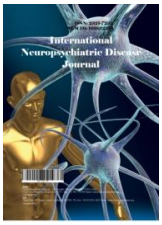

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Auditory Evoked Potentials P50: Pure-tones vs Clicks. There is a Similar Supression?

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SGL and MLAPR were involved in developing the experimental idea, analysis of the data and drafted the manuscript. Author GAS was involved in the theoretical framework, translate and revision of the manuscript. Author DC was involved in data analysis and revision of the manuscript.

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ABSTRACT

Objective: Clinical application of middle-latency auditory evoked potential (MLAEPs) has been increasing, highlighting the importance of understanding the nature of P50, a component of middle-latency auditory evoked potential. We manipulated stimulus frequency bands in auditory stimuli in order to investigate the nature of P50 in human auditory evoked potentials.
Methods: Two paradigms have been used to obtain P50: one is a conditioning /testing paradigm in which paired of pure tone (1000Hz) are delivered, and the other was presented paired of clicks, both with an intensity of 60 dB sound pressure level above the auditory threshold. A total of 30 healthy volunteers were recruited for this study among Center of genetic engineering (fifteen man and fifteen women, mean age of 36, 5). All without consumption of caffeine, cigarettes and drugs.
Results: No statistically significant differences occurred between the P50 amplitudes and latencies for the pure tone and those for the clicks.
Conclusions: Our present results indicate that P50 in humans may reflect a feed-forward mechanism of the brain where a preceding stimulus drives sensory gating mechanisms in preparation for a second stimulus, but the contained frequency doesn't influence on the P50. Both types (tones or clicks) can be used in the exploration of patient with this evoked potential.

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Keywords: P50; evoked potential; MLAEPs; tones; clicks.

1. INTRODUCTION

In the last decades there has been a notable increase in the clinical applications of the auditory evoked potentials (AEPs), especially the middle-latencyAEPs [1–5] and with this, there was an increase in interest by studies that explore the nature of its main components.

These responses were studied for the first time at the "Massachusetts Institute of Technology", in 1958, using a computerized device for measuring response [6]. This study infer that the waves observed were representative of auditory afferent activities related anterior regions in the cerebral cortex.

Since then, several studies have reported the relationship of middle-latency waves with primary sensory portions, for example: reticular substance, thalamus cortical pathways [7], especially in patients undergoing neurosurgery using surface electrodes, describing in detail the various waves and their starting points [8].

Three types of AEPs are known: short latency (1-10 ms) or brainstem auditory evoked potentials (BAEPs); middle-latency AEPs (MLAEPs, 10-50 ms) and the late cortical AEPs (5-500 ms) [9]. Thus, a positive wave of small amplitude, which occurs approximately between 40-90 milliseconds (ms) after applying a repetitive auditory stimulus, is also called the P50 [4,10, 11].

In the classical paradigm of auditory evoked potential suppression P50, there are pairs of auditory stimuli separated by 500ms between the first (conditioning stimulus-S1) and the second (test stimulus-S2) [12], with an approximate inter-stimulus interval of 10s (ten seconds) [13] (p160). In healthy subjects the amplitude of the second peak is suppressed about 50% in relation to that of the first (S2/S1 ratio <0.5) [14–17]. Possibly, this process helps the brain prevent an overload of irrelevant sensory information.

However, studies show that in patients with schizophrenic spectrum disorders [18–21] and other neurological disorders [22], like in the Huntington's disease [23], this reduction in amplitude is less. The studies suggest that while the temporal lobe is the main generator of the P50 component, the frontal lobe seems to be a substantial contributor to the process of sensory gating [24,25]. Thus, the hippocampus, the brain stem and the temporal cortices are invoked within the structures that mediate the suppression of the P50 component, and therefore in the sensory filtering of irrelevant or repetitive stimuli [26,27]. This mechanism is not yet fully understood, for example, recent evidence suggests that muscle fatigue may significantly reduce sensory block [15].

The neurochemical bases of this mechanism are not yet well clarified and involve cholinergic, GABAergic and monoaminergic systems as modulators of the phenomenon [10–12], although evidences has also demonstrated the dopaminergic role in this modulation [28].

Studies that explore the origin of the P50 component by performing different experimental manipulations of the stimulus are reportedin the literature [12,29]. For example, Chen et al. observed a notable increase in the amplitude of the P50 component generated by stimulation with human voices compared to the evoked responses by pure tones [11]. There are two possible explications for this phenomenon: One of them considers that the human voices contain several frequency bands in your spectral composition, while a pure tone has only one frequency band, in addition, the summation potentials generated by the human voice are significantly larger than those generated by a pure tone.

