Hit and False-Positive Rates for the Middle Latency Response in Patients with Central Nervous System Involvement

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Abstract

We sought to determine the test efficiency of the middle latency evoked response for identifying or differentiating subjects with and without central nervous system (CNS) involvement. Receiver operating characteristic curves were established for hit and false-positive rates for 26 subjects with CNS lesions and 26 control subjects matched for age and hearing sensitivity. The lesions involved but were not limited to the auditory regions of the CNS. Middle latency evoked response latency and amplitude measurements were made for the N\textsubscript{a} and P\textsubscript{a} waves recorded at C\textsubscript{3} and C\textsubscript{4} electrode sites following stimulation of the left and right ears. Intrasubject comparisons were made for ipsilateral and contralateral stimulation/recording conditions. Amplitude measures were superior to latency measures. For amplitude, percentage differences from contralateral comparisons proved to be the most sensitive and specific measure. The clinical implications of findings are discussed.

Key Words: Central auditory disorders, central auditory nervous system, central auditory processing, central nervous system, evoked potentials, middle latency evoked response

Abbreviations: ABR = auditory brainstem response, CANS = central auditory nervous systems, CNS = central nervous system, MLR = middle latency response, ROC = receiver operating characteristics

The (auditory) middle latency response (MLR) is a series of averaged neuro-electrical responses that can be recorded from the scalp. Geisler et al (1958) were the first to report on these evoked potentials. Since 1958, the progress and clinical use of the MLR has varied. Although flawed, early reports that the MLR was primarily attributable to muscle artifact hindered its acceptance as a research or clinical procedure. Fortunately, this is no longer the case. A better understanding as to recording techniques, generator sites, maturational influences, and sleep effects has made the MLR more applicable in both clinical and research settings (see Kraus et al, 1994; Chermak and Musiek, 1997). The advent of the auditory brainstem response (ABR) also played a role in the increase in popularity and use of the MLR. In many cases, the ABR and MLR are recorded simultaneously, providing information about a considerable portion of the auditory pathways.

Recently, the MLR has emerged as a possible test for central auditory abnormalities. Studies show that the MLR is often compromised in patients with central auditory nervous system (CANS) lesions and/or auditory processing prob-
lems associated with learning disabilities (Kraus et al., 1994; Arehole et al., 1995; Chermak and Musiek, 1997). Clinically, one factor that must be considered in the diagnostic use of the MLR is its intersubject variability. In normal populations, the amplitude of the N$_2$-P$_a$ complex varies considerably (Madell and Goldstein, 1972; Suzuki et al., 1983; Chambers and Griffiths, 1991; Musiek et al., 1994). Due to this amplitude variance in normal patients, diagnostic efficiency was compromised. Thus, other criteria and strategies emerged that were more usable for separating patients with CANS problems from those without them. Intrasubject rather than intersubject amplitude comparisons were used in diagnostic studies. This was based on data that showed similar amplitudes recorded from similar sites on each hemisphere in normal subjects (Kileny et al., 1987). However, this was not the case in subjects with central nervous system (CNS) lesions limited to one hemisphere (Kraus et al., 1982; Kileny et al., 1987).

In patients with CNS involvement, MLR abnormalities are most often observed in the amplitude of the N$_2$-P$_a$ wave on the side of the lesion. This amplitude reduction can be detected by comparing recordings from electrodes on both sides of the head. The electrode nearest the lesion often yields a reduced amplitude, and this is called the electrode effect (Kraus et al., 1982; Kileny et al., 1987; Ibanez et al., 1989; Shehata-Dieler et al., 1991; Musiek et al., 1994). At times, there also can be an ear effect, when one ear yields a significantly smaller wave than the other ear at the various electrode sites. However, the ear effect could be ipsilateral or contralateral to the lesion (Ibanez et al., 1989; Musiek et al., 1994). To our knowledge, there is no clear tendency for the ear effect to be either ipsilateral or contralateral to the involved hemisphere. Unlike the more popular auditory brainstem response (ABR), latency measures for the MLR do not appear to be as sensitive as intrasubject amplitude measures to CNS compromise (Kraus et al., 1982; Musiek and Lee, 1997).

