A Reexamination of the Long Latency N1 Response in Patients with Tinnitus

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Abstract
There have been disparate findings reported previously by investigators who have examined differences in the cortically generated N1 (i.e., N100) from control and tinnitus samples. Investigators have employed differing stimulation paradigms applied to relatively small subject samples. Accordingly, it is not surprising that there has been no unanimity in the reported findings. The present investigation was conducted to determine, once again, whether differences exist in the cortically generated N1 potential recorded from both normals and subjects with bothersome tinnitus. In this investigation both passive and selective auditory attention paradigms were employed. Subjects were a total of 63 adults (31 controls and 32 tinnitus patients). The mean score on the Tinnitus Handicap Inventory for the tinnitus group was 39 points. Results failed to reveal group differences in the latency of N1 across listening conditions. However, tinnitus patients demonstrated N1 potentials that were of significantly smaller amplitude than those obtained from normal subjects. These findings are consistent with those reported in previous investigations.

Key Words: Evoked potentials, N100, tinnitus

Abbreviations: AEF = auditory evoked field; AEP = auditory evoked potential; PN = Processing Negativity; THI = Tinnitus Handicap Inventory; EEG = electroencephalography; EOG = electrooculography

Sumario:
Han existido hallazgos desiguales, reportados previamente por investigadores que han examinado las diferencias en las N1 generadas corticalmente (p.e., N100), a partir de muestras de pacientes con acúfenos y en controles. Los investigadores han utilizado paradigmas de estimulación diferentes, aplicados a una muestra relativamente pequeña de sujetos. De hecho, no causa sorpresa descubrir que no ha existido unanimidad en los hallazgos reportados. La presente investigación fue conducida para determinar, de nuevo, si existen diferencias en los potenciales N1 generados corticalmente, tanto de individuos normales, como de sujetos con acúfenos muy molestos. En esta investigación se utilizaron paradigmas de atención auditiva tanto pasivos como selectivos. Los sujetos de estudio fueron un total de 63 adultos (31 controles y 32 sujetos con acúfenos). La media en el puntaje del Inventario de Discapacidad por Acúfenos fue de 39 puntos en el grupo con acúfenos. Los resultados no lograron revelar diferencias de grupo en la latencia de los potenciales N1, en diferentes condiciones de escucha. Sin embargo, los pacientes con acúfenos mostraron potenciales N1 de amplitud significativamente menor que los obtenidos de los sujetos normales. Estos hallazgos son consistentes con aquellos reportados en investigaciones previas.

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A number of investigators have recorded long latency auditory evoked responses from tinnitus patients and normal subjects in an attempt to understand further the brain processes underlying tinnitus generation and perception. Although occasionally investigators have reported auditory evoked potential (AEP) or auditory evoked field (AEF) differences when data from normal and tinnitus patients were compared, often these findings could not be replicated by other investigators. A lack of concurrence in the existing studies is complicated by the disparity in experimental designs and technologies that have been used to collect the evoked potentials data.

For example, Hoke et al. (1989, 1991; Hoke, 1990), using magnetoencephalographic (MEG) recording techniques, reported that the magnetic equivalent of the cortically generated N1 potential, the M100 evoked field, was larger in amplitude, and the magnetic equivalent of P2, the M200 evoked field, was smaller or absent in tinnitus patients. The investigators reported that the M200/M100 (i.e., P2/N1) amplitude ratio could be used to meaningfully categorize tinnitus patients and normal controls. Subsequent to this report and using identical stimulating and recording methods, Attias et al. (1993) reported that components N1, P2, and P3 were lower in amplitude for tinnitus patients compared to hearing loss and age-matched controls. There were no statistically significant differences in evoked potential component latencies. Later, Attias et al. (1996) reported in a similar investigation that tinnitus patients demonstrated significantly longer latencies for N1, N2, and P3 components to “nontarget” stimuli, and for the P3 component to the “target” stimulus. They reported that only P3 was lower in amplitude for both “target” and “nontarget” stimuli.

In a previous investigation evaluating the effects of selective auditory attention on cortically generated auditory evoked potentials, Jacobson et al. (1996) reported as an incidental finding significant group differences (i.e., control versus tinnitus subjects) in N1 latencies. Specifically, tinnitus subjects manifested longer N1 latencies in the “attended” channel.

The purpose of the present investigation was to attempt to replicate that finding. Accordingly, it was our hypothesis that patients

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with bothersome tinnitus might be making a more thorough analysis of all attended auditory signals, and this was reflected in a longer N1 latency. In this regard, the present investigation represented a prospective study conducted to determine whether the latency of N1 (N100) was significantly longer for tinnitus subjects in response to stimuli presented to the "attended" ear during selective auditory attention.

