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The mismatch negativity test in ears with and without tinnitus-a path to the objectification of tinnitus

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Abstract

Introduction: The mismatch negativity (MMN) test evaluates neural responses to unexpected sounds, providing objective data on the neural plasticity of the auditory system. **Objectives:** In this study, we assessed whether the MMN test could identify failure of neural habituation of the auditory pathway in patients with severe tinnitus. Materials and **Methods:** Patients with normal hearing were compared to tinnitus patients, via the MMN test. The Tinnitus Handicap Inventory (THI) and a visual analog scale (VAS) were used to evaluate tinnitus-derived annoyance. The Hospital Anxiety and Depression (HAD) scale was used to assess anxiety and depression. **Results:** The average MMN amplitudes in the tinnitus group were -0.88 uV in the right ear (RE), and -1.13 uV in the left ear (LE), while in control group the corresponding amplitudes were 1.01 uV and -1.19 uV. Mean latencies in the tinnitus group were 208.34 ms in the RE, and 209.92 ms in the LE, while in the control group the corresponding latencies were 217.38 ms and 215.69 ms. The differences in mean latencies between the groups were statistically significant. **Conclusion:** The MMN test may be useful for evaluating the habituation process of the central auditory pathways in tinnitus patients.

Keywords: earache, neurology, tinnitus.

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INTRODUCTION

Tinnitus is the perception of a sound without an external source[1], and it affects approximately 40 million people in America and England alone.

Severe tinnitus has been described as the worst problem that can afflict human beings[2]. It is usually caused by damage to the peripheral auditory system, however high structures of the cerebral cortex can also be involved in its emergence and persistence. Some people do not experience any discomfort related to the presence of tinnitus, while others experience intense discomfort, and may even develop psychiatric disorders such as stress, irritability, concentration problems, anxiety, depression, and sleep disorders, among others[3-6].

To explain the mechanisms involved in the development of chronic tinnitus, Hallam[7] developed the tinnitus habituation theory. He postulated the tinnitus sound to be a bodily symptom which some people pay more attention to than others. According to this theory, there is a deficit of habituation in patients complaining of significant tinnitus[8].

Based on these studies, Jastreboff[1] formulated the neurophysiological model of tinnitus, which holds that the origin of tinnitus can involve the limbic system and the autonomic nervous system, rather than being primarily an auditory system problem. This means that the same buzz generated by an injury to the peripheral auditory system may also involve central auditory mechanisms - the limbic system and autonomic nervous system - which act to increase the intensity of tinnitus, and the annoyance associated with it.

According to Gerken[9], it is difficult to study the central mechanisms of tinnitus due to interference from peripheral changes, and the intricate complexity of the central nervous system's interconnections with the auditory system. High brain structures are involved in tinnitus, and annoyance is perceived during the course of dealing with the internal sounds[3,4]. The mismatch negativity (MMN) test is a procedure that facilitates the study of habituation deficits thought to be present in patients with tinnitus. MMN is an electrical brain response to a different signal in the midst of a repetitive auditory stimulation signal. The MMN test facilitates the assessment of habituation. According to Hall III[10], MMN may be the most accurate objective measure of auditory processing within the central nervous system. It enables the objective measurement of auditory discrimination and other processes such as sensory memory[11], a very common complaint among patients with chronic tinnitus.

The MMN test is the only objective method for accurately measuring central auditory processing, echoic memory duration (auditory data retained for a short period of time), and traces of permanent auditory memory. It is an objective measure of the temporal window of integration of auditory perception and generators, the functional significance of which is relatively well-known. Thus, the MMN test is an objective way to verify habituation deficits, which according to the literature, occur in patients with severe tinnitus. The aim of the present study was to investigate the characteristics of event-related potential (MMN) in people who complain of tinnitus without hearing loss, and compare the results to those of a control group without tinnitus.

MATERIALS AND METHODS

A group of 25 tinnitus patients with normal hearing (the study group; SG) was compared with a group of 13 subjects with normal hearing and no tinnitus (the control group; CG). The inclusion criteria were an absence of other otological complaints, normal otological and audiological tests, and an age of 18 years or over. The study was approved by the relevant ethics committee of our institution (#079/2007).

Patients who attended the tinnitus clinic at the University Hospital of Brasília and met the inclusion criteria were invited to participate in the study. The participants were examined by an otolaryngologist, and were assessed via tonal and vocal audiometry, as well as imitanciometry, to qualify their hearing. Central pathways were evaluated via evoked potential MMN. A Midimate 622 (Madsen Corporation, USA) was used for the audiometry assessments, a Zodiac 901 (Madsen Corporation, USA) was used for the imitanciometry, and an Audiotest 615 (Interacoustics Corporation, Denmark) was used for the MMN tests.

