ORIGINAL ARTICLE

Maturational Changes in the Human Envelope-following Responses

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Abstract

Introduction: The auditory ability to discriminate rapid changes in the envelope of language sounds is essential for speech comprehension. Human envelope-following responses (EFRs) are useful for objective measurement of temporal auditory processing in subjects who are unable to give accurate behavioural responses (e.g., young children).

Objective: To evaluate age-dependent changes in EFRs during the first 2 years of life.

Methods: The EFRs were recorded in a sample of 16 healthy babies distributed into 2 age groups (G1: 12 newborns; G2: 4 babies of 2 years). The EFRs were evoked by white noise carrier stimuli with a sweep of modulation frequencies from 20 to 200 Hz presented at 50 dB HL.

Results: The age-related changes affected both morphology and EFR detectability. The main morphological differences were at the expense of frequencies below 50Hz, where the first component P1 was not well defined in either of the 2 age groups. For all modulation frequencies, age significantly affected EFR amplitude and detectability.

Conclusions: The present study provides the first evidence on EFR maturation. Some understanding of normal EFR development would facilitate a better use of this technique in clinically objective measurement of auditory temporal processing in infants who cannot provide reliable behavioural responses.

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KEYWORDS
Auditory system; Human envelope following responses; Temporal auditory processing

PALABRAS CLAVE
Sistema auditivo; Potencial evocado auditivo de seguimiento a la envolvente;

Cambios con la edad en la respuesta electrofisiológica de seguimiento a la modulación del estímulo acústico

Resumen

Introducción: La capacidad de detectar cambios temporales en la amplitud de modulación de los sonidos del habla es esencial para el adecuado desarrollo y comprensión del lenguaje. El potencial evocado auditivo de seguimiento a la envolvente (PEA-SE) permite estudiar

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Introduction

A proper understanding of language requires an auditory system which is able to detect temporal variations occurring in the modulation amplitude (envelope) of speech signals. The envelope of speech sounds in itself contains much of the information necessary for the identification of words, sentences, and phrases.\(^1,2\) Thus, a minimum amount of frequency information is essential for a proper understanding of the spoken word, with information about temporal patterns being most important.\(^2\)

It has been shown that a decreased capacity of the auditory system to behaviourally detect fluctuations in the envelope of acoustic stimuli is present in children with a primary delay in language development.\(^3\) Experimental evidence reinforces the importance of temporal auditory processing as a basis for the development of speech.\(^4,5\)

Most of the information about the study of auditory sensitivity to fluctuations in the envelope of sounds has been obtained mainly through 2 different psychoacoustic methods. The first method consists in detecting the presence of a short interval of silence within a continuous sound signal,\(^6,7\) and the second consists in determining the threshold for detecting changes in the amplitude of sound depending on the frequency modulation (FM),\(^8-10\) which is defined as the modulation transfer function (MTF). The MTF is one of the most comprehensive methods of studying temporal auditory processing.

These behavioural paradigms are unreliable to study uncooperative subjects such as young children and simulators. Therefore, the assessment of hearing ability to detect changes in the envelope of stimuli among these populations requires objective methods, such as auditory evoked potentials.

Steady-state auditory evoked potentials (SSAEP) obtained with continuous sinusoidally amplitude modulated tones have been used in the electrophysiological evaluation of auditory sensitivity in a wide range of audiometric frequencies among newborns, infants,\(^11,12\) children with normal hearing and hypoacusis children.\(^12-15\) The response generated by this stimulus can be detected as a peak or spectral component which appears limited to the FM. Therefore, the magnitude of the spectral component may be considered as a brain sensitivity indicator for that FM. Likewise, the minimum modulation depth at which the component is detected can be regarded as the modulation threshold for that frequency.\(^16\)

SSAEP can be recorded within a wide range of FM, and it is possible to obtain multiple, consecutive responses separately if each signal is modulated with a different frequency.\(^17,18\) However, the separate exploration of different modulating frequencies is very time-consuming, making it more efficient to carry out a continuous modulation sweep covering all the frequencies of interest.

Purcell et al.\(^16\) adapted the SSAEP methodology in order to obtain an electrophysiological representation of the MTF. Instead of using pure tones with different spectral contents as a stimulus and keeping the FM fixed and different for each tone as is usually done to obtain the SSAEP, these authors used a fixed carrier tone and performed a continuous FM sweep. The response obtained in this way is known as the EFR.

