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Effects of Stimulus Rate and Gender on the Auditory Middle Latency Response

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Abstract

The effects of stimulus rate and gender on the auditory middle latency response (AMLR) waveforms were examined in 20 young adult male and female subjects. Four different repetition rates were presented to subjects (1.1/sec, 4.1/sec, 7.7/ sec, and 11.3/sec). Stimulus repetition rate had a significant effect on Pa latency, Pa amplitude, and Pb amplitude. Pa and Pb amplitudes decreased with increasing the stimulus rate, and Pa latency significantly increased with increasing the stimulus rate. No significant differences were seen on Pb latency or site of recording. Gender had a significant effect on Pa latency and Pa amplitude. Pa latencies were longer in male subjects, and Pa amplitudes were larger in female subjects. Gender did not have a significant effect on the Pb waveform.

Key Words: Auditory evoked response, auditory middle latency response, repetition rate

Abbreviations: AMLR = auditory middle latency response

Sumario

Se examinaron los efectos de la tasa de estimulación y del género sobre la morfología de la onda en las respuestas auditivas de latencia media (AMLR) en 20 sujetos adultos jóvenes masculinos y femeninos. Se utilizaron cuatro tasas diferentes de repetición para estimular a estos sujetos (1.1/seg., 4.1/seg.,7.7/seg. y 11.3/seg.). La tasa de repetición del estímulo tuvo un efecto significativo en la latencia de la onda Pa, en la amplitud de la Pa y en la amplitud de la Pb. Las amplitudes de las ondas Pa y Pb disminuyeron con el incremento de la tasa de estimulación, y la latencia de la Pa se incrementó significativamente con el incremento de la tasa de estimulación. No se observaron diferencias significativas con relación a la latencia de la Pb o al sitio de registro. El género tuvo un efecto significativo sobre la latencia de la onda Pa y sobre la amplitud de la Pb. Las latencias de la onda Pa fueron más prolongadas en sujetos masculinos, y las amplitudes de la Pa fueron mayores en sujetos femeninos. El género no tuvo un efecto significativo en la morfología de la onda Pb.

Palabras Clave: Respuesta auditiva evocada, respuesta auditiva de latencia media, tasa de repetición

Abreviaturas: AMLR = respuesta auditiva de latencia media

The auditory middle latency response (AMLR) is an auditory evoked response waveform that occurs between 10 and 100 msec after the presentation of a brief acoustic stimulus. This waveform is composed of several positive and negative peaks (Picton et al, 1974; Jerger et al, 1988). The first prominent positive peak of the AMLR waveform is Pa, which occurs

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at a latency of approximately 25 msec (Hall, 1992). Researchers have identified underlying neural generators of the Pa waveform to be portions of the primary auditory pathway, including the temporal lobe and thalamus (Jacobson, 1994; Kraus and McGee, 1995). The second prominent peak Pb occurs at approximately 50 msec and arises from the thalamic reticular activating system (Erwin and Buchwald, 1986), thalamocortical projections (Shi and Barth, 1992), and auditory cortex in the supratemporal plane (Toyoda et al, 1998).

A number of subject and stimulus factors have been reported to affect the recordings of AMLR in humans. Subject parameters include state of arousal (Kraus et al, 1989), age (Tucker and Ruth, 1996; Pynchon et al, 1998), fluency (Dietrich et al, 1995), and gender (Woods and Clayworth, 1986). These subject factors can alter the amplitude, latency, and morphology of AMLR waveforms in normal-hearing subjects. Additionally, stimulus factors such as signal level (Tucker and Ruth, 1996; Tucker et al, 2001) and filtering (Scherg, 1982; Dietrich et al, 1995) have been reported to produce changes in amplitudes and latencies of AMLR waveforms. These subject and stimulus factors appear to have a more pronounced effect in AMLR recordings in young children (Kraus et al, 1985; Tucker and Ruth, 1996); consequently, AMLR tests currently have a limited clinical application in pediatric patients. For the AMLR to become a more effective diagnostic tool in children and in other special patient populations, clinicians must have a clear understanding of both subject and stimulus parameters on the AMLR Pa and Pb waveforms.

