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RESEARCH PAPER

Effect of Stimulus Rate and Gender on Auditory Middle Latency Response in Young Adults

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Purpose: The main objective of this study was to investigate the effect of stimulus rate and gender on the latency and amplitude of the auditory middle latency response (AMLR) in Korean young females and males. **Methods:** A total of thirty young subjects consisting of fifteen males and fifteen females participated in the study. The stimulus repetition rate was changed in five steps: 0.5, 1, 2, 4, and 8/s. **Results:** The results showed significant differences of the stimulus rates on the Na latency, Pa amplitude, and Nb amplitude. With faster stimulus rates, the Na latency and the Nb amplitude slightly increased while the Pa amplitude decreased. The Na, Pa, and Nb latencies were longest with the stimulus rate of 2/s. The Na and Nb amplitudes were largest with the stimulus rate of 4/s while the Pb amplitude was largest with the stimulus rate of 1/s. There were significant differences in the latency of Na and the amplitudes of Na, Pa, Nb, and Pb according to gender. The latencies of Na, Pa, Nb, and Pb in females were longer than in males while the amplitudes of Na, Pa, Nb, and Pb in males are larger than in females. **Conclusion:** The ranges of optimal stimulus rate to elicit the apparent AMLR waveform were 1–8/s. This provides clinical basic data of stimulus rate and gender-specific norms on the latency and amplitude of the AMLR waveform.

Key Words: Stimulus rate, Gender, Auditory middle latency response, Na · Pa · Nb · Pb.

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INTRODUCTION

After the auditory middle latency response (AMLR) had been introduced as an electrical response occurring between 10 and 100 ms after the introduction of an acoustical signal at a moderate intensity level, AMLR has been used a neurodiagnosis tool of cortical auditory function in children and adults with normal and abnormal hearing (Hall, 2007). In AMLR waveforms, there are four major components consisting of two negative voltage waves (Na and Nb) and two positive voltage waves (Pa and Pb). The first negative peak (Na) occurs within 10 msec while the prominent positive peak (Pa) normally shows a latency of about 22–30 msec. The second negative peak (Nb) occurs in 30–40 msec while the next positive peak (Pb) is present in 45–50 msec (Hall, 2007). These waves of the AMLR correspond to the specific locations of the auditory cortex. The Na component of the AMLR arises from the inferior colliculus within the midbrain region in animals and the primary auditory cortex (Heschl's gyrus) within the temporal lobe in humans (Liegeois-Chauvel et al., 1994; McGee et al., 1991). The Pa component is generated from the subcortical and cortical regions of the auditory system while the Pb component has multiple origins such as the reticular activating formation and the auditory cortex, particularly the posterior region of the planum temporale (Liegeois-Chauvel et al., 1994; McGee & Kraus, 1996; Polyakov & Pratt, 1994).

Recently, there was some evidence for improvement of the latency and amplitude of AMLR waveforms after cochlear implantation. The AMLR has been used as a measure of the effectiveness of cochlear implantation in restoring speech perception abilities in postlingually deaf adults. The relationship between auditory evoked potentials including AMLR, mismatch negativity, and auditory late response and word/sentence speech perception after cochlear implantation was investigated in postlingually deaf adults (Purdy & Kelly, 2016). There were no consistent changes over time in AMLR and consistent changes of N1 amplitude and P2 area in auditory late response. We need to confirm the optimal stimulus parameters to reveal the closer association between auditory evoked potentials and speech perception after cochlear implantation in postlingually deaf adults.