The morphological pattern of EFR obtained in adults\(^16,19-22\) is a non-monotonic function, whose amplitude decreases as the FM increases. It is also characterised by having 2 regions or peaks where the response amplitude reaches its maximum values. The first peak (P1) is detected between 30 and 50 Hz, and second peak (P2) reaches its maximum amplitude between 80 and 110 Hz.\(^16,22\)

However, despite the fact that an objective study of temporal processing would be especially useful among children, the EFR of this population has still not been characterised. The reviewed literature only contains 1 previous work that demonstrates the existence of age-related changes in the parameters of this potential obtained in rats.\(^23\)

This study aims to characterise the possible changes occurring in the EFR during the first 2 years of life in order to obtain an electrophysiological indicator for evaluating auditory temporal processing among infant populations.

Methods

Sample

The sample consisted of 16 infants with normal hearing divided into 2 groups according to their age. The first group
(G1) consisted of 12 healthy infants aged 5–18 days. The second group (G2) was composed of 4 infants aged 2 years.

The study was conducted at the Clinical Neurophysiology Laboratory of Paediatric Hospital Juan Manuel Marquez, after obtaining informed consent from the legal guardians of each child.

The following criteria were taken into account during the selection of the sample:

1. No risk factors for auditory loss.24
2. Normal otoscopy.
3. Electrophysiological threshold determined by auditory evoked potentials to clicks ≤30 dB nHL.
4. Normal result in the application of the "screening tool for deviations of neurodevelopment",25 which ruled out the existence of language, psychomotor development or auditory and visual sensory maturation disorders in children under 2 years.

Electrophysiological Recording of Envelope-following Responses

We used an experimental model developed at the Rotman Research Institute16 to obtain the EFR. This model was formed by the "Multisweep" program, developed on a Labview 5.1 platform, for stimulus generation and for the collection and off-line processing of EFR, a conventional audiometer (Madsen, Orbiter 922 model) to adjust the stimulus intensity, a Grass Instruments model P59C bioelectric amplifier and a precision, 16-bit, digital-analogue conversion card, model 6052E from National Instruments.

Stimulation Parameters

The stimulus used consisted of amplitude-modulated white noise (100% depth) with a frequency sweep between 20 and 200 Hz (in steps of 0.586 Hz) at a fixed intensity of 50 dB HL. For each sound file we recorded 30 EEG segments of 1024 s, with an alternate FM sweep. In the first half of the stimulus, the FM increased linearly from a minimum (20 Hz) to a maximum (200 Hz) frequency, whereas in the second half the modulation was decreased linearly from the maximum frequency to the minimum, symmetrically with respect to the first half.16 Each record included 30 averages.

Recording Parameters

We used disk electrodes (Ag/AgCl) attached with conductive paste to a section of the scalp which had been previously cleaned with alcohol. The active electrode was placed in Cz (midline, vertex of the head), the reference electrode was placed in the posterior midline, below the hairline, and the ground electrode was placed in FPZ (midline, frontal region). The impedance was maintained at ≤5 kΩ. The stimulus was presented monaurally through model 3A EarTone insertion headphones.

The bioelectrical activity was amplified with a gain of 10,000, filtered analogically between 1 and 300 Hz and then digitised at a frequency of 32 KHz with a 16-bit resolution digital-analogue converter. In all cases we activated the suppressor filter of the feed line centred at 60 Hz, so that in this work we excluded from the analysis the FM range between 50 and 70 Hz.

Recordings in newborns were made under spontaneous sleep conditions, whereas in young children they were obtained during sleep induced by chloral hydrate (25 mg/kg).

Analysis of Envelope-following Responses

Once the recording was complete, we performed its off-line data processing, which was then averaged synchronously in the time domain. Before obtaining the potential we averaged an analysis window (30 segments or sub-windows of 1024 s each) to determine the mean and standard deviation of the noise. The rejection threshold was set at 1.5 standard deviations of the noise mean.

We used Fourier analysis to estimate the amplitude and phase of EFRs independently for each FM. To do this, we averaged the 2 symmetrical halves of each analysis window jointly. Noise was estimated by a discrete Fourier transform, using 60 spectral components on each side of the FM of interest.

In order to determine if the signal amplitude differed significantly from the noise, we conducted a test for comparison of means, considering as statistically significant a value of \(P \leq 0.05\).

