 doi:10.20944/preprints202207.0098.v1

Article

Analysis of Confirmatory Auditory Responses in Unilateral Tinnitus Patients with Normal Hearing

Yong Jun Jeong[1,2,†], Kyoung Ho Oh[1,†], Sung Jin Lim[1], Dong Heun Park[1], Yoon Chan Rah[1] and June Choi[1,*]

[1] Department of Otorhinolaryngology - Head and Neck Surgery, Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea; yongjunj67@gmail.com (Y.J.J.); anamjigu@gmail.com (K.H.O.); dlatjdwls525@naver.com (S.J.L.); samho502@naver.com (D.H.P.); ycrah@naver.com (Y.C.R.); mednlaw@korea.ac.kr (J.C.)

[2] Republic of Korea Air Force, Gangneung, Republic of Korea

* Correspondence: mednlaw@korea.ac.kr

† These authors contributed equally to this work as first authors.

Abstract: In patients with unilateral tinnitus with normal hearing, several studies have compared the ipsilateral and contralateral ears; however, few studies have investigated its relationship with the duration of tinnitus. We compared the auditory brainstem response and otoacoustic emission parameters between ipsilateral and contralateral ears in adults with unilateral tinnitus and normal hearing. This retrospective review included 84 patients with unilateral tinnitus and normal hearing who underwent auditory brainstem response and otoacoustic emission; they were categorized according to the duration of tinnitus. The latencies and amplitudes of waves I, III, and V, and V/I ratio of both ears in auditory brainstem response, and the results of distortion-product otoacoustic emission and transient evoked otoacoustic emission were examined. The auditory brainstem response parameters, distortion-product otoacoustic emission parameters, and transient evoked otoacoustic emission parameters between the ipsilateral and contralateral ears along the duration of tinnitus were analyzed. Moreover, the failure rates of both distortion-product otoacoustic emission and transient evoked otoacoustic emission between the ears along with the duration and the effects of the variables on the amplitude and latency of each wave were examined. Although there was little significant difference between the ipsilateral and contralateral ears, laterality seemed to have an effect on wave I latency in the multiple linear regression analysis. The distortion-product otoacoustic emission failure rate of the ipsilateral ear was higher than that of the contralateral ear in all patients. However, there was no remarkable difference between the ears in the distortion-product otoacoustic emission and transient evoked otoacoustic emission parameters throughout the duration. We found that outer hair cells and the distal portion of the cochlear nerve are possible pathologic lesions in tinnitus with normal hearing and cochlear synaptopathy could be suspected. Further studies, including those on inner hair cells and higher central cortex, are needed.

Keywords: tinnitus; normal hearing; Evoked potentials; auditory; brain stem; otoacoustic emission

1. Introduction

Tinnitus is defined as a sound in the head or ears that occurs in the absence of any external source and is commonly observed in otolaryngology clinics. The prevalence of tinnitus is estimated to range from 5.1% to 42.7% [1].

Although the pathophysiology of tinnitus is uncertain, it is known that abnormal activity of the peripheral auditory system due to hearing loss or deafferentation causes neuroplastic changes in the central auditory pathway [2,3]. Principally, tinnitus can be divided into two sub-types: peripheral tinnitus (cochlear tinnitus) and central tinnitus [3-6]. Peripheral tinnitus is defined as a tinnitus subtype originating from an aberrant activity generated at the peripheral level of the auditory system, that is, before (cochlea itself or cochlear synapse) or at the cochlear nerve level. The neural activity provoked by

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

peripheral tinnitus can be considered a signal activity produced by an acoustic stimulus. This signal activity initially increases in the distal portion of the cochlear nerve and then broadcasts to the auditory cortex [3]. Central tinnitus is defined as the neural activity that is generated in the auditory cortex in the absence of circumstances that cause peripheral tinnitus [3]. However, it should not be overlooked that this classification cannot accurately describe the location of all tinnitus. It is impossible to have a completely independent pathway for each tinnitus subtype; hence, an overlapping pathophysiology for both subtypes should be considered [2,7]. Therefore, many auditory responses have been used to determine the location of tinnitus, and hence, auditory brainstem response (ABR) and otoacoustic emission (OAE) are widely utilized [2-4,8-18].

ABR is a test that evaluates the response of the auditory brainstem to auditory stimuli and is useful for detecting retrocochlear lesions, such as acoustic and vestibular schwannomas [19]. The test consists of various waves, of which waves I, III, and V are the most clinically significant and are generated in the distal portion of the auditory nerve, cochlear nucleus, and nuclei in the lateral lemniscus and inferior colliculus, respectively [4,20]. The ABR of tinnitus patients with normal audiograms has been used to evaluate the origin of tinnitus. It was reported that the amplitude of wave I decreased significantly; however, the amplitude of wave V was recovered to normal levels in tinnitus patients with normal hearing to compensate for the wave I response [2,13,14].