As shown in the auditory brainstem response (ABR), the latency and amplitude of the AMLR can be affected by multiple stimulus parameters such as rate, type, duration, intensity, and polarity (Choi et al., 2015). Among these factors, the optimal stimulus rate for AMLR is clinically important because it produces quality response with minimal test time. A reliable and robust AMLR is consistently produced at the stimulus rates of 8/s to 11/s. These stimulus rates are slower than those of ABR due to its relatively longer latency. However, the Pa component of the AMLR in infants and the Pb component of the AMLR in patients of all ages are generated by the stimulus rates of 1/s or 0.5/s (Jerger et al., 1987). Another research with four different stimulus rates (1.1, 4.1, 7.7, and 11.3/s) in normal young adults showed that the latency Pa increased and amplitudes of Pa and Pb decreased when the stimulus rates were increased from 1.1/s to 11.3/s (Tucker et al., 2002). It is valuable to note that there is no agreement of the optimal stimulus rates which are very sensitive for the AMLR waves in children and adults although the stimulus rates less than 11/s is slow enough to produce the AMLR.

The AMLR can be affected by subject parameters such as gender, age, body temperature, state of arousal, and drugs as shown in ABR (Choi et al., 2015). Among these factors, gender is one of the most important factors affecting the latency and amplitude of the AMLR (Amenedo & Díaz, 1998). Many previous studies have reported an apparent and consistent trend toward longer latencies and smaller amplitudes for males in comparison to females (Stewart et al., 1993). However, there is no agreement of a concrete gender effect on each AMLR wave (Na, Pa, Nb, and Pb). In more detail, the latency of the Na component is longer for males than females while the latencies of other components and amplitudes of all AMLR components for male adults were equal to female adults (Amenedo & Díaz, 1998). The Pb component for elderly patients with Alzheimer's disease was twice as large for females as for males (Phillips et al., 1997). In this study, the average amplitude of the Pa component was 0.83 μV for males and 1.35 μV for females while that of the Pb component was -0.21 μV for males and +0.21 μV for females. Absolute amplitude of the Pb component was equivalent for adult males and females aging from 19 to 78 years old (Rasco et al., 2000). In young male and female adults, there was a significant gender effect on the Pa component and not a significant effect on the Pb component (Tucker et al., 2002). In more detail, Pa latencies for males were longer than in females and Pa amplitudes for females were larger than in males.

We have sought the optimal stimulus rate leading to the robust latency and maximal amplitude of auditory evoked response, particularly ABR waves as well as gender effect (Choi et al., 2015). We expanded our goal to the AMLR waves. Therefore, this study investigated whether the latencies and amplitudes of the AMLR waves are affected by the different stimulus rates and genders in young adults. We attempted to seek the most optimal and stable stimulus rates leading the robust latencies and amplitudes of the AMLR. For this goal, we measured the latencies and amplitudes of the AMLR waves (Na, Pa, Nb, and Pb) with five different stimulus rates (0.5, 1, 2, 4, 8/s) in 30 young male and female subjects.

MATERIALS AND METHODS

Subjects

The experimental procedures and methods were reviewed and approved by the Bioethic Committee of the Catholic University of Daegu. The experimental processes and procedures are similar to another research previously described with ABR except the use of AMLR (Choi et al., 2015).

Total thirty young adults composed of fifteen males (mean = 25, SD = ± 3.7) and fifteen females (mean = 21, SD = ± 1.4) participated in the study. Hearing thresholds of all participants were within normal hearing range (less than 20 dB HL) at frequencies of 250 to 8,000 Hz. The history of all subjects is free of head injury, ear surgery, and audiological or neurological disorders.

Stimuli and ABR recording

AMLRs were recorded by a GSI Audera system (Grason-Stadler, Eden Prairie, MN, USA). For the AMLR recording, all participants were seated and relaxed in a soft armchair of a sound booth electrically shielded room during the AMLR testing. Before the electrode placement, the skin was cleaned by alcohol pads and the connection between the electrode and skin was enhanced by a conducting gel (NuPrep). For the AMLR recording, active electrodes (+) indicating the non-inverting electrode were placed on the middle of the forehead (Fz) or vertex (Cz) whereas the reference electrodes (-) meaning the inverting electrode were placed on the ipsilateral (A1 or A2) and the ground electrode was placed on the low forehead (Fpz). The electrodes were secured with tape. Interelectrode impedances were never exceeded 5 kΩ. Electrical responses were elicited by alternating clicks with 0.1 ms durations. The level of stimuli presentation was 75 dB normal Hearing Level (nHL) and the stimulus rates were 0.5, 1, 2, 4, and 8/s. The electrical responses were amplified with 100,000 times and the band-pass filter of 10 to 250 Hz was used with the sample rate of 400 sweeps, the analysis time of 100 ms, and the test duration of 200 s.