The other explanation is based in the fact that the human voice activates a more extensive auditory cortical area than the activation produced by non-human sounds. The different aspects of the P50 potential has been studied by manipulating the intensity of the used stimulus, demonstrating that the P50 obtained with repetitive stimuli at high intensities, greater than ninety decibels of sound pressure level (>90 dB SPL) presents a remarkable suppression of the amplitude in the P50 evoked response. There are no previous reports to evaluate the neurobiological foundations of the P50 component, where P50 evoked potentials are obtained in healthy subjects, comparing the use of click stimuli against pure tone stimuli [5,10].

2. MATERIALS AND METHODS

2.1 Subjects

30 healthy subjects, 15 men and 15 women, aged between 22 and 46 years (mean of 36.5)

were studied; all free of consumption of caffeine, tobacco and other drugs and without a history of psychiatric or neurological diseases, which also met the criteria of the normality scale and accepted and signed the terms of the informed consent.

2.2 Stimuli

Two stimulation paradigms were used to obtain P50 by suppression.

2.2.1 Paradigm 1

Using 60 pairs of stimuli at pure tones of 1000 Hz (total tone duration of 100 ms and a rise and fall time of 10 ms), consisting of a first stimulus called conditioning or S1 and a second stimulus called test or S2.

2.2.2 Paradigm 2

Using 60 pairs of stimuli at clicks (click produced by a square pulse of 0.1 ms duration), consisting of a first stimulus called conditioning or S1 and a second stimulus called test or S2.

Under both stimulation conditions, a time between 500 ms stimuli and an inter-stimulus interval (ISI) variable between 8,000 and 10,000 ms were used.

2.3 Stimulation Intensity

First, a conventional tonal audiometry was performed prior to otoscopy of the subject, using the technique of ascending and descending limits of BécKésy, with 5 dB test steps. The normal threshold of audibility of the subject was determined and a stimulation intensity was set at 60 dB above this, without exceeding 85 dB SPL.

2.4 Registration

For the acquisition of electrical brain activity, 19 surface electrodes (Ag/AgCL) were placed on the scalp according to the 10/20 system. The impedances were kept below 5 kiloohms(5 kΩ). The reference was placed in both earlobes and eye movement control was performed by training with a fixation point in the center of the screen of a television monitor. The signals obtained were amplified with a gain of 20,000 and filtered between 0.1 and 300 hertz (Hz), with 60 Hz filter off and a sampling period set at 500.

2.5 Averaging

A segment of brain electrical activity was averaged for each stimulus separately (S1 and S2), synchronized with the presentation of the stimulus, using a pre-stimulus analysis time of -200 ms and a post-stimulus of 600 ms. A rejection level of artefacts by amplitude was set at ± 100 microvolts (μv) and a second-order Butterworth bandpass digital filter between 10 and 100 Hz was also used. Rectification of linear trends was also performed and to avoid muscular contamination reflected in obtaining the PRE responses obtained to the first 4 pairs of stimuli were always excluded.

2.6 Potential Measurements

The P50 component was identified as the greatest positive deflection between 30 and 90 m/s in position Cz, after applying the conditioning stimulus (S1), which was generally preceded by the P40 or Pa peak, which appears between 15 and 40 ms that happen to the stimulus. When P40 was absent, P50 was referenced to the highest positivity in this range of mid-latency AEP and its presence was verified at other registration sites (generally Fz). The latency was determined as the time elapsed between the presentation of the stimulus and the appearance of the P50 wave peak and was expressed in milliseconds. The amplitude of the P50 wave was defined as the absolute voltage difference between the maximum peak of the component and the greater negative deflection that precedes it, coinciding with the P40 valley and was expressed in microvolts (μV). The P50 component of S2 was identified as the highest positivity between 500 ± 10 ms after the P50 in S1. The amplitude suppression ratio of the P50 wave was calculated by dividing the amplitude of the wave in S2 by the amplitude in S1 and subsequently multiplied by 100 to express it in percentages.

3. RESULTS

Fig. 1 shows a large average of the potentials obtained in both paradigms. Despite the morphological similarity between the responses obtained in the two stimulation modalities, in the potentials obtained by clicks, the P40 component presents greater amplitude and less temporal dispersion of the response than that observed in the tone potentials.

