17	0.09	0.08	0.052	**0.013***

Abbreviations as per previous table

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differences across different age groups (4, 22). According to Johnson et al. (4), the coding of sounds in a single stimulus or in a complex (speech or instrumental sounds) improve over the years in terms of neural timing and auditory skill. However, the ABR response of a 5 year old child is not so different to the responses of older children (i.e. 8–12 y old), although it is different in terms of latency and time morphology to the response from a 3–4 y old normal child (4).

The lack of an age effect between groups suggests that the age at which a subject had surgery was not a factor which affected their FFR responses.

ABR: monoaural stimulation in children

The brainstem has an important role in binaural sound processing (34, 35). Daily activities that require the perception of sound mostly involve the stimulation of both ears. A recommendation in the electrophysiological assessment performed with traditional stimuli (i.e. tones, clicks, etc.) is to use binaural stimulation in adults and monaural stimulation in children. However, when speech stimuli are used, the usual arrangement is to apply monaural stimulation to the right ear (8).

The preference for right ear stimulation is related to the right ear advantage and hemispheric dominance of the left side of the brain for language skills, both in right-handed and left-handed children (23, 36). However, data in the literature have suggested that binaural stimulation to the right or left ear appears to produce similar ABR responses (37, 38). Furthermore, under some specific conditions, as in epilepsy, it seems that the right ear advantage in the perception of speech sounds does not occur (24). For these reasons, and because this study aimed to evaluate children and adolescents, subjects were assessed monoaurally under separate conditions of right and left ear stimulation.

In children with normal hearing, there seems to be a difference in latencies for every FFR wave (V, A, C, D, E, F, and O), corroborating previous studies in the literature (37, 38). However, in children with a history of otitis media, we observed that the latencies differed, sometimes seeing a discrepancy in values between stimulated

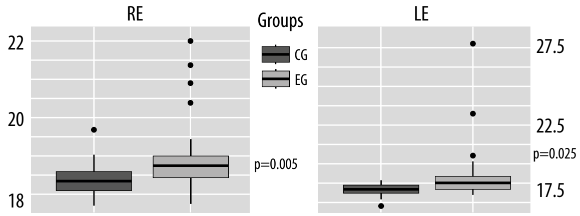

Figure 4. Boxplots of latencies of wave C values from the EG and CG for the right and left ears. Dots show outliers

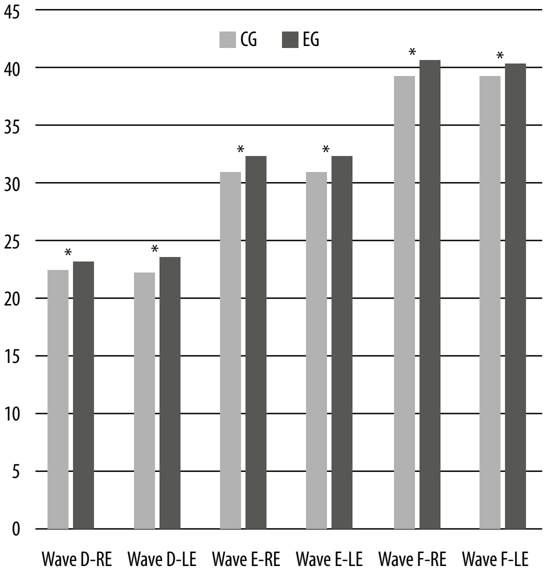

Figure 5. Comparison across groups of mean latency values of waves D, E, and F. Abbreviations as before

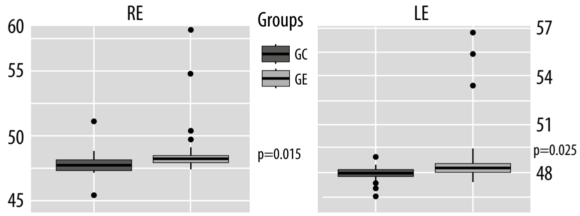

Figure 6. Boxplots of latency for wave O from the EG and CG for the right and left ears