Data analysis

The latencies and amplitudes of Na, Pa, Nb, and Pb in AMLR were visually identified and obtained from each subject at 5 different stimulus rate conditions (0.5, 1, 2, 4, and 8/s). The latency and amplitude data were compared and analyzed in five different stimulus rate conditions and two different gender groups (male and female). Three independent observers for high reliability confirmed the latencies and amplitudes of all AMLR data. All graphic presentations in the study were made in SigmaPlot (version 9; Systat Software, San Jose, CA, USA) and shown in a mean ± S.E.M.

Statistical analysis

Statistical differences in the latencies and amplitudes of Na, Pa, Nb, and Pb among the different experimental groups were also compared using one-way ANOVA (IBM SPSS 19.0; IBM corp., Armonk, NY, USA). The Fisher's least squares difference *post hoc* test was then used to evaluate the statistical differences of specific pairs of values. A statistical significant difference was determined by $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

RESULTS

We evaluated statistical differences in the latencies and amplitudes of Na, Pa, Nb, and Pb in AMLR waves according to stimulus rate and gender. Table 1 shows the descriptive statistics of latencies and amplitudes of Na, Pa, Nb, and Pb as a function of stimulus rate (0.5, 1, 2, 4, and 8/s).

Figure 1 shows the latencies of Na, Pa, Nb, and Pb as a function of five different stimulus rate conditions. When the stimulus rate increased from 0.25/s to 8/s, the latencies of Na, Pa, and Nb were unchanged. However, the latency of Pb increased from 46 ms to about 56 ms although there was no significant difference. The one-way ANOVA showed that there was significant difference among the five different stimulus rates for the latencies of Na [$F(4, 295) = 3.255$, $p < 0.05$].

Further analysis for within-subjects contrasts was performed to identify significant differences among five different stimulus rates in latencies of each AMLR wave.

As shown in Table 2, the latency of Na showed significant differences at the stimulus rates of 2/s and 8/s, respectively, in comparison with the stimulus rate of 0.5/s. Furthermore, significant differences were observed in the latency of Na at the stimulus rates of 2/s and 4/s in comparison with the stimulus of

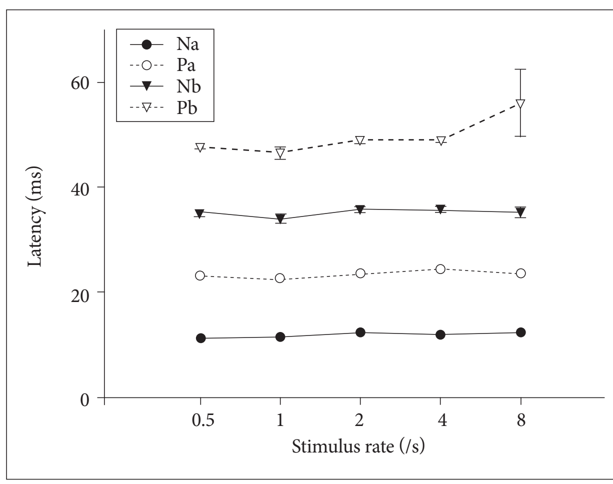

Figure 1. The latencies of Na, Pa, Nb, and Pb as a function of five different stimulus rates.