Data collection was performed at the Hearing Health Clinic at Brasilia University Hospital, and the participants signed a written informed consent form prior to data collection. Each patient's skin was cleaned with gauze and ether on the vertex (vertex electrode), behind the ears (ear pads, right and left ear), and on the left side of the forehead (ground electrode), and the electrodes were then positioned. Disposable 3M adhesive electrodes and conductive TEM-20 paste were used. The stimuli were delivered through inserted earphones. Measurements of acoustic impedance, which should be less than 3 kiloohms, and as a general rule should not exceed 5 kiloohms, measured at approximately 15 Hz[12] were made. The patient was instructed to remain seated, move as little as possible, and take their attention off the sound stimuli and focus on magazines that they were instructed to read during the evaluation. Separate measurements were taken from each ear, while the patient continued reading. All audiological tests were performed by the same professional.

The Tinnitus Handicap Inventory[13] (THI) was used to assess tinnitus annoyance levels. It consists of 25 questions divided into three categories: functional, emotional, and catastrophic. There are three possible response options for each question; yes (4 points), sometimes (2 points), or not at all (no points)[13]. The functional scale (F) measures the interference of tinnitus in mental, social, and occupational physical activities, and consists of 11 questions contributing to a maximum score of 44. The emotional scale (E) measures affective responses such as anxiety, anger, and depression and consists of 9 items contributing to a maximum score of 36. The catastrophic scale (C) quantifies the despair and incapacity the patient experiences in dealing with the symptom, and consists of 5 questions contributing to a maximum of 20 points. The THI was adapted to Brazilian Portuguese by Ferreira et al.[14] in 2005. The visual analogue scale (VAS) used is a scale from 1 to 10, where 1 corresponds to the lowest level of annoyance and 10 the highest. McCombe et al.[15] proposed the use of the THI to classify tinnitus ringing in uncategorized. According to the authors, by adding the points obtained via the THI, tinnitus can be classified as negligible (0-16%), light (18-36%), moderate (38-56%), severe (58-76%), or catastrophic (78-100%). Tinnitus categorized as "severe" or "catastrophic" is considered very rare in an epidemiological setting.

The Hospital Anxiety and Depression (HAD) scale is a means of screening for depression and anxiety, and is completed by the patient. It consists of a total of 14 questions, 7 relating to anxiety and 7 to depression. Each question has four response options ranging from 0 to 3, thus the scores for each of anxiety and depression can vary from 0 to 21. A score above 8 for anxiety is suggestive of an anxious state, and a score above 9 for depression is suggestive of a depressive state[16,17]. The HAD was validated for Brazilian Portuguese by Castro et al.[17] in 2006.

Long latency evoked potentials-MMN

The stimuli were presented monaurally, with an intensity of 70 dB, with a 1-30 Hz filter. The standard stimulus was presented at a frequency of 1000 Hz. 1100 Hz was the frequency of the rare stimulus, that produces the MMN wave. The standard stimulus was presented 80% of the time, and the rare stimulus 20% of the time. The window display was 600 ms. The results of this examination were analyzed for the presence of potential wave amplitude, and frequency range, and the tinnitus group was compared with the control group. The latencies of MMN waves were also recorded.

Procedures

After signing the consent form, the patients indicated the severity of their tinnitus using the VAS, and completed the HAD and THI. Otoscopy, imitanciometry, and audiometry were then performed in a soundproof booth. If the patient met the inclusion criteria, they were referred for MMN evaluation. Because not all subjects in the tinnitus group had tinnitus in both ears, only data derived from ears exhibiting tinnitus were included in the analysis of the tinnitus group.

The patients without tinnitus (the control group) underwent all the above-described tests, except the VAS, THI, and HAD. The statistical analyses included descriptive methods, and Student's *t*-student test for independent groups. All analyses were conducted using SPSS software, and $p < 0.05$ was deemed to indicate statistical significance.

RESULTS

The study group (SG; n = 25) were allright-handed, and their mean age was 49 years (SD 11.91). Twenty patients (80%) in the study group had bilateral tinnitus, 4 patients (16%) had tinnitus in the left ear only, and 1 (4%) had tinnitus in the right ear only. Therefore, 45 ears in the study group were included in the analysis. In the control group there were 26 ears in total. The bilateral pure tone average was 8 dB in this group, and the mean score in the VAS was 8.5. The control group (CG; n = 13) were also allright-handed, and their mean of age was 35 years (SD 15.99). The bilateral pure tone average was 9 dB in this group. These results are summarized in Table 1. The patients in the study group were significantly older than those in the control group ($p < 0.001$), but there were no statistically significant differences in gender ($p = 0.833$) or pure tone average ($p = 0.594$) between the groups.