The effect of gender on the AMLR waveforms has received little attention in previous studies. In Geisler and colleagues' landmark article that initially described the AMLR waveform (Geisler et al, 1958), the effect of gender was not given. In other classic works (Picton et al, 1974; Jerger et al, 1988; Kraus and McGee, 1988), the gender of the subjects is not described or considered in their data analysis. Other significant studies have given equal representation to both genders in their research design but did not report the effect of gender in their findings (Goldstein and Rodman, 1967; Goldstein et al, 1972; Özdamar and Kraus, 1983; Woods and Clayworth, 1985). Woods and Clayworth (1986) reported a gender effect on the Pa amplitude. They observed a trend of larger Pa amplitudes in females; however, this trend did not reach statistical significance. Clementz and colleagues (1998) reported a similar gender effect on Pb. These authors found that the Pb (P50) amplitude was significantly larger in women than in men. Clearly, there is a paucity in the literature on the effect of gender on the AMLR Pa and Pb waveforms. Gender differences have been reported in the earlier auditory brainstem response. These differences appear to be owing to faster response in the female cochlea (Don et al, 1993).

The effect of stimulus rate on AMLRs is complex and not clearly defined for both prominent peaks in the literature. The initial study by Geisler and colleagues (1958) describing AMLR waveforms reported that click rates as high as 10/sec could produce AMLR waveforms, but the authors noted that the amplitude of the most prominent component (Pa) tended to decrease with increasing stimulus rates. Picton et al (1974) also reported an adverse effect of increasing stimulus rate on early auditory evoked response waveforms. They used five stimulus rates (0.25/sec, 1/sec, 4/sec, 15.8/sec, and 62.5/sec) and found that the auditory brainstem response wave V remained resilient with increasing stimulus rate, whereas other auditory evoked response waveforms, including AMLR components, decreased in amplitude. Consequently, the general consensus has been that stimulus rates up to 10/sec can yield good recordable Pa waveforms (Goldstein and Rodman, 1967; Musiek and Donelly, 1983; Özdamar and Kraus, 1983). Some researchers have used rates as high as 13/sec to 15/sec with good success (Woods and Clayworth, 1985, 1986; Hall, 1992).

Several researchers have reported rate to be an insignificant factor in recording the Pa waveform. Vivion and colleagues (1977) did not find any signs of adaptation or habituation (reduction of response amplitudes) employing a series of stimulus rates from 1/sec to 16/sec. Likewise, Goldstein and colleagues (1972) varied stimulus rates in adult subjects from 1/sec to 15/sec and did not find a significant rate effect for Pa. In an investigation looking at the development of the AMLR in normal infants, children, and teenagers, Tucker and Ruth (1996) found that altering stimulus rate from 3.3/sec to 11.3/sec had no significant effect on Pa amplitude or latency. However, other investigators reported a significant adverse effect of stimulus rate on Pa (Jerger et al, 1988), as well as a significant development age and rate interaction for both infants and the elderly (Jerger et al, 1988; Hall, 1992).

The Pb waveform is also known as P50 in the auditory late latency response (Jerger et al,

1988). Since this waveform occurs later in time than Pa, its behavior appears more like the classic auditory late latency response waveform, which includes the need for very slow stimulus click rates in recording parameters (often 1/sec or less). Nelson and colleagues (1997) noted that the unpredictable nature of the Pb waveform has made its diagnostic use problematic. Their investigation found that using a click rate of 1.1/sec was more likely to invoke a recordable Pb waveform in most normal adult subjects. Dietrich and colleagues (1995) used three stimulus rates (1.1/sec, 4.1/sec, and 7.7/sec) and found that Pb amplitude was significantly reduced at higher click rates. In recent clinical studies using Pb/P50 in schizophrenia, alcoholism, males who stutter, and cocaine abuse, researchers have used very slow click rates in complex gating experiments (Dietrich et al, 1995; Fein et al, 1996; Clementz et al, 1998).

Clearly, very slow stimulus rates can be used for eliciting recordable Pa and Pb waveforms, but the use of extremely slow click rates is not clinically practical (Kraus et al, 1994). The purpose of this study was to record AMLRs in both normal male and female young adult subjects using various click rates and to determine the effects of stimulus rate and gender interactions on both Pa and Pb waveforms.