METHOD

Subject Sample

Subjects were 63 adults that were recruited either from the Henry Ford Health System (normal subjects) or from the clinic population in the Department of Otolaryngology—Head and Neck Surgery in the Henry Ford Health System (tinnitus patients). These subjects were divided into normal (N = 31, 12 male, mean age 39 yrs., SD = 13 yrs.) and tinnitus (N = 32, 19 male; mean age 46 yrs., SD = 11 yrs.) groups. The subjects with tinnitus demonstrated mean scores on the Tinnitus Handicap Inventory (THI; Newman et al., 1998) of 39 points (SD = 21 points) representing moderate self-perceived tinnitus disability/handicap. Additionally, their tinnitus was perceived bilaterally and had been present for a minimum of one year. Normal subjects did not report a history of tinnitus and demonstrated normal pure-tone audiometric thresholds (i.e., 20 dB HL or better thresholds for frequencies between 250 Hz and 8000 Hz). Tinnitus subjects demonstrated normal audiometric thresholds between 250 Hz and 2000 Hz. They demonstrated various degrees of hearing loss for frequencies above 2000 Hz. Table 1 shows the mean audiometric thresholds for the left and right ears of the patients comprising the tinnitus group.

Stimulus Characteristics and Paradigm

Stimuli were 500 Hz and 1000 Hz pure tones (i.e., frequencies where auditory sensitivity was normal for both groups) presented through ER3a insert earphones at an intensity of 60 dB HL. The stimuli were gated using 15 msec rise–fall time (Blackman weighting function). The stimulus presentation rate was 3 Hz. Both selective auditory attention and passive listening paradigms were utilized in this investigation.

Subjects initially received the toneburst stimuli in a passive listening paradigm. They were asked to view a subtitled movie during data acquisition. The video display was two meters in front of the subjects during the EEG recordings. The video display served to maintain subject alertness and reduce random electrooculographic interference. Following the passive listening paradigm, subjects were given a five-minute break, and then recordings were conducted while they were engaged in the selective auditory attention paradigm.

Selective Auditory Attention Paradigm

In the selective auditory attention paradigm, a total of 250 stimuli were presented per stimulus block. One stimulus frequency (e.g., 1000 Hz) was presented to the left ear, and the other frequency (e.g., 500 Hz) was presented to the right ear. Within a stimulus block, for each ear separately, 80% of the tone bursts were 125 msec in duration, and 20% of the tone bursts were 75 msec in duration. Presentation of the tone bursts was accomplished binaurally in an interleaved fashion such that no stimulus was presented to both ears simultaneously. This stimulus paradigm (described below) was identical to that used by Jacobson et al. (1996), which was an adaptation of a paradigm described by Arthur et al. (1991).

Condition 1 (2 presentations). 500 Hz stimuli in the left ear, 1000 Hz stimuli in the right ear; Instruction: “Listen for the occasional shorter tones in your left ear and press the button when you hear them.”

Condition 2 (2 presentations). 500 Hz stimuli in the left ear, 1000 Hz stimuli in the right ear; Instruction: “Listen for the occasional shorter tones in your right ear and press the button when you hear them.”

Condition 3 (2 presentations). 1000 Hz stimuli in the left ear, 500 Hz stimuli in the right ear; Instruction: “Listen for the occasional shorter tones in your left ear and press the button when you hear them.”

Condition 4 (2 presentations). 1000 Hz stimuli in the left ear, 500 Hz stimuli in the right ear; Instruction: “Listen for the occasional shorter tones in your right ear and press the button when you hear them.”

In such a manner, both the ear attended to (i.e., left/right) and the tone-burst frequencies presented to each ear (i.e., 500 Hz/1000 Hz) were equally represented.
**Figure 1** Group grand-averaged tracings showing N1 in the "attend frequent" (top) and "attend infrequent" (bottom) conditions for the Fz electrode location. Data from the tinnitus group is represented by a dashed line. Data from the normal group is represented by a solid line. Notice that in each case N1 is of larger amplitude for the normal group.

**Figure 2** Group grand-averaged tracings showing N1 in the "ignore frequent" (top) and "ignore infrequent" (bottom) conditions for the Fz electrode. Again, data from the tinnitus group is represented by a dashed line, and data from the normal group is represented by a solid line. Notice that again, in each case, N1 is of larger amplitude for the normal group.

**Figure 3** Group grand-averaged tracings showing N1 in the "attend frequent" (top) and "attend infrequent" (bottom) conditions for the Cz electrode location. Data from the tinnitus group is represented by a dashed line. Data from the normal group is represented by a solid line. Notice that in each case N1 is of larger amplitude for the normal group.