It is known which measurements of the MLR are advantageous for clinical use, and reports have shown potential diagnostic value of the MLR in detecting central lesions, but little is known about the sensitivity and specificity of the MLR. We know of no research that has studied receiver operating characteristics (ROC) of the MLR in regard to hit and false-positive rates for populations with and without CNS involvement. Therefore, we studied a large population of patients with CNS involvement and a control group to derive ROC curves for hit and false-positive rates for a variety of latency and amplitude criteria.

**METHOD**

**Subjects**

Fifty-two subjects, divided into two groups of 26 subjects each, participated in this study. One group served as control subjects (16 women, 10 men). The second group was composed of patients with medically confirmed lesions of the CANS (14 women, 12 men) (Table 1). The subjects in the experimental group had lesions that involved, but were not limited to, the central auditory system according to the anatomic boundaries of Galaburda and Sanides (1980). The subjects in the two groups were matched for age (within 5 years) and for hearing sensitivity (within 15 dB for frequencies 500, 1000, 2000, and 4000 Hz) on an individual basis. The ages of the subjects in the control group ranged from 17 to 64 years (mean 41.3 years). The ages of the subjects in the experimental group ranged from 16 to 64 years (mean 41.5 years). Seven subjects in each group presented with symmetric sensorineural hearing loss. All seven of these subjects in each group demonstrated normal hearing (20 dB HL or better) at 500 Hz and 35 dB HL or better hearing at 1000 and 2000 Hz. At 4000 Hz, thresholds ranged from 0 to 65 dB HL in both groups. The remaining subjects in both groups had normal hearing sensitivity (20 dB HL or better for frequencies 500 through 4000 Hz).

The subjects with CNS involvement were patients seen for audiologic evaluation at the Dartmouth-Hitchcock Medical Center or Gaylord Rehabilitation Hospital. The control subjects were volunteers, including some audiology patients.

**Procedures**

Audiologic testing was carried out in a sound-treated room. All subjects were awake during MLR testing. The stimulus for the MLR was a 100-μsec electric square wave passed through ER-3A sound insert phones worn by the subjects. This click stimulus was presented at a rate of 9.8 per second. The acoustic stimuli were presented at 60 dB nHL to the right and left ears of the subjects in a monaural condition, and the order of presentation was pseudorandomized. Impedance across electrode sites was 8 kilohms or less.
Table 1 Subjects with Central Nervous System Involvement Pathology

