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Variability of registration latency and amplitude of the auditory evoked potential long latency (P3) in the condition test and retest

Variabilidade do registro de latência e amplitude do potencial evocado auditivo de Longa Latência (P3) na condição teste e reteste

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ABSTRACT

Purpose: To analyze the variability of the amplitude and latency of the P3 cognitive potential in normal individuals, the condition test and retest, in the period of 7 days. **Methods:** We evaluated 32 subjects, with ages between 18 and 25 years, 20 females and 12 males, without hearing complaints. Were submitted to audiologic evaluation and cortical potential. **Results:** The mean values of latency and amplitude for the P3 obtained in this study were of 314.78 ms and 312.40 ms for latency and 5.04 µV and 4.58 µV, for amplitude, in positions Cz and Fz, respectively. No significant difference was found when compared to the latency and amplitude, in the test-retest reliability, with the fixing of the electrodes in Cz and Fz. There was no difference for the latency and amplitude of P3 in all the modalities studied: gender, fixation of the electrodes (Cz and Fz) and condition test and retest. For the latency of the P3 in the female gender and condition of test and retest, there was significant difference. **Conclusion:** The mean values of latency and amplitude found in this study were 313.6 ms and 4.81 µV, respectively. The values of latency and amplitude did not vary according to the position of the electrodes (Cz and Fz) and regarding the condition test as retest. There was a significant difference for the female gender when compared in condition test and retest.The mean difference of the latency of P3 in condition of reassessment was 10.50 ms (Fz) and 15.25 ms (Cz) for the female gender and of 6.00 ms (Fz) and 5.83 ms (Cz) for the male gender.

Keywords: Evoked potentials; Event-related potencials, P300; Evoked potentials, Auditory; Hearing; Auditory perception

RESUMO

Objetivo: Analisar a variabilidade da amplitude e latência do potencial cognitivo P3 em indivíduos normais, na condição teste e reteste, no período de sete dias. **Métodos:** Foram avaliados 32 sujeitos, com idades entre 18 e 25 anos, 20 do gênero feminino e 12 do gênero masculino, sem queixas auditivas. Todos foram submetidos à avaliação audiológica e potencial evocado auditivo de longa latência. **Resultados:** Os valores médios de latência e amplitude para o P3, obtidos neste estudo, foram de 314,78 ms e 312,40 ms para latência e 5,04 µV e 4,58 µV para amplitude, nas posições Cz e Fz, respectivamente. A média da diferença da latência da onda P3 na condição de reavaliação foi de 10,50 ms (Fz) e 15,25 ms (Cz) para o gênero feminino e de 6,00 ms (Fz) e 5,83 ms (Cz) para o gênero masculino. **Conclusão:** Não houve diferença significativa quando comparadas latência e amplitude, no teste e reteste, com a fixação dos eletrodos em Cz e Fz. Não houve diferença para as latências e amplitude do P3 em todas as seguintes modalidades estudadas: gênero, fixação dos eletrodos (Cz e Fz) e condição teste e reteste. No entanto, para a latência do P3, houve diferença significativa para o gênero feminino, quando comparado em condição de teste e reteste.

Descritores: Potenciais evocados; Potencial evocado P300; Potenciais evocados auditivos; Audição; Percepção auditiva

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INTRODUCTION

Auditory Evoked Potential (AEP) is an electrophysiological response to sound, often distinguished by latency: ECochG, ABR (short latency), MLR (middle latency), LLR (long latency)[1].

P300 is the best known endogenous auditory evoked potential and its latency ranges from 270 ms to 400 ms. It is a cognitive potential, voluntarily and actively generated during the performance of a specific task, unlike exogenous potentials (e.g. ECochG and ABR), which appear in a passive and reflex form once the individual listens to an appropriate stimulus[2]. P300 is a unique electrophysiological procedure in the sense it provides the researcher with a window to observe the neurophysiological substrate of processes that occur in the cerebral cortex related to cognition, such as memory and auditory attention necessary to central auditory processing[3] .