**Figure 4** Group grand-averaged tracings showing N1 in the "ignore frequent" (top) and "ignore infrequent" (bottom) conditions for the Cz electrode. Again, data from the tinnitus group is represented by a dashed line, and data from the normal group is represented by a solid line. Notice again, in each case, N1 is of larger amplitude for the normal group.

**Figure 5** Group grand-averaged tracings showing N1 in the "attend frequent" (top) and "attend infrequent" (bottom) conditions for the Pz electrode location. Data from the tinnitus group is represented by a dashed line. Data from the normal group is represented by a solid line. Notice that in each case N1 is of larger amplitude for the normal group.

**Figure 6** Group grand-averaged tracings showing N1 in the "ignore frequent" (top) and "ignore infrequent" (bottom) conditions for the Pz electrode. Again, data from the tinnitus group is represented by a dashed line, and data from the normal group is represented by a solid line. Notice again, in each case, N1 is of larger amplitude for the normal group.
Passive Listening Paradigm

Subjects received stimuli identical to that in the selective auditory attention paradigm as shown below but were asked only to watch a subtitled movie during data acquisition.

Condition 1 (2 presentations). 500 Hz stimuli in the left ear, 1000 Hz stimuli in the right ear. Subjects observed a subtitled movie during data acquisition.

Condition 2 (2 presentations). 1000 Hz stimuli in the left ear, 500 Hz stimuli in the right ear. Subjects observed a subtitled movie during data acquisition.

Stimulus generation and presentation was accomplished with a NeuroScan STIM system (Sterling, VA).

Recording Parameters

Non-inverting inputs consisted of scalp surface electrodes that were applied to Fz, Cz, Pz, C3, C4, T3, T4 sites using clean, conventional surface electrode preparation techniques. The inverting input for these electrodes was an electrode placed at A1. Additionally, a pair of electrodes placed at the left eye at infra-orbital and outer canthus locations (to record electrocorticographic interference) served as an eighth recording channel. The ground electrode was placed at Fpz.

The electrical activity recorded at these inputs was digitized (5000 Hz) and bandpass filtered 1-100 Hz. All data was recorded as a continuous EEG record. Data epoching (350 msec total epoch consisting of 50 msec prior to signal onset and 300 msec post signal onset), artifact rejection (+/- 85 uV rejection window) signal averaging was accomplished with a NeuroScan SCAN system (Sterling, VA).

Data Reduction

Passive Listening Paradigm

For each frequency and for each ear the two evoked potential tracings were grand averaged. These four tracings (i.e., 500 Hz left, 500 Hz right, 1000 Hz left, 1000 Hz right) were grand averaged to create a single tracing representing the evoked potential in a “passive” listening condition.

Selective Auditory Attention Paradigm

Each of the eight stimulus blocks yielded four evoked potential traces, one each for “attend frequent,” “attend infrequent (target),” “ignore frequent,” and “ignore infrequent.” The waveforms were grand averaged across conditions. The latency and amplitude of N1 in both ignore and attend conditions were tabulated across subjects and groups.
RESULTS

Data Analysis

Group, grand-averaged data, recorded from Fz, Cz, and Pz sites for the normal and tinnitus groups are shown in Figures 1–6.

Overall, the maximum amplitude of N1 occurred at the Fz electrode site. Accordingly, peak latency and the baseline-to-peak amplitude of N1 were gathered from this electrode location. Data were subjected to a series of two-factor (i.e., group x listening condition) analyses of variance (ANOVA). N1 latency and amplitude served separately as dependent variables for each analysis.

N1 Latency

Neither listening condition (attend/ignore/passive) nor group (normal/tinnitus) affected statistically significant changes in N1 latency (i.e., p > 0.05). The mean data for N1 latency is shown in Table 2.

N1 Amplitude

Both listening condition (df = 2, F = 3.80, p = 0.02) and group (df = 1, F = 10.87, p = 0.001) affected significant differences in N1 amplitude. Post hoc analysis (Bonferroni) showed that, across groups, N1 amplitude in the “attend” condition was significantly larger than N1 in the “ignore” condition (p = 0.02). Additionally, N1 amplitude for tinnitus subjects was of significantly smaller amplitude across listening conditions (p = 0.001). This trend is illustrated in grand-averaged data shown in Figures 1–6 and in individual subject data shown in Figures 7–8. Table 3 shows mean N1 amplitudes across conditions for control and tinnitus groups.