<table>
<thead>
<tr>
<th>Subject</th>
<th>Locus of Lesion</th>
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<tbody>
<tr>
<td>1</td>
<td>Right basal ganglia hemorrhage (internal capsule)</td>
</tr>
<tr>
<td>2</td>
<td>Left hemisphere CVA (superior temporal gyrus parietal lobe)</td>
</tr>
<tr>
<td>3</td>
<td>Left hemisphere CVA (superior temporal gyrus, inferior parietal lobe)</td>
</tr>
<tr>
<td>4</td>
<td>Left hemisphere CVA (superior temporal gyrus and inferior parietal lobe)</td>
</tr>
<tr>
<td>5</td>
<td>Left middle cerebral artery aneurysm (superior temporal and inferior parietal regions)</td>
</tr>
<tr>
<td>6</td>
<td>Right temporal lobectomy (anterior/mid superior temporal gyrus)</td>
</tr>
<tr>
<td>7</td>
<td>Left temporal lobectomy (anterior/middle superior temporal gyrus)</td>
</tr>
<tr>
<td>8</td>
<td>Left hemisphere epileptic focus (superior, posterior temporal gyrus)</td>
</tr>
<tr>
<td>9</td>
<td>Right temporal lobectomy (anterior/middle superior temporal gyrus)</td>
</tr>
<tr>
<td>10</td>
<td>Left and right hemisphere encephalitis (right temporal parietal area, left Heschl's gyrus)</td>
</tr>
<tr>
<td>11</td>
<td>Right temporal lobe CVA (superior posterior temporal gyrus)</td>
</tr>
<tr>
<td>12</td>
<td>Right hemisphere CVA (superior temporal gyrus, inferior parietal lobe)</td>
</tr>
<tr>
<td>13</td>
<td>Left temporal lobe CVA (mid/posterior superior temporal gyrus)</td>
</tr>
<tr>
<td>14</td>
<td>Left brainstem stroke (PICA) (inferior lateral pons superior lateral, medulla)</td>
</tr>
<tr>
<td>15</td>
<td>Left hemisphere CVA-AVM rupture (superior mid/posterior temporal gyrus, inferior parietal lobe)</td>
</tr>
<tr>
<td>16</td>
<td>Left hemisphere CVA-basal ganglia infarct (internal capsule)</td>
</tr>
<tr>
<td>17</td>
<td>Right hemisphere CVA-basal ganglia and cortex (internal capsule extending superior temporal gyrus)</td>
</tr>
<tr>
<td>18</td>
<td>Right temporal lobe CVA (posterior/superior temporal lobe)</td>
</tr>
<tr>
<td>19</td>
<td>Left basal ganglia, thalamic and pontine infarcts (internal capsule?, MGB?, left lateral pons)</td>
</tr>
<tr>
<td>20</td>
<td>Right hemisphere CVA basal ganglia infarct (internal capsule extending to the superior, mid temporal lobe)</td>
</tr>
<tr>
<td>21</td>
<td>Right temporal lobe CVA (posterior/superior temporal gyrus)</td>
</tr>
<tr>
<td>22</td>
<td>Left hemisphere CVA/basal ganglia infarct (midposterior temporal lobe, parietal lobe regions extending from basal ganglia insula internal capsule)</td>
</tr>
<tr>
<td>23</td>
<td>Left temporal lobe CVA (posterior superior temporal gyrus)</td>
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<tr>
<td>24</td>
<td>Left temporal parietal CVA (inferior parietal lobe)</td>
</tr>
<tr>
<td>25</td>
<td>Left temporal lobe CVA (superior/posterior temporal gyrus insula)</td>
</tr>
<tr>
<td>26</td>
<td>Right temporal lobe CVA (posterior/superior temporal gyrus)</td>
</tr>
</tbody>
</table>

CVA = cerebrovascular accident.

Neuroelectrical activity was detected by standard scalp electrodes attached at C3 and C4, which served as active sites. A clip electrode attached to the contralateral ear served as the reference. The ground electrode was placed at FPz. All waveforms were subjected to online analog filtering (20 to 3000 Hz) and offline digital filtering of varying bandwidths to help define Na and Pa waves. Waveforms were displayed on a 72-msec time window. One thousand accepted trials contributed to each waveform, and all waveforms were replicated. If the replicated waveforms did not have the same latency and amplitude, an average of the two waveforms was taken.

Latency measurements were taken for the Na and Pa waves of the MLR. Amplitude measurements were taken for the Na – Pa complex. Latencies were measured from the onset of the stimulus to the most negative repeatable peak (N a) occurring between 12 and 21 msec. The P a was determined as the most positive peak occurring between 21- and 38-msec post-stimulus onset. Amplitude measurements were taken from the trough of N a to the peak of P a.

Measurements Used in Analyses

ROC curves were established based on the two populations in this study. The ROC curves were generated by plotting the hit rate by the false-positive rate for various criteria (Turner et al, in press).