METHOD

Subjects

Twenty young adult human subjects (10 men and 10 women) between 21 and 30 years of age served as subjects for this study. The mean age for male subjects was 26 years (SD = 2.85), and the mean age for females was 23 years (SD = 2.16). All subjects had a normal otoscopic examination, normal middle ear function, normal hearing sensitivity, and no medical history of neurologic pathology, head trauma, drug use (illegal and/or prescribed mind-altering medications), or diagnosis of learning disorders (attention-deficit disorder, attention-deficit hyperactivity disorder, or specific learning disabilities). Middle ear function was assessed using the Grason-Stadler 28 Auto tympanometer, with normal results consisting of a Type A tympanogram with peak middle ear pressure between 100 daPa and +50 daPa. Normal hearing sensitivity was defined as threshold for pure tones between 0 and 20 dB HL at the frequencies 250, 500, 1000, 2000, 4000, and 8000 Hz.

Procedure

Subjects read and signed a consent form before testing. All subjects were first assessed with middle ear measurements and pure-tone audiometry. Following screening procedures, the skin of the subject's scalp was prepared for placement of surface electrodes. Electrodes were placed on the right and left earlobes (voltage negative), on the forehead (Fpz) (ground), and at vertex (Cz) (voltage positive). A Nicolet Spirit clinical averager was used to generate click stimuli and to record the scalp electroencephalography from which the AMLR was averaged. Click stimuli were presented to the right ears of all subjects via Nicolet 13-mm foam inserts and Nicolet TIP-300 transducers, and ipsilateral and contralateral recordings were obtained for each stimulus condition.

Stimulus Parameters

An alternating polarity click stimulus was presented to the subject's right ear at a stimulus intensity level of 85 dB nHL, and scalp electroencephalography was recorded over a 100-msec timebase. Four stimulus click rates were presented (1.1/sec, 4.1/sec, 7.7/sec, and 11.3/sec). To control for order effects, subjects were randomly assigned one of four click rate presentation groups, labeled A, B, C, or D. The order of four click rates was randomly varied within each group. Additionally, a 2- to 3-minute break was given to subjects between each click rate presentation. These rest intervals were provided to decrease patient fatigue. Recorded responses were filtered online using analog bandpass filters of 10 to 250 Hz. A total of 256 sweeps were presented at each recording. Two AMLR waveforms were recorded at each rate condition and were compared offline to check for reproducibility.

Data Analysis

Peak-to-peak amplitudes and peak latencies were analyzed for all stimulus conditions. Figure 1 shows a normal AMLR waveform recorded in an adult male subject. Major AMLR peaks and the auditory brainstem response wave V are shown. The two recordings from each condition were added, and the mean latency and amplitude values were used for statistical analyses. Amplitudes were measured from the lowest portion of the preceding negative component to the highest portion of Pa or Pb. Latencies were mea-

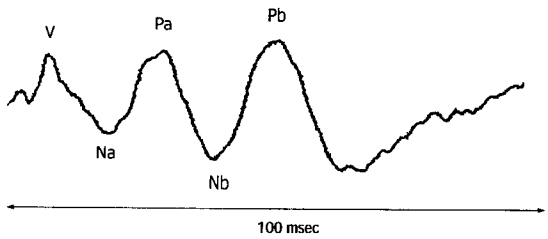

Figure 1 Normal auditory middle latency response waveform recorded in an adult male subject.

sured at the highest point of the AMLR waveforms. Both descriptive and inferential statistics were used to analyze the data. A multivariate analysis of variance was used to determine the main effects of gender, rate, and site of recording and for the interactions of gender*rate, gender*site, rate*site, and gender*rate*site on Pa amplitude, Pa latency, Pb amplitude, and Pb latency components.