The OAE is a propagation of the auditory signal into the external auditory canal from the cochlea, passing through the ossicular chain and tympanum. OAE is associated with the function of outer hair cells, and the presence of an OAE response is a reliable indicator of cochlear function [16-18]. Therefore, it can be a potential indicator of peripheral auditory responses in patients with tinnitus.

We hypothesized that the confirmatory auditory responses, such as ABR and OAE, can differ between tinnitus ears (ipsilateral ear) and non-tinnitus ears (contralateral ear) in patients with unilateral tinnitus with normal hearing, and that these differences can vary depending on the duration of tinnitus and the strength of the ABR stimulus. The aim of the present study was to analyze the confirmatory auditory responses in patients with unilateral tinnitus with normal hearing.

2. Materials and Methods

2.1. Study Population

A retrospective chart review was conducted using medical records from a single tertiary hospital from January 1, 2016, to December 31, 2018. A total of 450 patients who underwent ABR for tinnitus evaluation in a tertiary care hospital were selected. Patients with bilateral tinnitus, indistinct directions of tinnitus, hearing impairment, and imperfect ABR data were excluded. Patients were categorized according to duration. Patients with tinnitus for <1 month were assigned to the acute group, those with tinnitus for 1−6 months to the subacute group, and those with tinnitus for more than 6 months to the chronic group (Table 1).

Table 1. Demographic data of patients (N=84).

Variables	Results
Sex, No. (%)	
Male	26 (31)
Female	58 (69)
Direction, No. (%)	
Left	37 (44)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

Right	47 (56)
Duration, No. (%)	
Not answered	4 (5)
Acute (<1 month)	17 (20)
Subacute (1−6 months)	45 (54)
Chronic (>6 months)	18 (21)
Age, mean (SD), year	43.5 (11.2)
PTA, mean (SD), dB	
Ipsilateral	10.94 (5.95)
Contralateral	10.01 (6.25)
Duration, median (IQR), days	
Total	63 (34–148)
Acute	19 (12–24)
Subacute	63 (43–85)
Chronic	381 (318–775)

No, number; SD, standard deviation; dB, decibel; IQR, interquartile range; PTA, pure tone audiometry, (500 Hz + 2 × 1000 Hz + 2000 Hz)/4

2.2. Confirmatory Auditory Responses

Hearing impairment was defined as a threshold with air conduction of more than 25 dB at 0.25, 0.5, 1, 2, 3, 4, and 8 kHz in pure tone audiometry. ABR was estimated using Navigator Pro (2 channels, Bio-logic earphones, Natus Inc. USA) by a certified audiologist at our hospital. Two electrodes were attached to the midline of the frontal bone and vertex after the scalp skin of the patients was cleaned. The amplitudes of waves I, III, and V and the latencies of waves I, III, and V were collected at 90 dB, 80 dB, and 70 dB normalized hearing level (nHL). All amplitudes were regarded as the difference between the peak and trough values (Figure 1). The ratio of the amplitude of waves I to V (V/I ratio) was calculated.

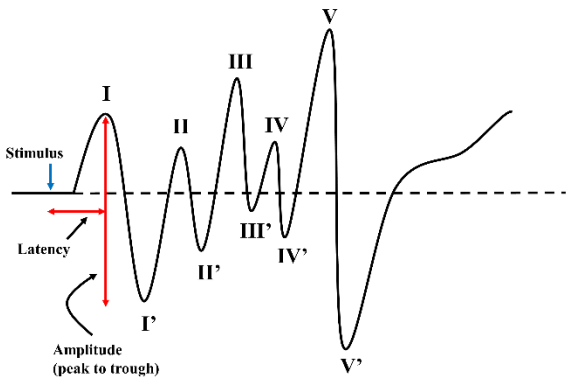


Figure 1. Measurement of ABR parameters. Latency was measured as the difference between the stimulation time and peak time, and the amplitude was measured as differences between peak to trough.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

Distortion-product otoacoustic emissions (DPOAEs) and transient evoked otoacoustic emissions (TEOAEs) were estimated using GSI audera (Grason-Stadler Inc. 10395 West 70th St. Eden Prairie, MN 55344, USA). DPOAE responses to pairs of primary tones were measured (f1 and f2; f2/f1 = 1.22). 2f1–f2 components and were analyzed for 10 f1 frequencies (410.2 Hz, 574.2 Hz, 820.3 Hz, 1160.2 Hz, 1640.6 Hz, 2753.9 Hz, 3996.1 Hz, 5660.2 Hz, 6726.6 Hz, and 8003.9 Hz). "Pass" in both OAE test was defined if the signal was -5 dB or more and signal to noise ratio (SNR) was 5 dB or more at 1 F1 frequency below 1 kHz, 2 F1 frequencies between 1 kHz and 2 kHz, and 2 F1 frequencies between 2 kHz and 4 kHz. Otherwise, the OAE test was defined as "Failure".