Table 1. Means and standard deviations for the latencies and amplitudes of Na, Pa, Nb, and Pb in five different stimulus rates

Component	Measurement	Rate 0.5	1	2	4	8	*p*-value
Na	Latency	11.32 ± 1.68	11.56 ± 2.90	12.38 ± 1.65	11.97 ± 1.66	12.37 ± 2.07	0.012*
	Amplitude	-0.61 ± 0.64	-0.58 ± 0.49	-0.60 ± 0.42	-0.51 ± 0.39	-0.63 ± 0.55	0.781
Pa	Latency	23.24 ± 3.03	22.74 ± 4.79	23.97 ± 3.09	24.39 ± 3.35	23.63 ± 2.75	0.090
	Amplitude	1.05 ± 0.71	0.79 ± 0.54	0.69 ± 0.51	0.78 ± 0.55	0.83 ± 0.69	0.025*
Nb	Latency	35.06 ± 6.89	34.04 ± 9.53	35.81 ± 7.24	35.56 ± 7.22	35.42 ± 10.23	0.800
	Amplitude	-0.78 ± 0.69	-0.65 ± 0.94	-0.51 ± 0.38	-0.42 ± 0.46	-0.52 ± 0.43	0.019*
Pb	Latency	47.72 ± 3.94	46.66 ± 10.02	48.87 ± 4.97	48.93 ± 4.34	56.02 ± 50.03	0.193
	Amplitude	0.48 ± 0.46	0.65 ± 0.36	0.50 ± 0.34	0.53 ± 0.40	0.50 ± 0.44	0.127

*$p < 0.05$

1/s. In the latency of Pa, significant difference was only shown between the stimulus rates of 1/s and 8/s. No significant differences in the latency of Nb were found any stimulus rates. Finally, significant differences in the latency of Pb were shown in the stimulus rates of 8/s and 1/s in comparison with the stimulus rate of 0.5/s.

Additionally, one-way ANOVA showed whether there were significant differences in the amplitudes of Na, Pa, Nb, and Pb among the five different stimulus rates as shown in Table 1. Table 1 and Figure 2 present the amplitudes of Na, Pa, Nb, and Pb according to five different stimulus rate conditions. Significant differences were observed in the amplitudes of Pa and Nb in different stimulus rates [$F(4, 295) = 2.84$, $p < 0.05$, $F(4, 295) = 3.01$, $p < 0.05$]. When the stimulus rate increased from 0.5/s to 8/s, the amplitudes of Na and Nb increased a little but the amplitudes of Pa and Pb decreased slowly. The amplitudes of Na and Nb were the largest at the stimulus rate of 4/s. The amplitudes of Pa and Pb were the largest at the stimulus rates of 0.5s and 1/s while the smallest at the stimulus rate of 2/s.

Table 2. Multiple comparisons of the latencies of Na, Pa, Nb, and Pb among five different stimulus rates

Component	Rate	*p*-value	Rate	*p*-value
Na	0.5−1	0.526	1−4	0.274
	0.5−2	0.005†	1−8	0.030*
	0.5−4	0.084	2−4	0.270
	0.5−8	0.005†	2−8	0.975
	1−2	0.028*	4−8	0.281
Pa	0.5−1	0.434	1−4	0.010†
	0.5−2	0.250	1−8	0.162
	0.5−4	0.070	2−4	0.506
	0.5−8	0.536	2−8	0.595
	1−2	0.054	4−8	0.232
Nb	0.5−1	0.505	1−4	0.319
	0.5−2	0.623	1−8	0.366
	0.5−4	0.742	2−4	0.871
	0.5−8	0.812	2−8	0.800
	1−2	0.247	4−8	0.927
Pb	0.5−1	0.802	1−4	0.591
	0.5−2	0.785	1−8	0.027*
	0.5−4	0.775	2−4	0.989
	0.5−8	0.050*	2−8	0.091
	1−2	0.601	4−8	0.093