RESULTS

Morphology

Table 1 shows the mean Pa and Pb amplitudes and latencies for the four stimulus conditions. The presence and shape of the Pa waveform are clearly defined in all four stimulus conditions. Figure 2 shows grand-averaged AMLR waveforms recorded ipsilaterally from female and male adult subjects in response to the four stimulus click rates. Additionally, the Pa waveform appears larger in female subjects than in male subjects in all conditions, a trend that proved to be statistically significant ($F = 17.926$, $df = 1$, $p = .0001$). The Pb waveform is most clearly recorded in the slowest (1.1/sec) stimulus condition, with the male Pb appearing larger than the female. However, this gender trend did not prove to be statistically significant ($F = .151$, $df = 1$, $p = .698$). Recordable Pb waveforms were seen at all other click rate conditions. However, half in the other click rate conditions reduced Pb amplitude. Post hoc Tukey testing showed that the Pb amplitude at 1.1/sec was significantly different than the other three click rates. As expected, morphology was poorest for the 7.7/sec rate condition.

Table 1 Amplitudes and Latencies of Ipsilateral Pa and Pb Waveforms Recorded in Male and Female Young Adult Subjects in Four Stimulus Rate Conditions

	Male	*SD*	*Female*	*SD*
Pa amplitude (μV)				
1.1/sec	1.07	0.60	1.78	0.79
4.1/sec	1.00	0.35	1.40	0.84
7.7/sec	0.84	0.43	1.03	0.37
11.3/sec	1.08	0.26	1.33	0.43
Pa latency (msec)				
1.1/sec	26.96	1.92	27.00	1.94
4.1/sec	29.08	2.02	26.52	1.83
7.7/sec	29.08	2.82	26.88	1.96
11.3/sec	29.44	1.37	28.48	1.94
Pb amplitude (μV)				
1.1/sec	1.43	1.25	1.35	0.52
4.1/sec	0.75	0.66	0.63	0.41
7.7/sec	0.56	0.34	0.48	0.21
11.3/sec	0.72	0.35	0.72	0.28
Pb latency (msec)				
1.1/sec	50.64	3.60	53.08	5.85
4.1/sec	51.40	2.82	51.96	3.92
7.7/sec	51.50	3.63	49.76	5.13
11.3/sec	52.13	1.40	49.42	3.14

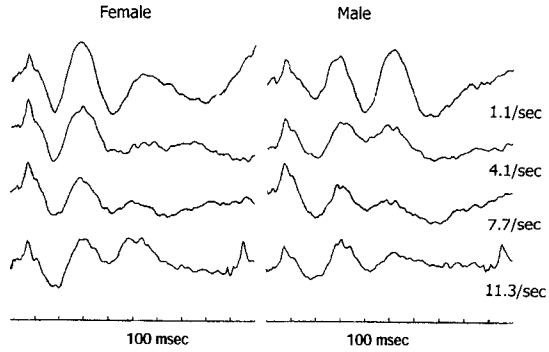

Figure 2 Grand-averaged auditory middle latency response waveforms recorded in male and female subjects using four stimulus rate conditions.

Site of Recording

Site of recording (ipsilateral vs contralateral) did not prove statistically significant for Pa latency ($F = .001$, $df = 1$, $p = .975$), Pa amplitude ($F = 2.47$, $df = 1$, $p = .118$), Pb latency ($F = 2.144$, $df = 1$, $p = .146$), or Pb amplitude ($F = .598$, $df = 1$, $p = .441$), so only ipsilateral means are given in this table, and ipsilateral tracings are shown in the grand-averaged waveforms.

Latency

For Pa latency, stimulus rate did have a significant effect ($F = 5.967$, $df = 3$, $p = .001$), with the trend of longer latencies being recorded using faster click rates. Gender also had a sig-

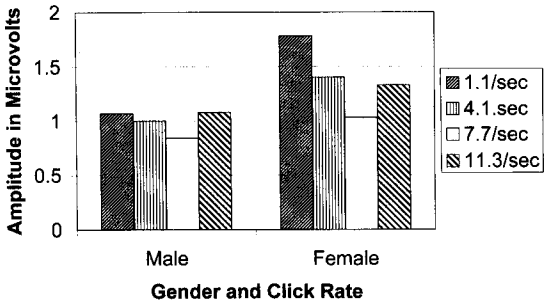

Figure 3 Pa mean amplitudes for male and female subjects at four stimulus rate conditions.