2.3. Statistical Analysis

ABR data between the ipsilateral and contralateral ears were compared using a paired t-test or Wilcoxon's signed-rank test. To investigate the effects of variables (age, sex, laterality, duration, and intensity) on the amplitude and latency of each wave, multiple linear regression was conducted. The enter method was used to examine the effects of all the variables. OAE data between the ipsilateral and contralateral ears were compared using paired t-test or Wilcoxon's signed rank test for the signal and chi-square test or Fisher's exact test for the failure rate. All statistical analyses were conducted using the IBM SPSS version 21.

2.4. Ethical approval

This study was approved by the ethics committee of our hospital (IRB No. 2018AS0211), and the requirement for informed consent was waived by the ethics committee of our hospital because of a retrospective study. All methods were performed in accordance with the relevant guidelines and regulations.

3. Results

3.1. Demographic Data of Patients

Out of the total of 84 patients who underwent ABR and had unilateral tinnitus with normal hearing, 65 underwent DPOAE, and 43 underwent TEOAE. In our clinical process, all patients who underwent OAE underwent ABR prior to the procedure. In the analysis of ABR parameters, four patients with extreme ABR parameter values were excluded. There were more female (69%) than male patients. The location of tinnitus was more frequent (56%) on the right side. The number of patients in the subacute group was greater than that in the acute and chronic groups. The median duration of tinnitus in all patients was 63 days (range, 34–148 days). The data are listed in Table 1.

3.2. Comparison of ABR Data between Ipsilateral and Contralateral Ears in Unilateral Tinnitus Patients

Although the amplitudes of ABR in the ipsilateral and contralateral ears were not significantly different according to three intensities (90, 80, and 70 dB nHL) in all patients and the three subgroups, the amplitude of wave I in the acute group with 90 nHL stimuli and that of wave V in the chronic group with 80 nHL stimuli were markedly reduced. However, there were no differences in the V/I ratios. The latencies in the ipsilateral ear showed noticeable delays in wave I in all patients with 90 and 70 nHL stimuli, wave I in the subacute and chronic groups with 90 nHL stimuli, and wave III in the acute group with 70 nHL stimuli (Table 2, Figure 2 and Supplementary Table S1-S3 online).

Table 2. Comparison of ABR data between the ipsilateral and contralateral ears in all patients (N=84).

	Ipsilateral	**Contralateral**	***P*-value**
Latency, mean (SD), ms			

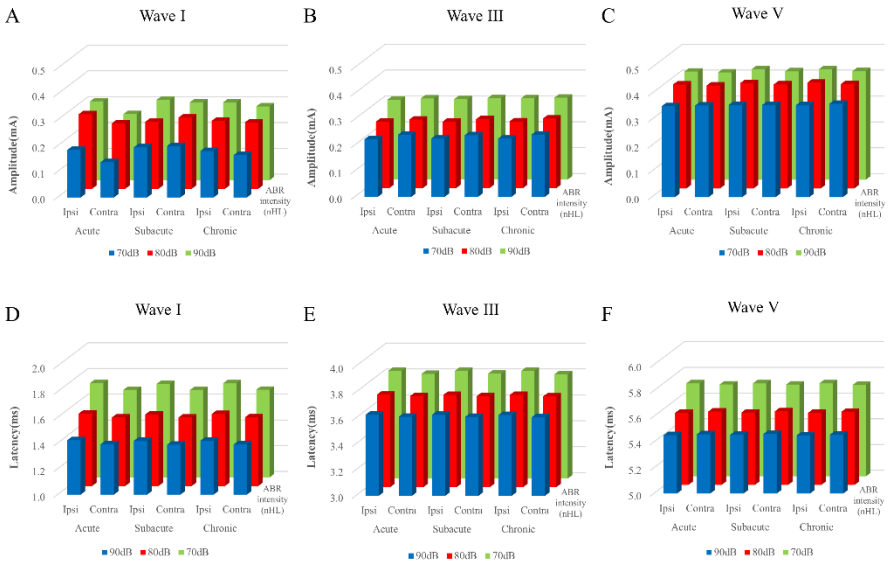
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