This study analyzed both latency and amplitude measurements, which were taken ipsilaterally and contralaterally. The ipsilateral measurement compared the MLR from the right ear and C4 electrode site with the MLR from the left ear and C3 electrode site. The contralateral measurement compared the MLR from the right ear and C3 electrode site with the MLR from the left ear and C4 electrode site. Therefore, in this paper, the ipsilateral and contralateral conditions refer to the electrode site on the head and the ear stimulated (and does not refer to electrode site in relation to the side of the brain lesion).
Absolute latency and amplitude difference between ipsilateral and contralateral measurements were used. We also used a percentage difference for amplitude measurements, which was computed as follows:

\[ \text{% difference} = \frac{\text{larger amplitude} - \text{smaller amplitude}}{\text{smaller amplitude}} \]

**RESULTS**

**Latency of the N\text{a} Wave**

The criteria used for developing the ROC curves for N\text{a} latency were latencies in 1-msec steps (range: >17 msec to >21 msec). As shown in Figures 1a, 1b, and 1c, the ipsilateral and contralateral measurements have similar curves, indicating only mediocre hit and false-positive rates. This situation is improved only slightly by combining ipsilateral and contralateral indices.

**Latency of the P\text{a} Wave**

The P\text{a} wave criteria were established using 1- or 2-msec steps (range: >28 to >36 msec) to derive the ROC curves. As shown in Figures 2a, 2b, and 2c, the contralateral condition yields the best ROC curve. The ROC curves are similar for absolute latencies of more than 30 msec. False-positive rates were low. Again, the hit rates were only fair.

**Percent Amplitude Difference of N\text{a}-P\text{a}**

Amplitude differences in percent were established using the formula mentioned above. The ROC curve was established using nine points, ranging from greater than 10 percent difference to greater than 100 percent difference for ipsilateral-only, contralateral-only, and ipsilateral and contralateral-combined conditions. Figures 3a, 3b, and 3c reflect that the contralateral-only condition yields the best results. Of note is the result showing that a 50 percent amplitude difference for the contralateral-only condition comparisons yields a 0 percent false-positive rate.

**Absolute Amplitude Difference of N\text{a}-P\text{a}**

Another analysis performed was absolute differences in amplitude. Although this measurement has inherent problems (i.e., great intersubject variability in MLR amplitude), the contralateral-only condition again showed a good hit and false-positive rate. Criteria ranged

**Figure 1** The ROC curves for hit and false-positive rates for N\text{a} absolute latency measures for (a) ipsilateral condition, (b) contralateral condition, (c) ipsilateral and contralateral conditions combined (latency criteria are shown in msec along the graph line).
Figure 2 The ROC curves for hit and false-positive rates for P1 absolute latency measures for (a) ipsilateral condition, (b) contralateral condition, (c) ipsilateral and contralateral conditions combined (latency criteria are shown in msec along the graph line).

Figure 3 The ROC curves for hit and false-positive rates for percentage of amplitude difference for (a) ipsilateral condition, (b) contralateral condition, (c) ipsilateral and contralateral conditions combined (percentage difference criteria are shown along the graph line).
The MLR is a potentially useful diagnostic test for identifying central auditory abnormalities (Kraus et al, 1982; Kileny et al, 1987; Ibanez et al, 1989; Shehata-Dieler et al, 1991; Musiek and Lee, 1997), but information is lacking on its hit and false-positive rates for populations with CNS lesions. To our knowledge, no studies have attempted to construct ROC curves for the MLR based on results from control subjects and those with CNS lesions. We sought to supply this information to better evaluate the diagnostic value of the MLR.

To evaluate the hit and false-positive rates of the MLR we used two main indices: those of latency and amplitude. These indices can be measured in reference to the ear stimulated and/or the electrode position on the head. Other measurements could have been used, but in our opinion the added complexity of additional electrodes and ear comparisons would increase clinical difficulty and would add little to the understanding of the MLR's diagnostic value.

**Latency**

The ROC curves for the absolute latencies of the $N_a$ and $P_a$ waves of the MLR indicated only moderate hit and false-positive rates for the measurements conducted. This finding is consistent with other reports showing little effect of central lesions on latencies of the MLR (Kileny et al, 1987; Musiek et al, 1994; Musiek and Lee, 1997).