Results

The morphology of EFRs in both age groups was a non-monotonous, continuous function whose amplitude decreased as the FM increased. Fig. 1 shows EFR records obtained in 1 representative subject from each group.

![Figure 1](http://www.elsevier.es) Auditory evoked potential of envelope-following response obtained in a representative subject from each age group. The solid lines show the amplitude of the response to modulation frequencies between 20 and 200 Hz. The dashed lines show the levels of residual noise.
The most notable differences in the morphology of EFRs were mainly observed for frequencies below 50 Hz. Both age groups displayed the P2 component in a stable manner (which, in adult subjects, appeared between 80 and 110 Hz). However, the P1 component (between 30 and 50 Hz) was absent in new-borns and appeared only as an ill-defined outline when recorded in young children. Therefore, the analysis of maturational changes in EFRs initially focused on the P2 component.

Table 1 shows the mean and standard deviation of the FM at which the maximum response amplitude was obtained (best FM, BFM) and its corresponding amplitude value for the FM between 80 and 110 Hz in the different age groups studied.

We noted that the BFM was significantly lower in G1 compared to G2 (P<.04). Furthermore, the amplitude of the BFM measured in the P2 component was significantly lower in G1 (P<.00), almost half of that obtained in G2. This is illustrated graphically in Fig. 2.

Fig. 3 shows the increase which took place with age in the detectability of the BFM in the P2 component. The detectability of the BFM in new-borns was 69.6%, reaching 100% detectability at 2 years of age.

We used the "bootstrapping" resampling method to examine possible maturational changes in EFR amplitude throughout the various FM studied. This method allowed us to calculate the mean, variance and standard deviation of the EFRs obtained in each group. Fig. 4 shows the mean and standard deviation of the EFR amplitude across the region of frequencies between 20 and 200 Hz, separately for each age group. We noted that the mean and standard deviation values were almost superimposed in both curves. Moreover, we also noticed an increase in the estimated EFR amplitude value with increasing age.

A repeated-measurement ANOVA test revealed a significant effect of age on the amplitude of the EFRs (F(1, 8596)=4485.76; P<.00). In addition, we also observed a significant effect of FM (F(306, 8596)=44.57; P<.00), as well as of the interaction between both factors (F(306, 8596)=7.63; P<.00).

The multiple comparisons test of this result revealed statistically significant differences between both groups for all studied FM (between 20 and 200 Hz, excluding frequencies between 50 and 70 Hz, which were not analysed).

Finally, the detectability of EFRs increased with age in the entire FM range. However, detectability was lower for the FM below 50 Hz in both age groups. At 40 Hz modulation, response detectability increased from 34.8% in G1 to 42.9% in G2. On the other hand, the detectability obtained in new-borns for the FM above 70 Hz was 50%–70%, while in infants under 2 years we were able to detect 100% of the responses from 80 Hz modulation.

**Discussion**

This work is the first to characterise the changes that occur in EFR parameters during the first 2 years of life and to offer some normality criteria for the use of this response in the objective study of temporal auditory processing maturation in the infant population.

We found age-related changes affecting the morphology and detectability of EFR in all studied FM, thus confirming findings obtained previously in animals. In general, we observed that the major morphological differences with respect to the pattern described for adults were at the expense of frequencies below 50 Hz and that the P1 component was not well defined in any of the age groups studied. We also found that a statistically significant increase in
Figure 4  Amplitude changes in the auditory evoked potential of the envelope-following response during the first 2 years of life. The curve built with points represents the mean amplitude of auditory evoked potential of the envelope-following response estimated in newborns, and the curve built with lines and points represents that estimated in infants less than 2 years. The solid line represents the standard deviation of G1 and the broken line represents that of G2.

The estimated EFR amplitude, as well as in detectability, took place as age increased.

There are no previous studies which characterise EFRs obtained with a continuous FM sweep at early ages with which we can compare our results. However, the morphological pattern of this response in adults has been described previously.\(^6\)\(^7\)\(^9\)\(^10\)\(^12\)\(^15\)

On the other hand, although EFRs have not been characterised previously in children, amplitude-modulated SSAEP have been studied in newborns, infants, and young children, both for responses at 40 Hz\(^16\)\(^20\)\(^28\) and at 80 Hz,\(^11\)\(^13\)\(^14\)\(^26\)\(^28\) so they can be used as a reference. The validity of this comparison is based on the study of Purcell et al.\(^8\) which showed that a potential estimated from multiple registrations obtained independently for different FM generates a response equivalent to that obtained with a continuous modulation sweep.