*$p < 0.05$, †$p < 0.01$

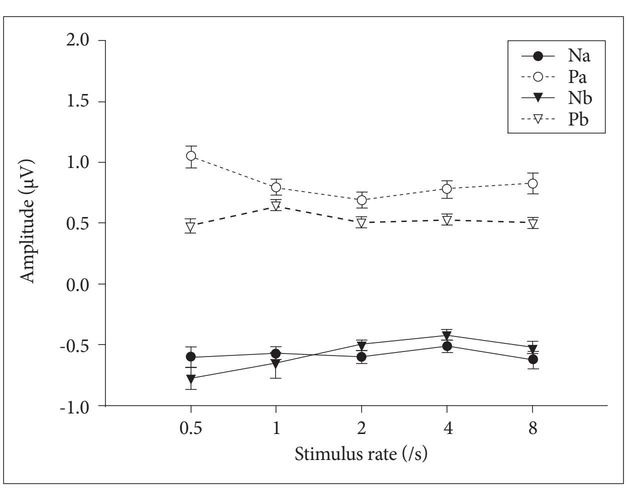

Figure 2. The amplitudes of Na, Pa, Nb, and Pb as a function of five different stimulus rate conditions.

Furthermore, multiple comparisons were performed to investigate the significant differences in the amplitudes of Na, Pa, Nb, and Pb among the five different stimulus rates as shown in Table 3.

For the amplitude of Na, no significant differences were observed among any stimulus rate of 0.5, 1, 2, 4, and 8/s. For the amplitude of Pa, significant differences were observed in the stimulus rates of 1, 2, 4 and 8/s in comparison with the stimulus rate of 0.5/s. For the amplitude of Nb, significant differences were observed in the stimulus rate of 2, 4, and 8/s in comparison with that of 0.5/s and between the stimulus rates of 1 and 4/s. For the amplitude of Pb, significant differences were observed in the stimulus rate of 0.5, 2, and 8/s in comparison with that of 1/s.

Table 3. Multiple comparisons of the amplitudes of Na, Pa, Nb, and Pb among five different levels of stimulus rates

Component	Rate	*p*-value	Rate	*p*-value
Na	0.5−1	0.770	1−4	0.489
	0.5−2	0.959	1−8	0.595
	0.5−4	0.326	2−4	0.352
	0.5−8	0.811	2−8	0.771
	1−2	0.810	4−8	0.222
Pa	0.5−1	0.023*	1−4	0.882
	0.5−2	0.002†	1−8	0.777
	0.5−4	0.016*	2−4	0.451
	0.5−8	0.046*	2−8	0.236
	1−2	0.367	4−8	0.665
Nb	0.5−1	0.275	1−4	0.044*
	0.5−2	0.018*	1−8	0.250
	0.5−4	0.002†	2−4	0.462
	0.5−8	0.025*	2−8	0.889
	1−2	0.198	4−8	0.382
Pb	0.5−1	0.017*	1−4	0.091
	0.5−2	0.694	1−8	0.037*
	0.5−4	0.478	2−4	0.751
	0.5−8	0.757	2−8	0.933
	1−2	0.045*	4−8	0.688

*$p < 0.05$, †$p < 0.01$

We also investigated the gender effect on the latencies and amplitudes of each AMLR wave. Table 4 shows the descriptive statistics of latencies and amplitudes of Na, Pa, Nb, and Pb according to gender (female and male).

Figures 3 and 4 present the latencies and amplitudes of Na, Pa, Nb, and Pb according to different gender groups. For the latencies of Pa, there were significant differences in different gender groups [$F(1, 298) = 21.74$, $p < 0.001$]. For the latencies of other AMLR waves, there were no significant differences between different gender groups. For the latencies of all AMLR waves, the female group was higher than the male groups. The difference was the largest in the latency of Pa. However, the amplitudes of all AMLR waves (Na, Pa, Nb, and Pb) were significantly higher in the male group than the female group [$F(1, 298) = 12.79$, $p < 0.001$, $F(1, 298) = 14.99$, $p < 0.001$, $F(1, 298) = 6.68$, $p < 0.05$, $F(1, 298) = 11.02$, $p < 0.01$]. The amplitudes of Na were similar to those of Nb at the same gender. The amplitude of Pa was the largest in comparison with those of other AMLR waves.