Among the different auditory procedures that assess the integrity of the central auditory system are the information obtained through auditory evoked potentials. These potentials, in turn, play a key role in Audiology, for the ability to capture electrical potentials created at various levels of the nervous system in response to acoustic stimulation, with no invasive techniques, is a breakthrough in the diagnosis of auditory pathologies, in addition to providing information that monitors the progress and treatment of these pathologies[4-6]. For that reason P300 is used in one of its most stable conditions: the intra-subject measurement.

Studies in this area have been developed with children in rehabilitation process after auditory training[7] and with individuals using electronic devices for deafness[8].

Cognitive potentials may vary from 15-20 ms at P3 response when examinations are performed at relatively short intervals on the same patient. At times, the N2-P3 complex is not identified or its amplitude reduced, even in the absence of any pathology, sometimes attributed to habituation to the auditory stimulus system[9].

Studies on P300 amplitude, related to gender and age have been found in the literature, although a consensus cannot be verified. As for latency, the literature describes that it increases with age and therefore it should be adjusted when analyzing the test result. Regarding the influence of gender in generating these potentials, authors have found no significant difference for P300, whereas N2 component presents higher values for males[4,10].

In Brazil, few studies demonstrate normality values in different age groups, P300 compared with other diagnostic procedures or even more scarcely, the assessment parameters and electrode positioning[11].

The need to establish an assessment and follow up protocol, associated with objective evaluations becomes increasingly present in the literature, not only for individuals with hearing loss or attention disorders, but also for degenerative diseases. Such protocol would allow data comparison to measure disease evolution, for speech, writing and auditory perception[12].

Because P300 is an electrophysiological measure of cognitive functioning, it is required that the clinician have knowledge, experience and systematization of protocols in order to avoid misinterpretations[13]. Trends obtained from this study are intended to assist clinicians on the stability of timing condition, latency and amplitude measures and the records of that potential.

This study aimed to analyze the variability of P300 latency and amplitude in normal subjects, in test-retest condition, on a 7-day period.

METHODS

This research was approved by the Ethics in Research Committee at Hospital das Clínicas de Ribeirão Preto, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (HCRP/FMRP/USP) (Document Number: 7334/2009).

The study is deductive, descriptive, cross-sectional, and comparative, focused on diagnosis.

We evaluated 32 healthy volunteers, 12 males and 20 females, aged between 18-25 years old. After the participants agreed to take part on the study, they all signed an Informed Consent.

As inclusion criteria, we accepted subjects aged between 18 years old and 25 years and 11 months, with normal hearing, no history of hearing, psychiatric and / or neurological problems.

By accepting to participate in the study, the subjects were instructed about the care to be taken for the exam in order to avoid influences of variables when measuring P300 (latency and amplitude). The following factors were controlled: time of day at which the test was performed, temperature, food intake and/or drugs and physical activities, emotional state at the exam day and exam's eve, whether the subjects were sleepy or worried, and for the women, the hormonal phase cycle.

Initially a separate interview with the subjects was conducted to collect data about their hearing condition, health status and overall conditions for the test. Then, we performed the inspection of the external auditory meatus, in order to check for any obstruction that could interfere with the basic audiological evaluation through audiometry tone threshold (Audiometer AD28®, 39 TDH) and logoaudiometry.

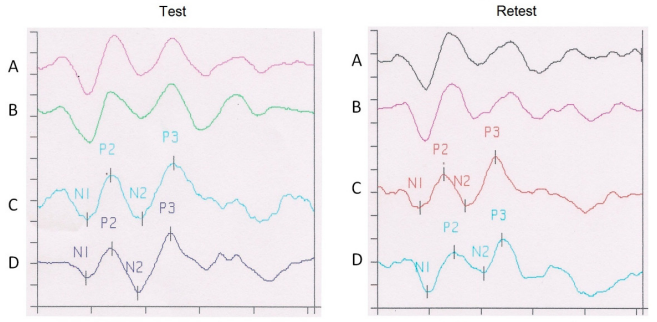
After basic audiological evaluation, P300 testing was initiated (Bio-logic® - two channels, coupled to a conventional computer).