The $P_a$ wave latency measure yields better ROC curves compared to the $N_a$ latencies. Kraus et al (1982) and Kileny et al (1987) reported little effect of latencies of the MLR for temporal lobe lesions, but there appeared to be a greater effect on $P_a$ waves than on $N_a$ waves. Ibanez et al (1989) reported that $N_a$ latency was seldom influenced by CNS lesions. Others report similar findings (Shehata-Dieler et al, 1991; Musiek et al, 1994). Celebisoy et al (1996), however, reported similar latency abnormalities for $N_a$ and $P_a$ in patients with multiple sclerosis, but in this study abnormal $N_a$ and $P_a$ latencies occurred in only a small portion of patients. The MLR $P_a$ wave, however, has been shown to shift in latency in patients with temporal lobe lesions (Ho et al, 1987; Shehata-Dieler et al, 1991). However, even

from microvolt differences of >0.1 to >0.6 (Figs. 4a–c).
in reports that show an extension of the Pa in temporal lobe involvement, the finding is not consistent and does not occur in a high percentage of subjects with CNS involvement (Ho et al, 1987; Shehata-Dieler et al, 1991).

The contralateral-only recording condition (comparing C3 and right-ear stimulation with C4 and left-ear stimulation) and the combined condition for the Pa provided better ROC curves than did the ipsilateral-only condition. For the ipsilateral, contralateral, and combined conditions, Pa latencies exceeding 30 msec yielded a low false-positive rate even though the hit rate was mediocre. Criteria of latencies that exceed 29 msec yield a clinically unacceptable false-positive rate. The 30-msec latency criterion, although not highly sensitive, could be valuable clinically because when this value is exceeded it is likely that CNS involvement is present if peripheral hearing sensitivity is essentially normal. Similar latency findings have been reported by others (Celebisoy et al, 1996).

Amplitude

Some authors suggest that amplitude is a better index than latency for diagnostic use of the MLR (for review, see Chermak and Musiek, 1997). Other authors suggest that intrasubject comparisons for the MLR (e.g., comparisons across electrodes or comparisons between ears) are the more valuable diagnostically (Kileny et al, 1987; Musiek et al, 1994). This is primarily because there is great variability in amplitude of the MLR waves in subjects who have normal auditory systems (Musiek, 1991; Hall 1992). Therefore, as with latency measurements, we made ipsilateral and contralateral comparisons for individual subjects. We reviewed amplitude differences by percentage of difference as well as on an absolute voltage basis.

The contralateral-only condition provided the best ROC curve (see Fig. 3b) and proved better than combining both ipsilateral and contralateral conditions. Although the combined condition yielded a better hit rate, its false-positive rate was much higher than that of the contralateral-only condition. A similar trend was noted for absolute amplitude differences, although overall percentage differences were slightly better than the absolute values.

Percentage differences in amplitude ranging from >50 percent to >20 percent for the contralateral condition would seem to be clinically useful criteria. The hit rates are not exceptional but the false-positive rates are good. Other MLR studies must be performed that examine the 20 percent to 50 percent amplitude difference between sites. Although this range of amplitude differences seems to hold promise as criteria for clinical use, the high degree of variability found in patients with CNS lesions argues for more data. The nature, size, and locus of CNS lesions are seldom even similar across patients, and therefore findings may vary (Musiek et al, 1994). This, in turn, may influence the determination and selection of a particular MLR criterion. This is also why we are reticent to suggest a specific criterion and prefer to discuss a range of criteria that may be useful.