DISCUSSION

Tinnitus represents the phantom perception of sound when none exists in the environment. Current theories of tinnitus generation suggest that perception of this phantom sound may occur as a function of processes that occur centrally following an injury to the auditory end organ. Recent evidence has suggested that these changes might begin at the brainstem level (e.g., Kaltenbach and McCaslin, 1996; Kaltenbach, 2000; Kaltenbach et al., 2002; Rachel et al., 2002; Zacharek et al., 2002) and that adaptive processes that occur “upstream” subcortically and cortically are partially responsible for the disabling and handicapping effects of tinnitus (Jastreboff, 1990; Jastreboff and Hazell, 1993). Despite the fact that investigators have been successful in (1) recording electrophysiological activity believed to underlay tinnitus directly from the VIIIth nerve and brainstem in animals (e.g., Salvi et al., 1978; Salvi et al., 1990; Martin et al., 1993; Kaltenbach and McCaslin, 1996; Kaltenbach, 2000; Kaltenbach et al., 2002; Rachel et al., 2002; Zacharek et al., 2002), and (2) imaging tinnitus processes in highly selected subclasses of tinnitus patients (Lockwood et al., 1998, 1999; Coad et al., 2001), they have been largely unsuccessful in recording consistently evoked potential correlates of tinnitus in humans. That is, as previously stated, although some investigators have reported success in identifying evoked potential differences in tinnitus patients (e.g., Hoke et al., 1989; Pantev et al., 1989; Kristeva et al., 1992; Attias et al., 1993; Jacobson et al., 1996; Norena et al., 1999), it was not unusual for other investigators to be unable to reproduce these findings (Jacobson et al., 1991; Colding-Jørgensen et al., 1992; Attias et al., 1996).

The disparate findings among the group of evoked potentials investigations may have occurred as a function of (1) differences in subject selection (e.g., lack of carefully screened experimental subjects [by cause of tinnitus, severity of self-perceived handicap] and carefully matched controls [matched by age, gender, hearing loss, etc.]), (2) differences in stimulating paradigms (e.g., passive listening, classical oddball paradigm, selective auditory attention paradigm), (3) differences in data acquisition and processing variables (e.g., pre/post filtering parameters, baseline setting, total samples acquired), (4) differences in peak labeling (e.g., electrode location selected for waveform measurement, baseline-to-peak measures versus peak-to-peak measures of amplitude), and (5) differences in recording modalities (e.g., electrical potentials versus magnetic field recordings).

Unfortunately, we could not replicate our findings reported previously (Jacobson et al., 1996) using an identical selective auditory attention protocol. In this regard, the findings of the present investigation did not support our research hypothesis. Subjects with tinnitus failed to demonstrate a longer N1 latency in the “attend” condition when compared to control subjects. However, across listening conditions (i.e., “attend” and “ignore”), N1 amplitude was
smaller for patients with tinnitus. These observations are consistent with those reported previously by Attias et al. (1993). This finding has been interpreted in the past as evidence for the presence of adaptive brain processes that occur for tinnitus patients. That is, the presence of continuous afferent signals (i.e., tinnitus) generated subcortically results in “upstream” adaptations in the manner by which all auditory signals are processed. In this regard, it has been suggested that the continuous afferent signal (i.e., tinnitus) may place the generator/s of the N1 potential into a relative refractory state in which they are unable to respond fully to a transient auditory stimulus (see Attias et al., 1993). This would have the effect of decreasing N1 amplitude for tinnitus subjects.

Finally, we observed that the N1 amplitude was larger in the “attend” condition across groups. This finding is not surprising. When recorded in a selective auditory attention paradigm, the N1 potential is superimposed on a low-frequency negative-going waveform called the processing negativity (PN). Accordingly, the admixture of the PN and the N1 resulted in N1 potential that was biased in the negative direction in the “attend” condition (Jacobson et al., 1996). This resulted in an enhanced N1 amplitude in the “attend” condition. This has been described previously as the “N1 effect” (see Jacobson et al., 1997).

It may be that evoked potential indices of tinnitus will remain elusive. Reasons for this would include the knowledge that tinnitus, for most, represents a low-level continuous auditory percept (i.e., tinnitus loudness matches at the tinnitus pitch match seldom exceed 15 dB SL; Meikle et al., 1984). Accordingly, the electrophysiological effect size, if it exists at all in evoked potentials recorded at the scalp surface, may be too small to be resolved with signal averaging.

It may well be that other technologies will assist us in the “objectification” of tinnitus perception. Recent evidence published by Lockwood and colleagues (Lockwood et al., 1998, 1999; Coad et al., 2001) has suggested that functional MRI techniques may be used to image the perception of tinnitus. The investigators have identified a unique subgroup of tinnitus patients who are able to modulate their tinnitus through oral facial movements. Unlike externally presented tones that expectedly provided bilateral cortical activation, these patients showed only unilateral (i.e., contralateral) auditory and limbic system activation. The authors interpreted these findings as evidence that tinnitus, at least in this subgroup of patients, was generated centrally. It is noteworthy that the work of Lockwood and colleagues recently has been independently replicated by Cacace et al. (1999).

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REFERENCES