For P300 recording, the active electrodes were placed at Cz and Fz and connected to input 1 of the preamplifier, channel 1 and channel 2, respectively. Reference electrodes were placed on the earlobes (A1 and A2), interconnected and connected to input 2 of channel 1 and interconnected to channel 2 through the jumper of the preamplifier. The ground electrode was placed at Fpz. For the electrophysiology examination,

individual impedance (Ω) below 5K electrodes and impedance between them less than 2K was necessary. The examination was performed in acoustic booth, the volunteers in semi-sitting position, half-open eyes and staring to a certain point in front of them. *Tone Burst* was used as auditory stimulus in tones of 1000 Hz for frequent stimulus and 2000 Hz for rare stimulus, presented randomly, at 20% probability for rare stimuli, recorded at 500ms window, 100 microvolts sensibility, alternated polarity, with 0.5-30 Hz bandpass filter, monoaural stimuli and stimulation rate of 1.1 stimulus/second, at 70 dB intensity NA. The volunteers were asked to identify the rare stimulus, mentally counting the number of times it occurred.

The examination took place twice successively to allow good definition and replication.

For the P300 investigation, considering the variation of time - test and retest (VTR), all procedures described above were repeated in two successive passages on a seven-day period, on average, with a variation of two days (Figure 1).



		N1	P2	N2	P3
Latency (ms)	C	91,20	135,20	193,20	251,20
	D	89,20	137,20	185,20	245,20
Amplitude (μV)	C	-6,92	+4,52	-6,70	+7,58
	D	-3,64	+3,41	-7,06	+7,05

		N1	P2	N2	P3
Latency (ms)	C	81,20	127,20	169,20	227,20
	D	95,20	147,20	205,20	239,20
Amplitude (μV)	C	-5,69	+2,85	-5,17	+6,94
	D	-5,43	+3,40	-1,33	+6,20

Figure 1. Example of N1, P2, N2 components and P3 of Long Latency Auditory Evoked Potential (P3), captured simultaneously by the electrodes placed at Fz and Cz

The values of P3 amplitude and latency were scored according to criteria established in the literature: higher positive wave, just after N1-P2-N2 complex, taking place in the replication of the waveforms for the rare stimulus, between 240 and 700 ms[4]. The marking of the waves was performed by an experienced electrophysiology.

Exploratory data analysis was performed. To compare the results of the test and retest conditions, we carried out linear regression models with mixed effects (random and steady effects). We used SAS software version 9.0 to adjust the model.

RESULTS

The mean values of latency and amplitude for P300 in this study, independent of evaluation condition (test and retest), were 314.78 ms and 312.40 ms for latency and 5:04 μV and 4:58 μV for amplitude, at Cz and Fz placement, respectively.

The results of the descriptive analysis (mean, standard deviation and median) for P300 measures of latency and amplitude in different electrodes positioning (Cz and Fz), in test and retest conditions and in comparison between males and females in the same situation of P300 variability are presented in Tables 1 and 2.

We found no significant differences (p>0,05) by comparing latency and amplitude values in test and retest condition for placing the electrode at Cz and Fz and between the electrodes.

The comparison of the results of P300 latency and amplitude in test and retest, in all forms studied, males and females and at Cz/Fz may be observed in Table 3.

Of all the comparisons studied, for P3 latency, we found a significant difference in females, test and retest condition, (p=0.0092).

The average difference in latency and amplitude, when compared with males and females, registered at Fz ranged between, 6.00 to 10.50 ms and 0.40 to 0.11 μV, respectively, and at Cz it ranged from 5.83 to 15.25ms and 0,36 μV and 15.25 ms and 0,01 μV, respectively as shown in Table 4.

DISCUSSION

According to the study, we could demonstrate that the P300 research was feasible to be conducted in this population and all individuals assessed presented the P300 component recording at Fz and Cz, respectively.