90 dB			
Wave I	1.42 (0.13)	1.39 (0.10)	0.02*
Wave III	3.63 (0.15)	3.61 (0.14)	0.14
Wave V	5.46 (0.22)	5.47 (0.23)	0.60
80 dB			
Wave I	1.56 (0.15)	1.53 (0.13)	0.19
Wave III	3.72 (0.17)	3.71 (0.16)	0.66
Wave V	5.57 (0.22)	5.58 (0.22)	0.57
70 dB			
Wave I	1.73 (0.16)	1.68 (0.14)	0.03*
Wave III	3.83 (0.18)	3.81 (0.17)	0.63
Wave V	5.72 (0.24)	5.72 (0.22)	0.71
Amplitude, mean (SD), mA			
90 dB			
Wave I	0.30 (0.12)	0.28 (0.13)	0.16
Wave III	0.31 (0.12)	0.31 (0.14)	0.77
Wave V	0.42 (0.14)	0.42 (0.13)	0.54
80 dB			
Wave I	0.26 (0.13)	0.26 (0.13)	0.64
Wave III	0.26 (0.11)	0.26 (0.12)	0.50
Wave V	0.40 (0.15)	0.40 (0.12)	0.70
70 dB			
Wave I	0.18 (0.12)	0.16 (0.13)	0.13
Wave III	0.22 (0.10)	0.24 (0.13)	0.33
Wave V	0.35 (0.13)	0.35 (0.12)	0.96
V/I ratio, mean (SD)			
90 dB	1.79 (1.33)	1.89 (1.51)	0.45
80 dB	1.77 (0.99)	2.06 (1.65)	0.22
70 dB	2.27 (1.89)	2.38 (2.81)	0.68

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

P-values were acquired using a paired t-test. *: *P*-value was <0 .05.

Figure 2. Amplitude and latency of ABR waves I, III, and V along the tinnitus duration and intensity



of ABR stimuli (N=84). (A) wave I amplitude; (B) wave III amplitude; (**C**) wave V amplitude; (**D**) wave I latency; (E) wave III latency; (F) wave V latency.

3.3. Multiple Linear Regression Analysis of ABR Parameters Based on Demographic Data.

This study has five independent variables (age, sex, laterality, duration, and intensity) and two dependent variables (amplitude and latency). Multiple linear regression analysis was conducted on the dependent variables for each wave. Compared to female patients, male patients had smaller amplitudes and longer latencies; however, these differences were small. The amplitude of the ABR decreased, and the latency of AR increased with increasing age (Table 3, 4 and Supplementary Tables S4-S7 online).

Table 3. Multiple linear regression of wave I amplitude presented with coefficients and p-values.

Model		**Unstandardized coefficient**		**Standardized coefficient**	**t**	***P*-value**
		B	**SE**	β		
(Constant)		0.37	0.02	-	15.64	<0.01*
Age		-0.004	0.001	-0.30	-7.05	<0.01*
Sex	M=0, F=1	0.09	0.01	0.30	7.40	<0.01*
Laterality	Ipsilateral =0, Contralateral=1	-0.01	0.01	-0.04	-1.06	0.29
Duration	Acute	-	-	-	-	-
	Subacute	0.04	0.01	0.14	2.81	0.01*
	Chronic	0.02	0.02	0.05	0.940	0.35
Intensity	90 dB	-	-	-	-	-
	80 dB	-0.03	0.01	-0.11	-2.47	0.01*
	70 dB	-0.12	0.01	-0.41	-9.02	<0.01*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

SE: standard error, *: P-value was < 0.05 and Enter method was used, Adjusted-R^2: 0.265

Table 4. Multiple linear regression of wave I latency presented with coefficients and p-values.

Model		Unstandardized coefficient		Standardized coefficient		
		B	SE	β	t	*P*-value
(Constant)		1.34	0.03		47.63	<0.01*
Age		0.00	0.00	0.13	3.36	<0.01*
Sex	M=0, F=1	-0.03	0.01	-0.07	-1.88	0.06
Laterality	Ipsilateral=0, Contralateral=1	-0.04	0.01	-0.10	-2.81	<0.01*
Duration	Acute	-	-	-	-	-
	Subacute	0.00	0.02	0.01	0.20	0.85
	Chronic	0.02	0.02	0.05	1.06	0.29
Intensity	90 dB	-	-	-	-	-
	80 dB	0.14	0.02	0.37	9.30	<0.01*
	70 dB	0.30	0.02	0.76	19.18	<0.01*

SE: standard error, *: P-value was < 0.05 and Enter method was used, Adjusted-R^2: 0.461.

In the subacute group, the amplitude of wave I tended to be larger than that in the acute group, but this trend was not observed in the chronic group (Table 3). Similarly, a trend was observed in the chronic group where the amplitude of wave V was larger than that in the acute group; however, this trend was not observed in the subacute group (Supplementary Table S5 online). Laterality seemed to have no effect on ABR parameters, except for the latency of wave I. The latency of the ipsilateral ear was longer than that of the contralateral ear in wave I (Table 4).

3.4. Otoacoustic Emission between The Ipsilateral Ear and The Contralateral Ear

The failure rate in the ipsilateral ear was significantly greater than that in the contralateral ear in all patients, but not in the TEOAE and in the three subgroups. Signals at all frequencies in DPOAE were not significantly different in all patients and in the three subgroups (Table 5, Figure 3 and Supplementary Tables S8-S10 online).