Table 4. Means and standard deviations for the latencies and amplitudes of AMLR in two gender groups

Component	Measurement	Gender		*p*-value
		Female	Male	
Na	Latency	11.95 ± 2.09	11.89 ± 2.07	0.787
	Amplitude	-0.69 ± 0.56	-0.48 ± 0.42	0.000†
Pa	Latency	24.50 ± 3.38	22.68 ± 3.40	0.000†
	Amplitude	0.69 ± 0.60	0.96 ± 0.60	0.000†
Nb	Latency	35.85 ± 10.42	34.50 ± 5.38	0.160
	Amplitude	-0.67 ± 0.74	-0.48 ± 0.47	0.010*
Pb	Latency	50.32 ± 4.39	48.96 ± 32.49	0.610
	Amplitude	0.46 ± 0.43	0.61 ± 0.36	0.001*

*$p < 0.01$, †$p < 0.001$. AMLR: auditory middle latency response

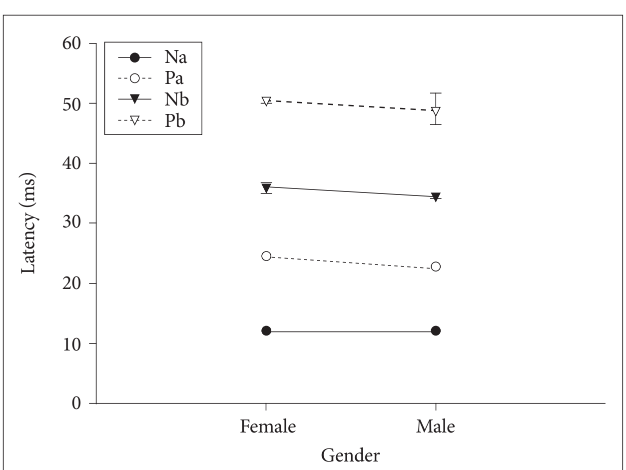

Figure 3. The latencies of Na, Pa, Nb, and Pb in different gender groups.

DISCUSSIONS

The purpose of this study was to investigate the effects of stimulus rates and gender on the latencies and amplitudes of the AMLR waves (Na, Pa, Nb, and Pb) in Korean young adults with normal hearing. The results of this study showed that there were significant differences in the Na latency and the Pa and Nb amplitudes with increasing the stimulus rate. The Na latency slightly increased with faster stimulus rates. The Pa amplitude decreased with faster stimulus rates while the Nb amplitude increased with increasing stimulus rates. This finding is inconsistent with the findings of other previous studies showed the that Pa latency significantly increased and the Pa and Pb amplitudes decreased with faster stimulus rates (Dietrich et al., 1995; McFarland et al., 1975; Nelson et al., 1997; Picton et al., 1974; Tucker et al., 2002). However, the Pb amplitudes showed a significant decrease in Alzheimer's disease (Buchwald et al., 1989), multiple sclerosis (Hendler et al., 1990), and stuttering males (Dietrich et al., 1995). The discrepancy may result from the differences in stimulus rates, subject types, and age used in each study. More research is needed to determine the effects of stimulus rates on the AMLR waveforms in different subjects.

On the other hand, this study investigated the effect of gender on the latency and amplitude of the AMLR waveforms such as Na, Pa, Nb, and Pb. The results showed that the latencies of all AMLR waveforms in females were longer than in males but the amplitudes of all AMLR waveforms in males were larger than in females. This finding is consistent with the finding of Amenedo & Díaz (1998) that the latency of Na was longer in females than males. However, the results of this study are in-

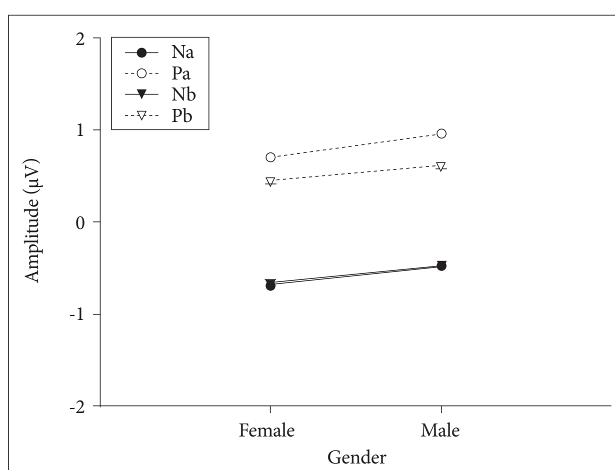

Figure 4. The amplitudes of Na, Pa, Nb, and Pb in different gender groups.