Table 1. Mean, standard deviation and median for P3 latencies and amplitudes, in test and retest conditions

Group	Electrode placement	n	Variable	Mean	SD	Median
Test	Cz	32	Latency (ms)	311.11	40.10	308.20
			Amplitude (μv)	4.98	2.09	4.86
	Fz	32	Latency (ms)	310.26	40.31	312.20
			Amplitude (μv)	4.54	1.96	4.48
Retest	Cz	32	Latency (ms)	318.45	33.05	320.20
			Amplitude (μv)	5.12	2.23	4.69
	Fz	32	Latência (ms)	314.58	32.14	313.20
			Amplitude (μv)	4.62	2.25	4.72

Note: SD = standard deviation; Cz = central midline; Fz = frontal midline; ms = milliseconds; μv = microvolts

Table 2. Mean, standard deviation and median for P3 latencies and amplitudes comparing males and females

Group	Electrode placement	Gender	n	Variable	Mean	SD	Median
Test	Cz	F	20	Latency (ms)	307.75	47.92	300.20
				Amplitude(μv)	4.91	2.14	4.97
		M	12	Latency (ms)	316.70	22.57	319.20
				Amplitude(μv)	5.10	2.10	4.86
	Fz	F	20	Latency (ms)	310.40	47.35	312.20
				Amplitude(μv)	4.45	1.98	4.83
		M	12	Latency (ms)	310.03	26.57	308.20
				Amplitude(μv)	4.70	2.00	4.15
Retest	Cz	F	20	Latency (ms)	323.00	37.01	325.20
				Amplitude(μv)	4.92	2.44	4.35
		M	12	Latency (ms)	310.87	24.74	315.20
				Amplitude(μv)	5.46	1.89	5.56
	Fz	F	20	Latency (ms)	320.90	37.22	318.20
				Amplitude(μv)	4.33	1.95	4.59
		M	12	Latency (ms)	304.03	18.00	302.20
				Amplitude(μv)	5.10	2.70	4.72

Note: SD = standard deviation; Cz = central midline; Fz = frontal midline; F = female; M = male; ms = milliseconds; μv = microvolts

Table 3. Difference estimate, p-value, lower and upper limit for P3 latencies and amplitudes

P3	Comparisons	Estimate of the difference	p-value	LL	UL
Latency (ms)	Cz (F x M)	1.5917	0.8988	-22.6616	25.8449
	Fz (F x M)	8.6167	0.4821	-15.6366	32.8699
	F/Test (Cz x Fz)	-2.6500	0.6996	-16.2486	10.9486
	F/Retest (Cz x Fz)	2.1000	0.7597	-11.4986	15.6986
	M/Test (Cz x Fz)	6.6667	0.4526	-10.8890	24.2223
	M/Retest (Cz x Fz)	6.8333	0.4414	-10.7223	24.3890
	Test/Cz (F x M)	-8.9500	0.5067	-35.6240	17.7240
	Retest/Cz (F x M)	12.1333	0.3686	-14.5406	38.8073
	Test/Fz (F x M)	0.3667	0.9783	-26.3073	27.0406
	Retest/Fz (F x M)	16.8667	0.2123	-9.8073	43.5406
	F (Test x Retest)	12.8750	0.0092*	3.2594	22.4906
	M (Test x Retest)	-5.9167	0.3462	-18.3304	6.4971
	Cz (Test x Retest)(F x M)	6.3000	0.6400	-20.3740	32.9740
	Fz (Test x Retest)(F x M)	10.8667	0.4204	-15.8073	37.5406
Amplitude (μv)	CZ (F x M)	-0.3702	0.5816	-1.7003	0.9598
	FZ (F x M)	-0.5077	0.4502	-1.8378	0.8223
	F/Test (Cz x Fz)	0.4545	0.3741	-0.5564	1.7733
	F/Retest (Cz x Fz)	0.5830	0.2549	0.4279	1.5939
	M/Test (Cz x Fz)	0.4033	0.5408	-0.9018	1.7084
	M/Retest (Cz x Fz)	0.3592	0.5859	0.9459	1.6643
	Test/Cz (F x M)	-0.1953	0.8048	-1.7607	1.3700
	Retest/Cz (F x M)	-0.5452	0.4908	-2.1105	1.0202
	Test/Fz (F x M)	-0.2465	0.7551	-1.8118	1.3188
	Retest/Fz (F x M)	-0.7690	0.3317	-2.3343	0.7963
	F (Test x Retest)	-0.05325	0.8827	-0.7681	0.6616
	M (Test x Retest)	0.3829	0.4119	0.5399	1.3058
	Cz (Test x Retest)(F x M)	-0.1843	0.8156	-1.7497	1.3810
	Fz (Test x Retest)(F x M)	-0.3640	0.6452	-1.9293	1.2013