Table 5. Comparison of OAE data between ipsilateral and contralateral ears in all patients (TEOAE N=45 and DPOAE N=63).

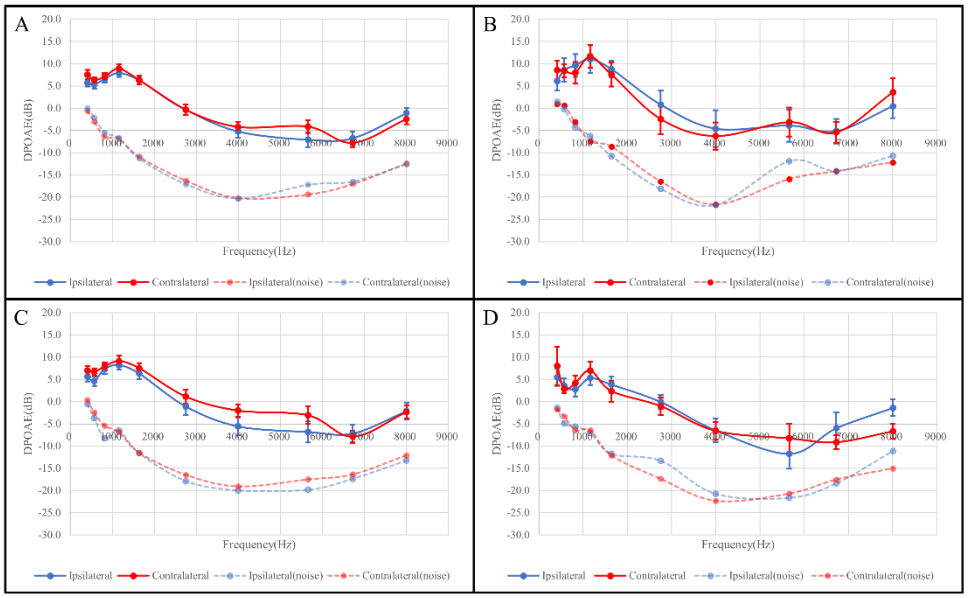
	Ipsilateral	Contralateral	*P*-value
TEOAE			
Failure, No. (%)	9 (20)	4 (9)	>0.99
Response, mean (SD), dB	7.6 (11.9)	6.7 (5.6)	0.74
DPOAE			
Failure, No. (%)	25 (40)	18 (29)	<0.05*
Signal in 410.2 Hz‡, mean (SD), dB	5.6 (5.4)	7.0 (4.9)	0.52
Signal in 574.2 Hz‡, mean (SD), dB	4.6 (5.9)	6.7 (4.7)	0.74

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 July 2022 doi:10.20944/preprints202207.0098.v1

Signal in 820.3 Hz‡, mean (SD), dB	7.3 (6.4)	7.9 (5.1)	0.84
Signal in 1160.2 Hz‡, mean (SD), dB	8.2 (5.9)	9.1 (7.4)	0.44
Signal in 1640.6 Hz‡, mean (SD), dB	6.3 (7.9)	7.5 (6.6)	0.55
Signal in 2753.9 Hz‡, mean (SD), dB	-1.1 (10.4)	1.1 (9.0)	0.26
Signal in 3996.1 Hz‡, mean (SD), dB	-5.6 (11.0)	-2.0 (8.2)	0.07
Signal in 5660.2 Hz‡, mean (SD), dB	-6.8 (11.4)	-3.0 (10.4)	0.13
Signal in 6726.6 Hz‡, mean (SD), dB	-7.2 (9.0)	-7.9 (7.1)	0.50
Signal in 8003.9 Hz‡, mean (SD), dB	-2.2 (8.1)	-2.3 (7.4)	0.91

TEOAE, transient-evoked otoacoustic emission; DPOAE, distortion-product otoacoustic emission. P-values were acquired by paired t-test, except for the failure rate (chi-square test) and signal at 410.0 Hz, and 574.2 Hz (Wilcoxon's signed rank test), *: *P*-value was < 0.05, ‡ : F1 frequency.

Figure 3. Distortion-product otoacoustic emission (DPOAE) between ipsilateral ear and contralateral ears (N=63). No significant differences were observed in each frequency. All data were conducted paired t-test or Wilcoxon's signed rank test. (**a**) total, (**b**) acute group, (**c**) subacute group, (**d**) chronic group. Blue: ipsilateral ear, Red: contralateral ear, *: *P*-value < 0.05.



4. Discussion

The causes and mechanisms of tinnitus have not yet been accurately established. It may originate either peripherally or centrally. ABR and OAE can be used to evaluate the function of retrocochlear lesions and outer hair cells, respectively; therefore, they can be candidates for determining the cause of tinnitus [2-4,12].