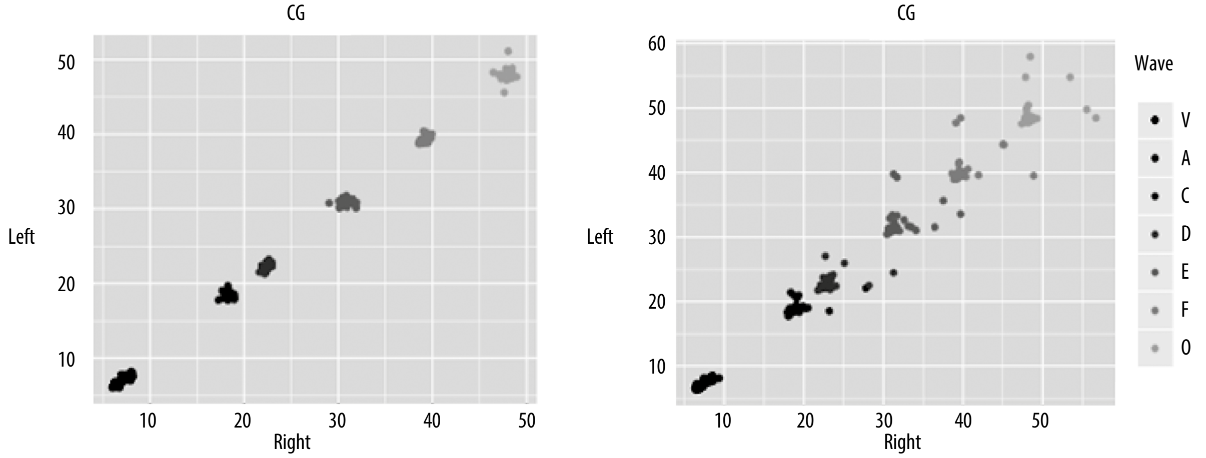

Figure 7. Scatterplot showing latency values of all waves for right and left ears in both groups

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ears. More generally, children with a history of otitis media showed increased latency of waves C, D, E, F, and O and greater dispersion of these values in the left ear, corroborating the findings of Krishnan et al. (39). These authors described a difference in responses between ears during the sustained portion of the speech stimulus. It should also be noted that in children with a history of otitis media there is a common phenomenon called asymmetric conductive hearing loss (40-42) in which affected individuals have a higher risk of amblyaudia later in life. All considered, it is advisable to perform FFR monaurally in both ears.

FFR: onset portion of the response in OM cases

Waves V and A are considered the most stable elements in the assessment of FFR (27, 43). In the present study, analysis of the onset portion, composed of wave V and A, showed an increase in latency, in both right and left ears, for the group of children and adolescents with a history of otitis media compared to the control group. Recent studies corroborate the data from this study and suggest that patients affected by different pathologies – such as learning disabilities, scholastic difficulties, attention deficit hyperactivity disorder (ADHD), dyslexia, hearing loss, epilepsy, and auditory processing disorders – may have an inappropriate brainstem processing of speech sounds. This suggests inaccuracies in the structures underlying waves V and A: the lateral lemniscus and the inferior colliculus (7-9, 22, 24, 31, 44, 45).

FFR: transition portion of the response in OM cases

Wave C is an important marker in FFR assessment and represents the zone of transition between the consonant and the vowel (7). In children with a history of otitis media, significant latency differences were observed compared to values from normally developing children. This suggests that these subjects had poorer electrophysiological responses to speech stimuli. Processing changes in the fast transition elements (between consonant and vowel) are related to temporal processing deficits and might be associated with language and learning impairments (46). Similar alterations are found in children with a history of otitis media tested with the gap-in-noise test, which evaluates temporal resolution ability (47). Data in the literature suggest that children with a history of otitis media and alterations in auditory processing are more likely to show learning impediments, with difficulties in reading and writing, possibly due to difficulties in processing acoustic elements with a fast transition (14, 15).