*Significant values (p≤0,05) – Linear regression models with mix effects (random and steady)
Note: LL = lower limit; UP = upper limit; Cz = central midline; Fz = frontal midline; F = female; M = male

Table 4. Mean difference in test and re-test regarding for P3 latencies and amplitudes

Electrodes	Gender	Latency (ms)	Amplitude (μv)
Cz	Females	15.250	0.011
	Males	5.830	0.360
Fz	Females	10.500	0.117
	Males	6.00	0.405

Note: Cz = central midline; Fz = frontal midline; ms = milliseconds; μv = microvolts

Some authors reported that the central nervous system is mature only approximately at the age of seventeen due to the neurological maturation process[14], when increased intra and inter cortical connectivity occurs[15]. However, it is believed that P300 may be performed in children from eight years old[10].

The mean P300 latency, in test and retest condition, obtained in this study – 225 to 365[16], ranging from 250 to 350 ms[4] – is close to the values found in the literature[17], for adolescents and adults (17-30 years).

Comparing P300 latency and amplitude results in test and retest condition, we found no significant difference for P3 wave latency and amplitude in all forms studied in females and males, respectively at Cz/Fz in test and retest condition. However, for P3 latency, in test and retest condition, we found a significant difference for females. It is noteworthy that the factors that could influence the exam results, described in the literature[3,6], were controlled as previously described. As to this result, a possible explanation may be the influence of the incontrollable menstrual cycle.

In the study comparing P300 latency and amplitude measurements, in test and retest conditions, we found significant differences for P300 latency recorded at Fz and Cz, when analyzing the gender variable (Table 3). This finding is not consistent with the literature[18] which found that, during assessment and reassessment, there was no difference in latency for male and female.

Comparing the results of latency and amplitude, we found no significant difference in the forms studied in this research, i.e., placements of the electrodes (Cz and Fz), gender and test and retest condition. In the literature[19], similar result was found for electrodes' position[10,11,19], when comparing males and females in test and retest condition[19].

Studies have indicated that P300 latency is reliable in test and retest condition in normal adults[20-22]. Authors observed P300 component reliability inter and between sessions, suggesting that such patterns, observed at long-term, may reflect habituation or dis-habituation of certain processes in the central nervous system[20].

Also in relation to gender, in a study to measure P3 Long-Latency Auditory Evoked Potential, the author observed no statistical difference between genders when comparing latency and amplitude of P3 component. However, this difference exists when comparing N2 component latency[19]. On the other hand, another study showed statistical difference between male and female, with females showing mean values and standard deviation of P3 component latency smaller than in males[23].

Although there is no consensus in the literature regarding the number of active electrodes to be used for an effective recording of P-3 Long Latency Auditory Evoked Potential and their placement on the skull, using two active electrodes, in this study Fz and Cz, is a parameter that can be used in clinical practice to determine the presence of P3 component[19].

The mean difference of P3 latency in reassessment condition was of 10.50ms (Fz) and 15.25 ms (Cz) for females and 6.00 ms (Fz) and 5.83 ms (Cz) for males, which corroborates the findings in the literature[4] which reported that the cognitive potential may range from 15-20 ms at P3 response when performed on the same patient at relatively short intervals.

CONCLUSION

We found no significant difference, when comparing latency and amplitude in test and re-test, placing the electrodes at Cz and Fz. There was no significant difference for P3 latencies and amplitudes in the studied forms: gender, electrode position (Cz and Fz) and test and re-test condition. However, for P3 latency, there was a significant difference for females, when in test and re-test condition.

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