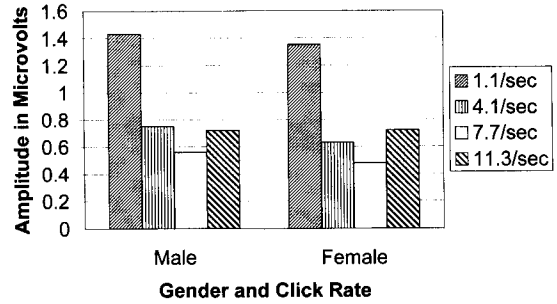

Figure 4 Pb mean amplitudes for male and female subjects at four stimulus rate conditions.

nificant effect (F = 23.82, df = 1, p = .0001), with the male Pa latency consistently showing a longer latency than females. There was also a significant rate*gender interaction (F = 3.807, df = 3, p = .012), with male subjects showing a more prolonged Pa latency as stimulus rate increased. There were no significant interactions of rate*site (F = .426, df = 3, p = .734), site*gender (F = .524, df = 1, p = .470), or rate*site*gender (F = .345, df = 3, p = .793). Stimulus rate (F = .957, df = 3, p = .415) and gender (F = .035, df = 1, p = .852) did not have a significant effect on Pb latency. Additionally, there were no significant interactions for rate*site (F = .709, df = 3, p = .548), rate*gender (F = 2.478, df = 3, p = .064), site*gender (F = .095, df = 1, p = .759), or rate*site*gender (F = .160, df = 3, p = .923).

Amplitude

Figure 3 shows a graph of the means of Pa amplitude for males and females in the four stimulus conditions. For both males and females, Pa amplitude is largest for the slowest (1.1/sec) and fastest (11.3/sec) click rates, and Pa amplitude is larger in females. Both stimulus rate (F = 6.363, df = 3, p = .0001) and gender (F = 17.926, df = 1, p = .0001) had a significant effect on Pa amplitudes. Increasing the stimulus rate decreased the Pa amplitude for both male and female subjects, and for all stimulus rate conditions, the female Pa amplitude was larger. However, there were no statistically significant interactions between main effect variables (rate*site: F = .045, df = 3, p = .987; rate*gender: F = 1.845, df = 3, p = .142; site*gender: F = .633, df = 1, p = .428; rate*site*gender: F = .270, df = 3, p = .847).

Figure 4 shows a graph of the mean of Pb amplitude for male and female subjects in the four stimulus conditions. Clearly, the largest Pb amplitude was recorded in the slowest (1.1/sec) stimulus condition. Only rate (F = 12.065, df = 3, p = .0001) proved to have a statistically significant effect on Pb amplitude. Other factors and interactions (gender: F = .151, df = 1, p = .698; rate*site: F = .196, df = 3, p = .899; rate*gender: F = .415, df = 3, p = .743; site*gender: F = .289, df = 1, p = .592; rate*site*gender: F = .019, df = 3, p = .996) did not prove to have a significant effect on Pb amplitude.

DISCUSSION

The results of this study showed that gender affects Pa and Pb waveforms differently. Gender has a significant effect on the Pa waveform's latency and amplitude. The Pa amplitude was consistently larger in female subjects, and amplitudes consistently decreased with increasing the stimulus rate. This finding is consistent with the finding of Woods and Clayworth (1986) showing larger Pa amplitude in females. However, the results of our study showed that Pb amplitude and latency were not significantly affected by gender. This finding is inconsistent with the observations of Clementz and colleagues (1998), who found larger Pb amplitudes in females. This different finding may be attributable in part to the fact that the subjects in the Clementz and colleagues (1998) study included normal and schizophrenic patients. The effect of gender on wave Pb is not clearly defined. Researchers have reported findings showing varying effects of gender on late auditory evoked waveforms. Onishi and Davis (1968) found auditory late latency response amplitudes to be larger in females. However, Polich (1986) reported no significant difference in male and female P300 responses. Clearly, more investigation is needed in determining the effect of gender on cortical auditory evoked responses, including the middle

latency Pb (P1) response. The results of this study indicate that earlier Pa response has a significant gender effect, similar to the gender effect seen on the earlier auditory brainstem response (Jerger and Hall, 1980).