FFR: sustained portion of the response in OM cases

Components of the sustained portion of the FFR (also called the frequency following response, FFR) reflect the fundamental frequency of coding as well as the harmonic structure of the speech sounds that originate in the midbrain in adults (48, 49). However, in children, the subcortical component involved in FFR encoding is still not well known. Data from this study might contribute to an understanding of how these components of the auditory system function in this specific segment of the population. The control group showed lower latencies of waves D, E, and F compared to children with a history of otitis media. At the same time, it was possible to verify that there was greater bilateral variability in the responses of waves E and F, as well as of wave D associated with the right ear, in the control group – a different pattern of responses from previous published studies. The previous data in the literature regarding between-ear variations are controversial. Hornickel et al. have reported an advantage in waves D and F from the right ear (50); other studies have reported no differences in responses from the right and left ears (23, 37).

FFR: offset portion of the response in otitis media cases

The offset portion of the response, which corresponds to the end of the syllable /da/, is represented by wave O. The data showed that children with a history of otitis media had significantly longer latencies, in both ears, in comparison to the control group. Slower latencies in FFR generally have a negative impact on the fast processing of acoustic signals (51).

The control group showed outlier latencies in the right ear, while both groups presented outlier values for the left ear. Language exposure can also shape how the auditory brainstem responds to complex stimuli, and processing of speech sounds requires plasticity in the human auditory brainstem which depends on experience (52, 53).

FFR in OM and normal hearing cases

The data from Figure 8 (data from all waves, comparing children and adolescents with a history of otitis media with control subjects) showed that the control group was characterized by homogenous latency values bilaterally. However, the right ear responses in the control group were found more homogeneous than in the left. These observations might be related to the fact that children with a history of otitis media in the early years of life experienced some auditory deprivation, and therefore a compromised experience of language. If so, the processes of attention, discrimination, and recognition of sound stimuli may have been impaired, with fewer established neural connections and lesser involvement of speech coding in subcortical and brainstem regions.

The amplitude values of waves V, A, C, D, E, F, and O in both groups showed outlier responses in the right and left ears. Thus, the variation in FFR amplitude values suggests that these are not reliable indices or parameters for the assessment of normal and impaired hearing subjects.

Furthermore, this is the first study in individuals with a history of otitis media and these results relate only to this particular population type.

Specific findings of patients with a history of OM

The literature has shown that otitis media can cause reduced binaural masking, poor accuracy in sound localization, and deficits in complex spectro-temporal processing that may persist for years after the peripheral hearing

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loss has been restored (54-56). Children with a history of otitis media demonstrate a temporal processing disorder, causing a distortion of speech perception and perhaps additional impairment in language and literacy (14, 15, 17, 57). In this context, it is imperative to understand how the FFR responses are modified in children with a history of otitis media, since the responses can be considered a preschool marker for literacy (58).

A FFR assessment allows fine-grained auditory processing deficits associated with real-world communication skills to be identified, deficits which are not identifiable by traditional click-ABR testing. Thus, it can be used for early identification of auditory processing impairments in very young children. Information from FFR responses can contribute to an understanding of the biological basis of hearing disorders and language, and can identify at an early age those subjects who might develop auditory processing disorders and who might benefit from an auditory training program (3, 59-61).

This study shows that the evaluation of FFR seems to be a promising method in identifying changes in the coding of speech stimuli in children with a history of otitis media who might be undetected by a traditional electrophysiological evaluation. The changes in the electrophysiological responses observed in these children might serve as an alert to parents and educators, who can adopt strategies to minimise the negative consequences to language development and academic achievement.

5. Conclusion

Children suffering from secretory otitis media in the first 6 years of life, and who have undergone myringotomy for bilateral ventilation tube placement, exhibit changes in their electrophysiological responses to speech compared to normally developing children.

Author contributions

Conceived and designed the experiments: MDS, MFC. Performed the experiments: MDS, LRB, CD. Analyzed the data: MDS, TADH, TB, MFC. Contributed reagents/materials/analysis tools: MDS. Wrote the paper: MDS, SH, PS, MFC.

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