Several studies have reported that there was a decrease in the amplitude of wave I in the presence of cochlear lesions, when ABR wave analysis was performed on female patients with tinnitus and controls, with normal hearing over 6 months, and the amplitude of wave V was not markedly different [10,21]. This was interpreted as central compensation for the cochlear lesion by the reduction of afferent signals. Therefore, although considering normal hearing in pure tone audiometry, it was suggested that tinnitus is due to "hidden hearing loss" [14]. Many studies have been conducted on this topic; however, few studies in humans have reported significant differences in ABR waves between tinnitus patients and normal subjects. Some studies showed no statistically significant decrease in wave I amplitude when comparing patients with tinnitus and normal participants, and the V/I ratio was considered as a parameter for the degree of central gain was not

 doi:10.20944/preprints202207.0098.v1

remarkably different. Amplitudes of waves I and V and the V/I ratio were compared between the tinnitus and control groups with ABR stimuli (90 and 100 nHL). They reported that the level of noise exposure is related to tinnitus [22].

In the current study, the ABR stimuli ranged from 70 dB nHL to 90 dB nHL[14]. We found that the potential differences in ABR parameters between the ipsilateral and contralateral ear may be associated with lower ABR intensity, although the differences were not significant at higher ABR intensities. Furthermore, we suspected that there was a correlation between ABR intensity and tinnitus laterality in latencies and amplitudes. However, differences in almost all ABR parameters between the ipsilateral and contralateral ears were not significantly different in all patients and in the three subgroups. In multiple linear regression analysis, laterality had an effect on ABR latency, but not on amplitude in wave I. It is thought that the pathologic lesion of tinnitus patients might be placed in the distal portion of the cochlear nerve although the amplitude of wave I did not significantly decrease in patients with tinnitus.

Some researchers compared DPOAE and TEOAE between patients with tinnitus and normal adult male participants. There was no marked difference in TEOAE; however, the signal of DPOAE in the left and right ears between patients with tinnitus and controls was significantly different [17]. In the present study, there was remarkable difference in TEOAE; however, the failure rate of DPOAE was markedly higher in the ipsilateral ear than the contralateral ear.

Meanwhile, it was reported that there was no significant difference in the latency and amplitude of ABR, but there was a statistically significant difference in the V/I ratio. There was no significant difference in TEOAE; therefore, it was assumed that tinnitus was caused by retrocochlear lesions rather than outer hair cells [23].

Recently, several studies have reported that the summation potential/action potential ratio (SP/AP ratio) of electrocochleography (ECoG) reflects the function of synapses between cochlear inner hair cells and cochlear spiral ganglion neurons. The SP/AP ratio noticeably increased in children with auditory synaptopathy/auditory neuropathy than in those with sudden sensorineural hearing loss, and the SP/AP ratio in tinnitus patients with normal hearing was markedly higher than that in normal participants [24]. According to previous studies, the SP of ECoG originates in presynaptic hair cells, and AP originates in the postsynaptic cochlear nerve and is equivalent to the amplitude of wave I in the ABR [9,24]. In the current study, ABR for retrocochlear lesions and OAE for outer hair cells were considerably different between the ipsilateral and contralateral ears; however, responses for higher central lesions (e.g., auditory middle latency response) or ECoG are needed to explore differences between tinnitus and normal ears.

To the best of our knowledge, no study has compared ipsilateral and contralateral ears in tinnitus patients with normal hearing over time.

However, this study has some limitations. First, this study is a retrospective chart review, and there are no data on prescriptions for ototoxic medication or exposure to noise. Although we have defined the duration of tinnitus, this classification is arbitrary and subject to change. In addition, our ABR data did not contain data regarding the cochlear microphonic (CM) potential. Several studies have indicated that CM potential is generated by outer hair cells; therefore, it is regarded as a good indicator of outer hair cell impairment.

In conclusion, there was a significant difference in the latency of ABR wave I between ipsilateral and contralateral ears in patients with unilateral tinnitus with normal hearing, and the failure rate of the ipsilateral ear in DPOAE was significantly higher than that of the contralateral ear in all patients, although not in the acute, subacute, and chronic groups, and signals at specific frequencies were not significantly different between the ears. TEOAE was not significantly different between ipsilateral and contralateral ears. Therefore, from the outer hair cells to the distal portion of the cochlear nerve, there may be pathologic lesions in tinnitus with normal hearing, but more research is needed, including on inner hair cells, cochlear synapses, and the higher central cortex.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Comparison of ABR data between the ipsilateral ear and contralateral ear in the acute group (N=17); Table S2: Comparison of ABR data between the ipsilateral ear and contralateral ear in the subacute group (N=45); Table S3: Comparison of ABR data between the ipsilateral ear and contralateral ear in the chronic group (N=18); Table S4: Multiple linear regression of wave III amplitude presented with coefficient and p-value; Table S5: Multiple linear regression of wave V amplitude presented with coefficient and p-value; Table S6: Multiple linear regression of wave III latency presented with coefficient and p-value; Table S7: Multiple linear regression of wave V latency presented with coefficient and p-value; Table S8: Comparison of OAE data between the ipsilateral and contralateral ears in the acute group (TEOAE N=5, DPOAE N=12); Table S9: Comparison of OAE data between the ipsilateral and contralateral ears in the subacute group (TEOAE N=27, DPOAE N=32).