The EFRs recorded at 40 Hz modulation have a lower amplitude in G1 (53.1±32.5 nV) than those obtained in G2, where the amplitude of this response is increased to 99.4±24.7 nV, reaching values similar to those reported in adults.\(^16\)\(^22\) This corresponds to reports for steady-state responses to 40 Hz modulation.\(^29\)

Age also increases the detectability of EFRs obtained at 40 Hz modulation. However, in children, the detectability of the response at 40 Hz was lower than that found at 80 Hz, coinciding with previous reports.\(^28\) Only 42.9% of the EFR records at 40 Hz were identified in 2-year-old children compared to 100% of detectability above 80 Hz achieved in this same age range.

The inconsistency found in children for EFRs at frequencies below 50 Hz could be due to 2 possible reasons. First, it is likely that immaturity of the cerebral cortex at early ages prevents the auditory system from maintaining a sustained, synchronous response at those FM. A second possibility is that the absence or inconsistency of the P1 component is due to the effect of sleep (spontaneous or induced). It is known that mean latency responses (generators of SSAEP at 40 Hz) are diminished or absent during deep sleep stages in young children.\(^30\) In addition, it has been shown that sedation affects the amplitude of auditory evoked potentials generated at a cortical level.\(^31\) Hence, it has been suggested that SSAEP obtained at 40 Hz are not reliable to estimate the audibility threshold at early ages\(^27\)\(^29\) and, similarly, the EFR component in this region does not seem to be useful.

Unlike the case with SSAEP at 40 Hz, steady-state responses between 70 and 110 Hz modulation have been obtained reliably in sleeping newborns\(^11\)\(^13\)\(^14\)\(^28\) and young children.\(^26\) Consistently with the reports for SSAEP at 80 Hz, the EFR amplitude measured at this FM was approximately 2 times lower in G1 (29.5±15.1 nV) than in G2 (54.2±17.9 nV). Furthermore, the BFM amplitude of the P2 component in 2-year-old children was similar to that reported by Mijares et al.\(^22\) for sleeping adults.

In order for EFRs to be used as an objective index of temporal processing it would be necessary to reliably register them from birth in all children with normal hearing. Moreover, it would be desirable that the response at 50 dB HL was identifiable in 100% of the sample. In the case of the P2 component, although it was detectable in all infants in G2, it was only possible to identify it in 69.6% of newborns. This could reflect an immaturity of the auditory system of some infants to follow the envelope of the stimulus at these FM, which disappears as children grow and develop their language skills.

However, this study has some methodological limitations related to the procedures and equipment that were used for recording and statistical signal processing and which could contribute to the reduced detectability found in G1. One problem is the number of averages used. Previous studies\(^16\) used a larger number of averages (between 50 and 100) achieving a better response detectability. However, this extends registration time to 45–90 min, which is impractical when assessing young children. For this reason, in this work we decided to reduce the number of averages to 30. Nevertheless, the EFR recording time in both ears took 30 min, which is still a very long time when testing newborns.
Another limitation of the method used to estimate the EFRs was the use of Fourier analysis. It has been suggested that this method is not suitable for estimating non-stationary responses, such as EFRs, so some authors\textsuperscript{19,20,21} have proposed the use of time-frequency analysis methods to study EFRs. The technology and recording and stimulation peripherals should also be improved in order to facilitate work with young children in a hospital setting. This study was conducted with an experimental model specifically designed for work within a research laboratory. When recording at a hospital, the equipment should be better protected from noise contamination (electrical and acoustic). Moreover, unlike in this study, appropriate peripherals for early ages should also be used (headphones with noise shields, disposable electrodes) in order to facilitate and accelerate the recording procedure and reduce the preparation time of infants prior to testing.

Conclusions

This study provides relevant information about the maturation of the EFR to a continuous acoustic stimulus. The fact that it was possible to describe the changes that occur with age in the EFR parameters suggests that recordings of this potential could be a useful tool to study temporal auditory processing maturation in children. However, the variability in EFRs observed below 50 Hz modulation hampers the use of these frequencies as an objective index of temporal processing. Instead, once the equipment and signal analysis methods are perfected, the recording of EFRs between 70 and 200 Hz could be used to study maturational changes occurring in temporal auditory processing.

Conflict of Interests

The authors have no conflicts of interest to declare.

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