Contralateral versus Ipsilateral

The present findings indicate, especially for amplitude, that the contralateral recording conditions yield better ROC curves compared to the ipsilateral recording condition. These findings are consistent with the report by Ibanez et al (1989). It is interesting to note that the MLR does not seem to be consistent in regard to ear laterality effects in patients with lesions. Patients with CNS lesions may have abnormal MLRs for the ear ipsilateral or contralateral to the involved hemisphere (Ibanez et al, 1989). However, evidence indicates that the electrode over or closest to the lesion yields reduced amplitude (Kraus et al, 1982). The measurements used in this study are a promising way of taking into account both of these effects on the MLR waveform.

It is not clear why the contralateral measures are more sensitive than the ipsilateral measures, but several factors can be considered. One factor has an anatomic basis. It is well known that the contralateral afferent auditory pathway has more fibers compared to the ipsilateral pathway. Some MLR data indicate that in normal subjects the contralateral MLR is larger in amplitude compared to the ipsilateral MLR (Ibanez et al, 1989; Shehata-Dieler et al, 1991). These anatomic and MLR data may be consistent with the dipole orientation for the MLR (Pool et al, 1989). The contralateral MLR recording may reflect the disruption of the dipole more readily than the ipsilateral MLR; hence, there is a greater differential when comparing each pathway's resultant MLR. The contralateral route also covers a greater neural area than does the ipsilateral route and thus may be more susceptible to compromise by a lesion. Upon a reinterpretation of Ibanez et al's data (1989), we
similarly found that contralateral measures were more sensitive than ipsilateral measures.

These contralateral MLR findings may be related to the contralateral ear effects noted on central auditory behavioral tests. As shown many times, scores on various behavioral tests of central auditory function will be decreased in the ear opposite the hemisphere with the lesion (see Musiek and Baran, 1991, for review). In this situation, the contralateral pathway for a given ear is damaged, making that ear more dependent on the ipsilateral pathway, which is weaker. However, for the opposite ear its contralateral pathway is intact, yielding a normal score. Thus, when the two contralateral systems are compared, the one with the lesion provides the lower score. This mechanism may be similar for the MLR.

Study Implications

The present study has several implications for clinical diagnostic audiology. Our data are consistent with those of reports indicating that the amplitude measurements are of greater value than MLR latency measurements in the identification of CNS lesions (Ibanez et al., 1989). It is important to take into account the latency measures for the MLR, but this index usually provides little differential diagnostic information.

The hit and false-positive rates reported in this study show what can be achieved with the MLR in situations where CNS integrity is in question. In these cases, the clinician must make decisions about which tests can be used to best provide information about CNS status. Information on hit and false-positive rates is important since it allows the clinician to evaluate the MLR for the purpose of CNS assessment. In a similar manner, the present study provides information on hit and false-positive rates that can be used to compare with other electrophysiologic and behavioral tests of central auditory function (Chermak and Musiek, 1997; Hurley and Musiek, 1997). This enables the clinician to select tests with the best sensitivity and specificity for a central auditory test battery. Moreover, the ROC curves represent new information for the MLR that can be applied cautiously to establish pass-fail criteria for making clinical decisions. The ROC curves also provide a reference for comparison to future studies on the MLR.

Comparing ipsilateral ear and electrode results with contralateral ear and electrode results yields measurements that can be accomplished easily for clinical use; this approach can also provide laterality measurements. Certainly, more detailed measurements can be made by examining various ear and electrode interactions, but the more simple approach was selected for this report. This measurement approach is clinically adaptable and does not sacrifice sensitivity and specificity.

CONCLUSIONS

The present study establishes ROC curves for hit and false-positive rates for control subjects and those with CNS lesions involving, but not limited to, the auditory regions. The ROC curves indicate that MLR amplitude measures are more valuable diagnostically as compared to latency measures. The contralateral MLR amplitude measurements alone were superior to ipsilateral-only or ipsilateral and contralateral measurements combined. It was also noted that percentage of amplitude differences were superior to absolute amplitude differences. Finally, the MLR contralateral amplitude measurements indicated that a 20 percent difference provided the best hit and false-positive rates, although low false-positive rates were obtained for 30 percent through 50 percent differences.

REFERENCES