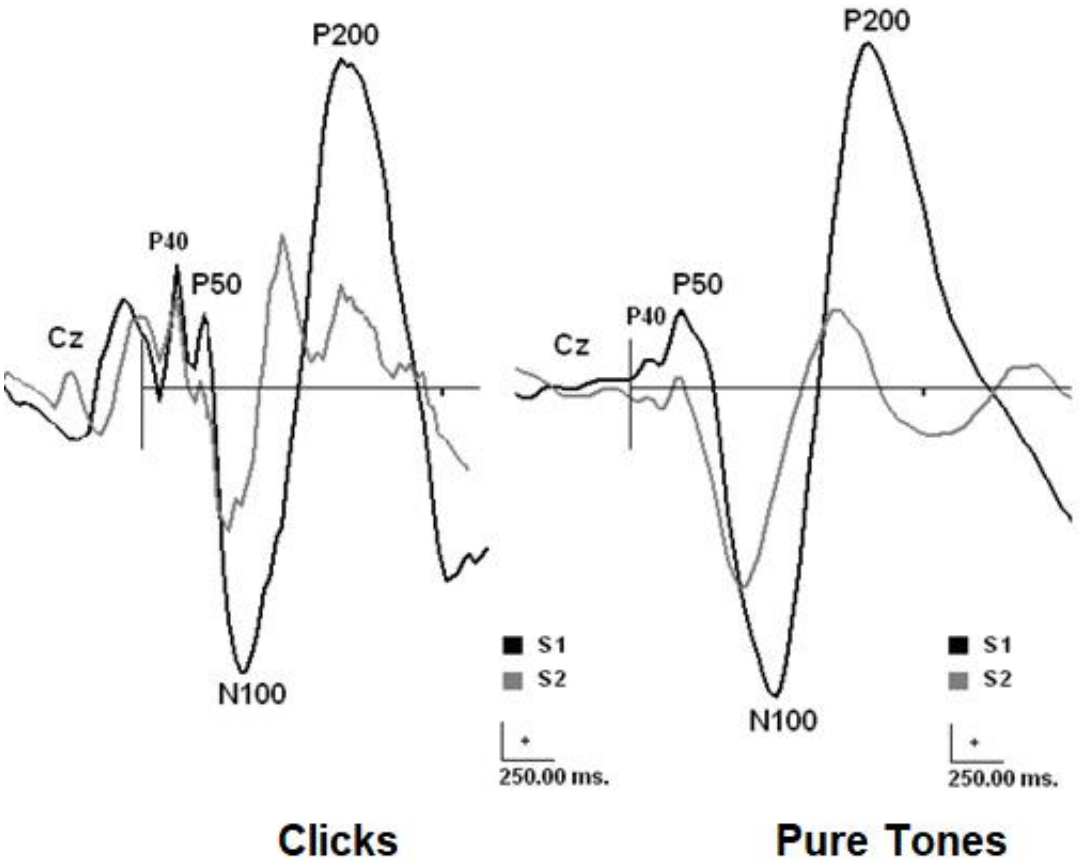

Fig. 1. Large average of the potentials obtained by clicks (Left) and PureTones (Right), in derivation Cz (center midline), for both stimuli S1 (Conditioning - represented in color black) and S2 (Test - represented in color Gray)

The vertical line of the graph marks the beginning of the stimulus. All components are marked with their name (P40, P50, N100 and P200)

Table 1. Amplitude (μv) and latency (ms) values of the P50, N100 and P200 components of the MLAEPs

Variables	Clicks	Pure tones	t	p
S1 Amplitude P50	2.05 μv.	2.94 μv.	t = 1.64	.1278
S1 Latencia P50	52.44 ms.	46.70 ms.	t = 1.53	.1540
S2 Amplitude P50	0.64 μv.	1.59 μv.	t = 1.97	.0740
S2 Latency P50	55.84 ms.	46.82 ms.	t = 1.72	.1124
% Suppression P50	66.68%	40.82%	t = 2.01	.0695
S1 Amplitude N100	-4.56 μv.	-6.49 μv.	*t = 2.55*	.0267 *
S1 Latency N100	99.45 ms.	102.51 ms.	t = 0.42	.6773
S2 Amplitude N100	-2.00 μv.	-2.83 μv.	*t = 2.79*	*.0172**
S2 Latency N100	84.36 ms.	83.91 ms.	t = 0.10	.9204
% Suppression N100	53.75%	52.70%	t = 0.17	.8656
S1 Amplitude P200	5.26 μv.	7.18 μv.	t = 2.98	.0125 *
S1 Latency P200	169.87 ms.	168.77 ms.	t = 0.24	.8098
S2 Amplitude P200	2.35 μv.	2.20 μv.	t = 0.30	.763834
S2 Latency P200	138.54 ms.	156.07 ms.	t = 2.18	.0167*
% Suppression P200	42.97%	61.05%	t = 2.98	.0125*

Significant statistically differences (p < 0.05)