Based on the HAD scale, the study group's mean anxiety score was 9.2 (SD 4.54), and their mean depression score was 7.3 (SD 4.42). Considering the parameters of the HAD scale, these scores indicate an anxious state, but not a depressive state, in this particular study group. Conversely, in the control group the corresponding means were 4.1 (SD 2.93) for anxiety and 1.4 (SD 1.98) for depression, which are not suggestive of an anxious state or a depressive state.

Patients in the study group were assessed via the THI scale, yielding the following scores and classifications: 20.8 functional, 19.2 emotional, and 12.1catastrophic. The sum of the means from all categories combined is 52.1 points (Figure 1).

Table 1. Number of ears assessed, age, gender, pure tone average, and tinnitus annoyance.

Group	Ears assessed	Age	Gender		Pure tone average (dB)	Annoyance VAS
		(Mean (SD))	Male	Female	Mean	Mean
SG	45*	49 (11.91)	16	9	8	8.5
CG	26	35 (15.99)	5	8	9	-

VAS: Visual analogue scale; SG: Study group; CG: Control group; * Ears without tinnitus were not assessed in the study group (SG).

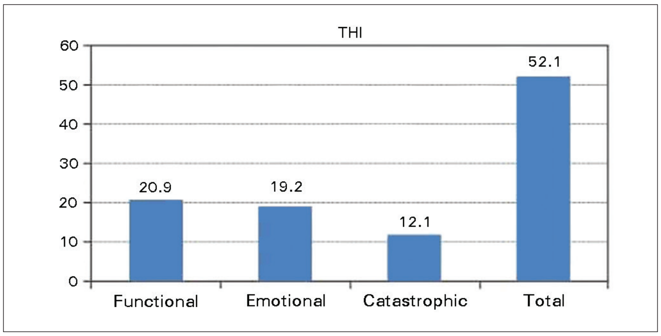

Figure 1. Mean scores for functional, emotional, and catastrophic questions evaluated by the THI.

In the MMN tests, the study group exhibited mean latencies of 208.57 ms in the right ear (n = 21 ears) and 211.08 ms in the left ear (n = 24 ears). Mean amplitudes were -1.13 uV in the left ear and 0.88 uV in the right ear. When both ears were evaluated together (total 45 ears), the mean latency was 209.91 ms, and the mean amplitude was 1.01 uV. The control group exhibited mean latencies of 217.38 ms in the right ear (n = 13 ears) and 215.69 ms in the left ear. Mean amplitudes were -1.01 uV in the right ear and -1.19 uV in the left ear. When both ears were evaluated together (total 26 ears), the mean latency was 216.54 ms, and the mean amplitude was -1.10 uV. These data are summarized in Table 2. Not all patients in the study group had bilateral tinnitus, and data was only derived from ears exhibiting tinnitus in that group, therefore we considered the number of ears assessed in each group in the analysis, not the number of patients in each group.

A more detailed comparison of the MMN latency and amplitude data from the right and left ears in each group is shown in Table 3. MMN testing in right ears yielded mean latencies of 208.57 ms (SD 12.82) in the study group and 217.38 ms (SD 9.22) in the control group. This difference was statistically significant (p = 0.03). In contrast, the mean latencies in the left ears were 211.08 ms (SD 13.11) in the study group and 215.69 ms (SD 7.83) in the control group; a difference that was not statistically significant (p = 0.255) (Figure 2A and B).

MMNtesting in right ears yielded mean amplitudesof -0.88 uV in the study group and -1.01 uV in the control group (Table 3). These values did not differ statistically significantly (p = 0.557). The mean amplitudes in the left ears were 1.13 uV in the study group and -1.19 uV in the control group; also not astatistically significant difference (p = 0.881) (Figure 2C and D).

Whenboth ears were measured together (Table 4), there was a statistically significant difference in MMN latency between the study group andthe control group (p = 0.022) (Figure 3A). The mean amplitudes did not differ statistically significantly between the groups (p = 0.682) (Figure 3B).

DISCUSSION

MMN testing is a means of investigating the detection of unexpected signals presented during regular sound stimulation[18]. It has been widely used in healthy populations, and in the context of various diseases including schizophrenia, and cognitive changes[19,20]. There are no standard normative values for amplitude or latency determined via the MMN test[21]. Latency refers to the time required for the cortex to differentiate the standard sound from the “rarer” deviant stimulus. Amplitude is influenced by aspects of the rare deviant stimulus, including its acoustic characteristics[10]. The analysis of MMN amplitude is performed via visual identification, which is necessary to compare the mean results of a control group with those of a study group[22-24]. When comparing the control group with the tinnitus group in the present study, we did not find statistically significant differences between the mean amplitudes.