Author Contributions: Conceptualization, Y.J.J, K.H.O., and J.C. ; methodology, Y.J.J, K.H.O.Y.C.R., and J.C.; validation, Y.J.J, K.H.O., S.J.L.,D.H.P., and J.C. ; formal analysis, Y.J.J, K.H.O., and J.C.; investigation, Y.J.J, K.H.O., and J.C. ; writing—original draft preparation, Y.J.J, K.H.O., and J.C.; writing—review and editing, Y.J.J, K.H.O., and J.C.; visualization Y.J.J, K.H.O., S.J.L.,D.H.P., Y.C.R., and J.C.; supervision, J.C.; All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by a Korea University Grants and the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1F1A1069424) and the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (NTIS 9991006786, KMDF_PR_20200901_0113).

Institutional Review Board Statement: This study was approved by the ethics committee of our hospital (IRB No. 2018AS0211), and the requirement for informed consent was waived by the ethics committee of our hospital because of a retrospective study. All methods were performed in accordance with the relevant guidelines and regulations.

Informed Consent Statement: Due to the retrospective study design, the requirement for informed consent to participate has been waived by the local ethics committee.

Data Availability Statement: Data are available upon reasonable request to the corresponding author.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. McCormack, A.; Edmondson-Jones, M.; Somerset, S.; Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. *Hear. Res.* **2016**, *337*, 70-79, https://dx.doi.org/10.1016/j.heares.2016.05.009.
2. Haider, H.F.; Bojić, T.; Ribeiro, S.F.; Paço, J.; Hall, D.A.; Szczepek, A.J. Pathophysiology of Subjective Tinnitus: Triggers and Maintenance. *Front. Neurosci.* **2018**, *12*, 866, https://dx.doi.org/10.3389/fnins.2018.00866.
3. Noreña, A.J. Revisiting the cochlear and central mechanisms of tinnitus and therapeutic approaches. *Audiol. Neurootol.* **2015**, *20 Suppl 1*, 53-59, https://dx.doi.org/10.1159/000380749.
4. Milloy, V.; Fournier, P.; Benoit, D.; Noreña, A.; Koravand, A. Auditory Brainstem Responses in Tinnitus: A Review of Who, How, and What? *Front. Aging Neurosci.* **2017**, *9*, 237, https://dx.doi.org/10.3389/fnagi.2017.00237.
5. Noreña, A.J. An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neurosci. Biobehav. Rev.* **2011**, *35*, 1089-1109, https://dx.doi.org/10.1016/j.neubiorev.2010.11.003.
6. Henry, J.A.; Roberts, L.E.; Caspary, D.M.; Theodoroff, S.M.; Salvi, R.J. Underlying mechanisms of tinnitus: review and clinical implications. *J. Am. Acad. Audiol.* **2014**, *25*, 5-22, https://dx.doi.org/10.3766/jaaa.25.1.2.
7. Zhao, Y.; Song, Q.; Li, X.; Li, C. Neural Hyperactivity of the Central Auditory System in Response to Peripheral Damage. *Neural Plast.* **2016**, *2016*, 2162105, https://dx.doi.org/10.1155/2016/2162105.