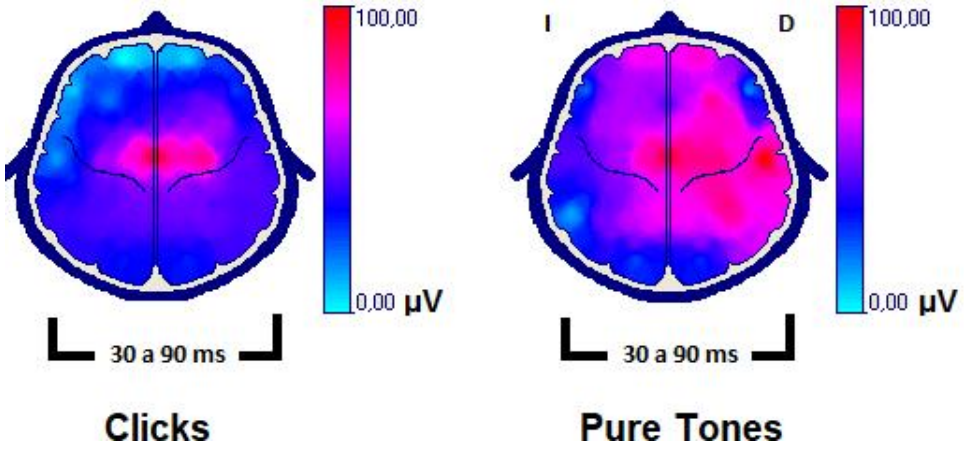

Fig. 2. Topographic distribution of the P50 component in both stimulation conditions. The color of the map is indicative of the maximum positivity in red and the highest negativity in blue (µV)

3.1 The Overall Analysis of the Amplitude, Latency and Suppression Percentage of the P50, N100 and N200 Components of the Potentials Obtained in Both Stimulation Conditions

Consistent with previous reports in the literature, a significant decrease in amplitude of the P50 component obtained with the test stimulus was observed, in relation to that obtained with the conditioning stimulus, for both stimulation paradigms.

Table 1 shows the amplitude (µv) and latency (ms) values of the P50, N100 and P200 components of the MLAEPs, obtained with the conditioning stimulus and the stimulus tested in both stimulation conditions (clicks and pure tones).In addition, the suppression percentages of the three components studied are reflected.

There are no significant statistically differences for any of the variables evaluated in the P50 component between the two types of stimuli used. The reported differences correspond to components N100 and P200, which also show great variability in other reports.

3.2 Analysis of the Topographic Distribution of the P50 Component in F the Middle-Latency AEPs Obtained With Pure Tones and Clicks

Fig. 2 shows the topographic distribution of the P50 component obtained with the conditioning stimulus for the two categories (clicks and pure tones). The graphs correspond to the distribution on the scalp of the raw amplitude values obtained by calculating the area under the curve between two cursors set between 30 and 90 ms.

It is appropriate to highlight that although in both paradigms the amplitude of the P50 component obtained with the conditioning stimulus is maximum in Cz, in the one obtained by clicks the answers are more restricted to the central midline, there is differences of the topographic distribution of the P50 before the tone pure, where the response is more dispersed and lateralized towards the temporo-parietal areas of the right hemisphere.

4. DISCUSSION AND CONCLUSIONS

Several studies have been carried out in an attempt to find better technical parameters to be used in the AEPs paradigm, for example: the patient's position during the exam (subjects lying or sitting); auditory stimulus intensity (85dB, 95dB and 110dB); repetition number of stimuli; stimulus interval (S1 and S2); location of electrode fixation; polarization; etc [30]. In some situations, the researchers indicate that there are significant differences of results, but in others of that situations, there is no uniformity of findings between the surveys. However, in relation to the types of stimuli: click vs. pure tones, there is not enough research or results released.

Our research has shown that, although the clicks as a stimulus produces little circumscribed

activation of the auditory receptor [10], the responses obtained with it, have less temporal dispersion and greater amplitude and are also topographically restricted to the Cz position of the 10/ 20 system. This could be related to the mechanisms underlying the suppression of the P50 component and do not obey general mechanisms of adaptation of the receptors [31]. There is a sensory filtration process at higher levels, a feed-forward mechanism, which allows the brain to prepare for a second stimulus and get rid of irrelevant stimuli [26,27]. Apparently, this mechanism it makes possible to protect cortical centers from an influx of unnecessary information that would only hinder global interpretation. However, the artificially generated tones produce stimulation of more circumscribed areas in the cerebral cortex than the human voice, and the clicks as a stimulus are more distant than the pure tone and even more than the mixed tones in the frequency composition of the voice [32]. Possibly this is the reason why the pure tones presented more scattered and lateralized responses to the right than the clicks. In any case, none of the responses obtained differ significantly between them, allowing either of the two stimuli to be used interchangeably to explore patients with this potential. These results show the equivalence between the two paradigms used, as evaluators of the P50 response in healthy subjects.

On the other hand, although there is a presumption that regional topographic differences between clicks and pure tones are due to the number of auditory receivers stimulated respectively, more studies are needed to safely clarify the reason for this difference between clicks and pure tones.

Thus, the fact that there are no differences between pure tones and clicks in the results of P-50 AEPs demonstrates that both are eligible as tools for clinical use, after clinical studies confirm these results.

CONSENT

Which also met the criteria of the normality scale and accepted and signed the terms of the informed consent.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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