consistent with many previous studies reported that there is a clear trend toward longer latencies and smaller amplitudes of the AMLR waves in females in comparison to males (Clementz et al., 1998; Rodríguez-Holguín et al., 2001; Tucker et al., 2002). This disagreement may result from the differences in sampling size, stimulus rate, intensity levels, subject age, skull size, and height size in each research. More investigation is needed to determine the effects of gender on the latency and amplitude of the AMLR waveforms in different subjects.

The effects of stimulus rate and gender on the AMLR waveforms investigated by our present study can be affected by age. The average ages used in our study were about 25 years old for males and 21 years old for females. Many previous studies have reported age-related changes in the AMLR waveforms such as poorer waveform morphology, increased latency, and increased amplitude (Amenedo & Díaz, 1998; McGee & Kraus, 1996; Woods & Clayworth, 1986). These changes include a slight increase or no increase in the latencies of Na, Pa, and Pb with age and a linear increase in the amplitudes of Pa and Pb with age. In more detail, the amplitude of Pb increased with age in women (Pfefferbaum et al., 1979). The Pb latency was longer in older women (Erwin & Buchwald, 1986). Slower stimulus rate (1 to 2/s) has been used to obtain a true AMLR waveform in neonates and young children and the Pa components of the AMLR were not reliably recorded for stimulus rates exceeding 5/s (Jerger et al., 1987). In pathology, slow stimulus rate of 1/s is required to consistently record the Pb components of the AMLR (Buchwald et al., 1989; Hall, 2007). Furthermore, in individuals with Alzheimer's disease, the latency and amplitude of Pa was normal but the amplitude of Pb significantly decreased (Buchwald et al., 1989). In patients with Alzheimer's disease, the latency of Pb was longer and the amplitude of the Pb was larger than in age-matched controls (Irimajiri et al., 2005). In patients with Parkinson's disease, there was a Pb abnormality (Pekkonen et al., 1998). Therefore, the larger amplitudes of all AMLR waveforms in males shown in this study may come from the difference in the average age of the subjects participated in the study. More investigation is needed to consider advancing age for future study investigating the effects of stimulus rates and gender on the AMLR waveforms in relation to the effects of age.

We investigated the optimal stimulus rates characterizing the latency and amplitude of the AMLR waveforms in different gender. In this study, it is valuable to note that there are some limitation on generalization and clinical application due to the small size of subjects, the selected subjects in the specific locations, the limited ranges of stimulus rate, and the different stimulus conditions as shown in our previous study of ABR (Choi et al., 2015). Nevertheless, this study provides gender-specific norms for male and female subjects for the AMLR waveforms. These norms will be usefully applied to individuals with aging related hearing loss, noise induced hearing loss, and different hearing loss.

In conclusion, this research investigated the effect of stimulus rate and gender on the latency and amplitude of the AMLR waveforms in young adults. Significant differences in the latency and amplitude of Na, Pa, Nb, and Pb were investigated with the stimulus rates of 0.5, 1, 2, 4, and 8/s in female and male subjects. Stimulus rates showed a significant effect on the Na latency, Pa amplitude, and Nb amplitude. The Na latency slightly increased with faster stimulus rates. The Pa amplitude decreased with increasing stimulus rates while the Nb amplitude slightly increased with faster stimulus rates. Significant differences in gender were observed on the latency of Na and the amplitudes of all AMLR waveforms. The latencies of Na, Pa, Nb, and Pb in females were longer than in males while the amplitudes of Na, Pa, Nb, and Pb in males are larger than in females. This provides useful information of gender-specific norms on the latency and amplitude of the AMLR waveform and clinical insight of the optimal stimulus rates to elicit the apparent AMLR waveform.

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