The results of this present investigation showed a significant rate effect for both Pa and Pb amplitudes, although the grand average waveforms show the Pa peak to be more resilient when using faster click rates. Pa latency was also adversely affected by increasing stimulus click rates. The Pb waveform's amplitude appears to be more adversely affected when using click rates above 1.1/sec, whereas the latency of Pb was unaffected by stimulus rate. These findings are in accordance with the findings of Picton and colleagues (1974), Dietrich and colleagues (1995), and Nelson and colleagues (1997). The results from this study showed that the Pb (P1) waveform had the poorest morphology at the 7.7/sec condition, which is consistent with the finding of Dietrich and colleagues (1995). Research has shown differences in Pb latency in some disordered populations (Buchwald et al, 1989; Hendler et al, 1990; Dietrich et al, 1995). More investigations are needed to determine the effects of click rate and development of the two different AMLR waveforms in younger subjects and in other abnormal patient populations.

The resiliency of the Pa waveform may account for the higher click rates advocated by previous investigators (Goldstein et al, 1972; Vivion et al, 1977; Tucker and Ruth, 1996). For obvious reasons, the use of higher click rates is more desirable when testing in a clinic setting. Consequently, recognizing the differences in the Pa and Pb waveforms is critical and may indicate a need for separate clinical test protocols for each. Given the effects of gender and rate observed in this study, we recommend that clinicians develop gender-specific norms for male and female subjects for Pa waveforms. Higher click rates (up to 11.3/sec) may be used when testing for Pa. However, when the recordability of Pa is poor, the acoustic stimulus should be presented at a slower rate prior to making clinical judgments. A slower click rate (1.1/sec or lower) is optimal to record Pb waveforms in both normal subjects and in subjects with various pathologies affecting the auditory system. However, as a test protocol with a very slow click rate will take more time, patients should be aware of this in scheduling this type of testing.

A possible limitation of this study is the use of a two-electrode montage to record AMLR waveforms. Data recorded from numerous electrode sites would certainly give us more information on scalp distribution; however, the two-electrode montage is traditionally used in clinical settings and may allow these findings to be more readily generalized to the clinical population. Further understanding of gender and rate effects on Pa and Pb components of the AMLR waveform will be investigated using more advanced brain-mapping techniques in future research.

It is important for clinicians to understand the underlying neural generators contributing to individual AMLR components when selecting appropriate test protocols that may optimize either the Pa or the Pb waveforms. Previous researchers have hypothesized that Pa primarily arises from the telencephalon (tangentially oriented dipole sources within the posterior temporal lobe), with some influence from deep midline generators in the brainstem (Woods et al, 1987; Cacace et al, 1990; Jacobson and Newman, 1990). In contrast, wave Pb primarily arises from the diencephalon, midbrain, and thalamic portions of the reticular activating system (Buchwald et al, 1981; Erwin and Buchwald 1986; Harrison et al, 1990). The significant contribution of the reticular activating system to Pb would explain why it demonstrates more characteristics of late auditory potentials, such as its longer latency and its adverse response to rapid click rates and sleep.

Given the differences of neural generators for these two middle latency components, it would follow that clinical applications for the Pa and Pb response differ. The Pa response has been used to assess hearing thresholds for low-frequency hearing (Musiek and Geurkink, 1981; Maurizi et al, 1984; Musiek et al, 1984), to manage pediatric patients with cochlear implants (Kileny and Kemink, 1987), and for neuroaudiologic assessment (Musiek et al, 1984; Hall and Tucker 1985, 1986). The Pb response has been used in clinical studies to assess metabolic differences in thalamic and reticular activating system regions. Current research is determining the implications of Pb in patients with schizophrenia, autism, Alzheimer's disease, alcoholism, males who stutter, and cocaine abuse (Buchwald et al 1988, 1989; Erwin et al, 1988; Dietrich et al, 1995; Fein et al 1996; Clementz et al, 1998). Thus, for differing clinical applications of the AMLR assessment, it may be advantageous to have two separate AMLR test protocols, one that optimizes identification of Pa and that can be done in a shorter time span and one that best optimizes Pb and uses a longer test time.

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