8. Suresh, C.H.; Krishnan, A. Search for Electrophysiological Indices of Hidden Hearing Loss in Humans: Click Auditory Brainstem Response Across Sound Levels and in Background Noise. *Ear Hear.* **2021**, *42*, 53-67, https://dx.doi.org/10.1097/aud.0000000000000905.
9. Kara, E.; Aydın, K.; Akbulut, A.A.; Karakol, S.N.; Durmaz, S.; Yener, H.M.; Gözen, E.D.; Kara, H. Assessment of Hidden Hearing Loss in Normal Hearing Individuals with and Without Tinnitus. *J. Int. Adv. Otol.* **2020**, *16*, 87-92, https://dx.doi.org/10.5152/iao.2020.7062.
10. Joo, J.W.; Jeong, Y.J.; Han, M.S.; Chang, Y.S.; Rah, Y.C.; Choi, J. Analysis of Auditory Brainstem Response Change, according to Tinnitus Duration, in Patients with Tinnitus with Normal Hearing. *J. Int. Adv. Otol.* **2020**, *16*, 190-196, https://dx.doi.org/10.5152/iao.2020.7951.
11. Aedo, C.; Aguilar, E. Cochlear synaptopathy: new findings in animal and human research. *Rev. Neurosci.* **2020**, *31*, 605-615, https://dx.doi.org/10.1515/revneuro-2020-0002.
12. Makar, S.K.; Mukundan, G.; Gore, G. Auditory System Synchronization and Cochlear Function in Patients with Normal Hearing With Tinnitus: Comparison of Multiple Feature with Longer Duration and Single Feature with Shorter Duration Tinnitus. *Int. Tinnitus J.* **2017**, *21*, 133-138, https://dx.doi.org/10.5935/0946-5448.20170025.
13. Gu, J.W.; Herrmann, B.S.; Levine, R.A.; Melcher, J.R. Brainstem auditory evoked potentials suggest a role for the ventral cochlear nucleus in tinnitus. *J. Assoc. Res. Otolaryngol.* **2012**, *13*, 819-833, https://dx.doi.org/10.1007/s10162-012-0344-1.
14. Schaette, R.; McAlpine, D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *J. Neurosci.* **2011**, *31*, 13452-13457, https://dx.doi.org/10.1523/jneurosci.2156-11.2011.
15. Kehrle, H.M.; Granjeiro, R.C.; Sampaio, A.L.; Bezerra, R.; Almeida, V.F.; Oliveira, C.A. Comparison of auditory brainstem response results in normal-hearing patients with and without tinnitus. *Arch. Otolaryngol. Head Neck Surg.* **2008**, *134*, 647-651, https://dx.doi.org/10.1001/archotol.134.6.647.
16. Ami, M.; Abdullah, A.; Awang, M.A.; Liyab, B.; Saim, L. Relation of distortion product otoacoustic emission with tinnitus. *Laryngoscope* **2008**, *118*, 712-717, https://dx.doi.org/10.1097/MLG.0b013e318161e521.
17. Mokrian, H.; Shaibanizadeh, A.; Farahani, S.; Jalaie, S.; Mahdi, P.; Amali, A.; Arian Nahad, H. Evaluation of distortion and transient evoked otoacoustic emission in tinnitus patients with normal hearing. *Iran. J. Otorhinolaryngol.* **2014**, *26*, 19-24.
18. Granjeiro, R.C.; Kehrle, H.M.; Bezerra, R.L.; Almeida, V.F.; Sampaio, A.L.; Oliveira, C.A. Transient and distortion product evoked oto-acoustic emissions in normal hearing patients with and without tinnitus. *Otolaryngol. Head Neck Surg.* **2008**, *138*, 502-506, https://dx.doi.org/10.1016/j.otohns.2007.11.012.
19. Kotlarz, J.P.; Eby, T.L.; Borton, T.E. Analysis of the efficiency of retrocochlear screening. *Laryngoscope* **1992**, *102*, 1108-1112, https://dx.doi.org/10.1288/00005537-199210000-00004.
20. Rupa, V.; Job, A.; George, M.; Rajshekhar, V. Cost-effective initial screening for vestibular schwannoma: auditory brainstem response or magnetic resonance imaging? *Otolaryngol. Head Neck Surg.* **2003**, *128*, 823-828, https://dx.doi.org/10.1016/s0194-5998(03)00358-9.
21. Shim, H.J.; An, Y.H.; Kim, D.H.; Yoon, J.E.; Yoon, J.H. Comparisons of auditory brainstem response and sound level tolerance in tinnitus ears and non-tinnitus ears in unilateral tinnitus patients with normal audiograms. *PLoS One* **2017**, *12*, e0189157, https://dx.doi.org/10.1371/journal.pone.0189157.
22. Guest, H.; Munro, K.J.; Prendergast, G.; Howe, S.; Plack, C.J. Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy. *Hear. Res.* **2017**, *344*, 265-274, https://dx.doi.org/10.1016/j.heares.2016.12.002.
23. Nemati, S.; Faghih Habibi, A.; Panahi, R.; Pastadast, M. Cochlear and brainstem audiologic findings in normal hearing tinnitus subjects in comparison with non-tinnitus control group. *Acta Med. Iran.* **2014**, *52*, 822-826.
24. Stuermer, K.J.; Beutner, D.; Foerst, A.; Hahn, M.; Lang-Roth, R.; Walger, M. Electrocochleography in children with auditory synaptopathy/neuropathy: diagnostic findings and characteristic parameters. *Int. J. Pediatr. Otorhinolaryngol.* **2015**, *79*, 139-145, https://dx.doi.org/10.1016/j.ijporl.2014.11.025.

 doi:10.20944/preprints202207.0098.v1