It has been reported that MMN occurs approximately 100-200 ms after the stimulus[25,26]. According to Näätänen et al.[23], MMN can detect a latency range of 150-250 ms. According to Hall III[11], MMN can detect a latency range of 100-300 ms. The average latency responses detected via MMN in this study varied from approximately 200-220 ms.

No studies that followed the same methodology used in this work were detected via a comprehensive search of the literature. However, other studies utilizing different protocols and group selection methods to evaluate the central auditory system by the medium and long latency evoked potentials suggest that these potentials may represent a method of assessing habituation failures[5,27,28].

Weisz et al.[27] used MMN to evaluate 15 people with tinnitus and hearing loss, and compared them with a control group of 15 people with normal hearing.

Table 2. Mean amplitude and latency in both groups, derived from the MMN test.

	Right ear			Left ear			Both ears		
	Number of ears	Amplitude (uV) Mean	Latency (ms) Mean	Number of ears	Amplitude (uV) Mean	Latency (ms) Mean	Number of ears	Amplitude (uV) Mean	Latency (ms) Mean
SG	21	-0.88	208.57	24	-1.13	211.08	45	-1.01	209.91
CG	13	-1.01	217.38	13	-1.19	215.69	26	-1.10	216.54

SG: Study group; CG: Control group.

Table 3. MMN latency and amplitude in the right and left ears.

	MMN latency				MMN amplitude			
	Right ear		Left ear		Right ear		Left ear	
	SG	CG	SG	CG	SG	CG	SG	CG
Number of ears	21	13	24	13	21	13	24	13
Minimum	190	200	188.00	202.00	-3.05	-2.25	-4.20	-3.47
Maximum	232	230	228.00	226.00	-0.04	-0.19	-0.05	-0.02
Mean	208.57	217.38	211.08	215.69	-0.88	-1.01	-1.13	-1.19
SD	12.82	9.22	13.11	7.83	0.67	0.64	1.01	1.00
CI (95%) SL	202.73	211.82	205.55	210.96	-1.18	-1.40	-1.56	-1.79
IL	214.41	222.95	216.62	220.42	-0.57	-0.63	-0.71	-0.58

MMN: Mismatch negativity; SG: Study group; CG: Control group; CI: Confidence interval; SL: Superior limit; IL: Inferior limit.

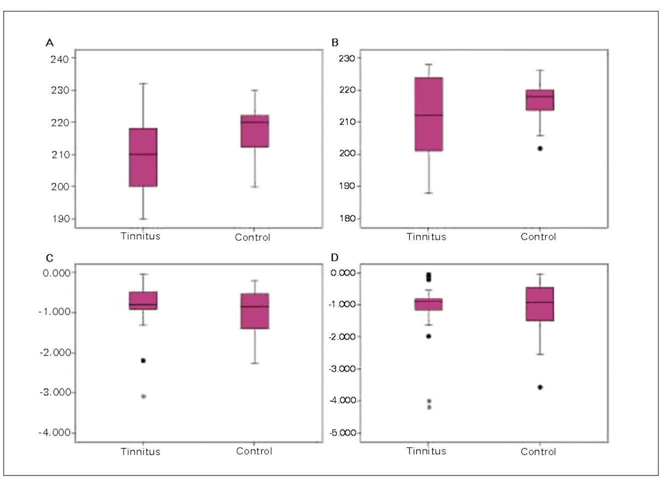

Figure 2. The distributions of latencies in (A) the right and (B) the left ears, and amplitudes in (C) the right and (D) the left ears.

Their findings showed that tinnitus is a more complex phenomenon than pure reorganization of neural responses in the auditory cortex after damage to the receptors. They suggest the involvement of regions responsible for emotions and attention in tinnitus perception. Emotional aspects of the subjects in this present study were evaluated via the HAD scale. Our data corroborates the findings of other studies that have used similar methodologies as a tool to evaluate anxiety and

Table 4. MMN latency and amplitude when means from both ears were considered together.

	Latency (ms)		Amplitude (uV)	
	SG	CG	SG	CG
Number of Records	45	26	45	26
Minimum	188	200	-4.20	-3.47
Maximum	232	230	-0.04	-0.02
Mean	209.91	216.54	-1.01	-1.10
SD	12.89	8.42	0.87	0.83
CI (95%) IL	206.04	213.14	-1.27	-1.43
SL	213.78	219.94	-0.75	-0.77

MMN: Mismatch negativity; SG: Study group; CG: Control group; CI: Confidence interval; SL: Superior limit; IL: Inferior limit.

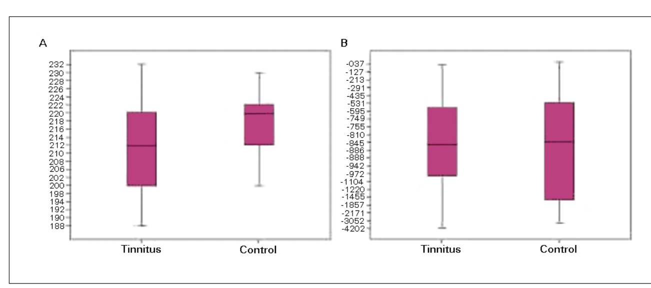

Figure 3. Distribution of (A) latency and (B) amplitude measurements derived from both ears together. Tinnitus is the perception of a sound without an external source[1], and it affects approximately 40 million people in America and England alone.

depression in patients with tinnitus. The control group exhibited no significant anxiety or depression, while the study group exhibited mean HAD scores of 9.2 for anxiety and 7.3 for depression; values that suggest a high degree of anxiety in the study subjects, corroborating previous research[6,29,30].

In this present study, a VAS and the THI were used to characterize tinnitus. The mean annoyance score determined via the VAS was 8.5 points, which can be considered indicative of major annoyance. Holdefer et al.[6] utilized the THI in a group of patients with severe tinnitus, and reported mean values of 29.16 for the functional category, 24.11 for the emotional category, and 12.53 for the catastrophic category. A cumulative total value of 65.8% was considered indicative of severe tinnitus according to the classification of McCombe et al.[15]. Our study yielded lower values, with means of 20.8, 19.2, and 12.1 in the functional, emotional, and catastrophic categories respectively, adding to a total of 52.1%; classified as moderate tinnitus. These values however, suggest that tinnitus had a major impact on the quality of life and emotional status of these subjects.

Although many studies using MMN in the evaluation of various pathologies[31,32] and symptoms such as tinnitus[33] report differences in MMN amplitudes, our findings showed no statistically significant differences in MMN amplitudes between the two groups. As withother assessments of the auditory system by means of evoked potentials where the amplitudes of the waves do not have associated standardized values (short latency and P300 for example), the findings of this research suggest that the wave amplitude in MMN is not a useful measure for the evaluation of tinnitus, at least within the context of the evaluation methods and equipment used.

In this study, there was a statistically significant difference between the mean MMN latencies of the control group and the group with tinnitus. When the ears were evaluated individually, there was only a statistically significant difference for the right ear. However, although there was no statistically significant difference in latency for the left ear, the average latency in these ears was noticeably smaller in the tinnitus group than in the control group.

It is known that verbal auditory stimulus recognition occurs in the left hemisphere, while non-verbal auditory stimuli are initially processed by the right hemisphere[34]. This may have been the reason for our observation of smaller latencies in the right ear, since tinnitus is a nonverbal stimulus processed first in the right hemisphere. Morgan et al.[35] studied P300 cortical potentials in stutterers and non-stutterers, and found smaller P300 amplitudes in the left hemisphere for tonal stimuli. They suggested that this may be due to functional hemispheric asymmetry, with greater amplitude in the right hemisphere, which is responsible for the processing of nonverbal stimuli. Frizzo et al.[36] point out the great variability obtained when recording these potentials. Due to a lack of general agreement among researchers on the application of this technique, it is not commonly used by audiologists.

The findings of this study may suggest a change in the activation of the central auditory system in the tinnitus group, with participation of the limbic system and prefrontal cortex, which is not present in those without tinnitus. There may be differences in the auditory system, and other systems involved in hearing and habituation, in those who fail to achieve normal habituation to tinnitus.

CONCLUSION

Our findings suggest that people who experience tinnitus annoyance have lower MMN latency than subjects who do not have tinnitus. The higher HAD scores for anxiety in tinnitus patients also suggests higher centers as modifiers of tinnitus annoyance. This difference was statistically significant for latencies in the right ear, and was also observed in the left ear, although that difference was not statistically significant. The amplitude of the MMN wave is not a good parameter for the measurement and evaluation of tinnitus. MMN is of little potential use in audiology, but can be a useful tool for the evaluation of the auditory cortex. Our findings are encouraging of further research. MMN may prove to be a useful method for objective tinnitus identification and assessment, as well as for monitoring treatment progress.

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