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Review Article

Electrophysiological Evidence for the Sources of the Masking Level Difference

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Purpose: The purpose of this review article is to review evidence from auditory evoked potential studies to describe the contributions of the auditory brainstem and cortex to the generation of the masking level difference (MLD).
Method: A literature review was performed, focusing on the auditory brainstem, middle, and late latency responses used in protocols similar to those used to generate the behavioral MLD.
Results: Temporal coding of the signals necessary for generating the MLD occurs in the auditory periphery and brainstem. Brainstem disorders up to wave III of the auditory brainstem response (ABR) can disrupt the MLD. The full MLD requires input to the generators of the auditory late latency potentials to produce all characteristics of the MLD; these characteristics include threshold differences for various binaural signal and noise conditions. Studies using central auditory lesions are beginning to identify the cortical effects on the MLD.
Conclusions: The MLD requires auditory processing from the periphery to cortical areas. A healthy auditory periphery and brainstem codes temporal synchrony, which is essential for the ABR. Threshold differences require engaging cortical function beyond the primary auditory cortex. More studies using cortical lesions and evoked potentials or imaging should clarify the specific cortical areas involved in the MLD.

The abilities of humans to understand speech and localize target signals in noisy backgrounds are attributed to the binaural system. The *binaural masking level difference* (MLD), so named by Webster (1951), is a measure of the ability of the auditory system to separate target signals from background noise based, in part, on timing differences of signals from two sources. The discovery of the MLD phenomenon (anecdotally) was made by pilots in World War II whose noisy cockpits made hearing the air traffic controller difficult. The pilots reversed the prongs on one of their earphones, effectively causing the speech to be in opposite polarity at the two ears. The speech coming over the earphones was distinct from the background noise; the pilots had discovered a way to hear better in their noisy situations without increasing the signal level. No source for this discovery has been found, but Tobias (1972) confirmed the effect. He took equipment on a small airplane and tested speech intelligibility in phase and out of phase at the ears, and confirmed that the speech intelligibility was indeed improved in the out-of-phase condition in the noisy airplane environment. In 1948, two individuals developed this concept into an experimental form that allowed psychoacousticians to define the parameters of the phenomenon; Hirsh (1948) developed the MLD with pure-tone signals and Licklider (1948) did the same with speech signals. This article reviews the electrophysiological literature with the purpose of describing the evidence from auditory evoked potentials (AEPs) about the generators of the behavioral MLD. Findings are corroborated with magnetoencephalography (MEG), imaging, and lesion studies that also focus on the MLD.

The response to MLD paradigms from single neural units in the brainstem has been reviewed by Palmer and Shackleton (2002) and is not included here. The authors concluded that neurons in the inferior colliculus responded to MLD stimuli much as they would to interaural delays of the tone and masking sounds, although different MLD paradigms could involve different sets of neurons. This conclusion corresponds to the neural timing information in the human brainstem studies. Only recently Gilbert, Shackleton, Krumbholz, and Palmer (2015) reported finding cortical neurons in guinea pigs that had a wide range of thresholds, the lowest of which could produce the MLD.

There is a family of MLDs, but in its simplest form, the MLD is the release from masking that is obtained between two signal-in-noise conditions. In the most common

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configuration, the MLD is derived from the threshold difference between a homophasic signal-in-noise condition (SoNo, or signal in phase and noise in phase between the ears) and an antiphasic signal-in-noise condition (SπNo, or signal out of phase and noise in phase between the ears), with the latter showing the better (lower) thresholds. Hence the MLD requires a background of binaural noise (N) and threshold differences in that noise with differences to signals (S) in phase (0 radians or 0°) and out of phase (π radians or 180°) between the ears. The size of the MLD is proportional to the noise level (Hirsh, 1948; McFadden, 1968) and inversely proportional to signal frequency (Hirsh, 1948; Licklider, 1948) and noise bandwidth (Hall & Harvey, 1985). Other conditions, such as SoNπ (signals in phase, noise out of phase), S_{90}No (signals 90° out of phase, noise in phase), and SmNo (signals monaural, noise out of phase), produce smaller MLDs than the SoNo-SπNo condition does. Hirsh (1948) determined that the MLD was largest for the SoNo-SπNo condition using low frequency signals. Jeffress (1948) proposed a model of binaural localization that included binaurally innervated neurons that converted timing information into sound-source localization. He hypothesized that these neurons, unidentified at the time, could exist in the superior olivary complex (SOC), but in deference to some contemporaneous research, suggested that they could as well be in the higher brainstem levels and the auditory radiations to the cortex.

After psychoacousticians described many of the variables, clinicians appropriated the MLD. For clinical applications, the largest MLD, SoNo-SπNo for a 500-Hz signal, is typically used. A large MLD (> 7 dB) was found for individuals with normal hearing and those with minor hearing losses defined as < 20 dB difference between ears or thresholds < 40 dB HL in the low frequencies (Jerger, Brown, & Smith, 1984). Acoustic tumors, however, were shown to reduce the MLD to 4.7 dB, whereas cortical lesions did not affect the MLD (Olsen, Noffsinger, & Carhart, 1976). These results reinforced the psychoacoustic MLD findings, and the MLD assumed its place in the battery of special diagnostic tests used for the identification of neural pathology between the eighth nerve and the SOC.

With the advent of electrophysiological measures of the auditory system, identification of the neural structures contributing to the MLD in humans became possible. To qualify as the electrophysiological correlate of the MLD, responses must have the same characteristics as the behavioral MLD. Some of the required characteristics include the following: (a) SπNo has lower thresholds than SoNo; (b) SoNo-SπNo produces the largest MLD; (c) smaller MLDs are recorded with the reference condition SoNo compared with other conditions, including SπNπ, SmNm (m is monaural), SmNo, and SoNπ; (d) MLDs are greater at lower frequencies compared with higher frequencies; (e) a background of noise is required; (f) MLDs are larger for narrowband noise than for wideband noise; and (g) MLDs are larger for higher levels of noise than for lower levels of noise.

Several early electrophysiological studies attempted to document the MLD using the auditory late latency responses (ALLRs) at a time when the auditory brainstem response (ABR) was not readily available. One of the earliest was a dissertation by Edwards (1971), for which she collected electrophysiological threshold data (N1-P2) on five participants. She obtained MLDs using SmNm as the referent because she was focused on both monaural versus binaural hearing and MLDs. A recalculation of the MLDs using SoNo as the referent shows MLDs of −4.00 dB for SmNm, 2.92 for SmNo, and 14.16 for SoNπ. The SπNo condition was not included in the stimulus conditions. Putting her data together with animal data led Edwards to the conclusion that the MLD must originate at or above the SOC.

Several other studies used the ALLR in MLD conditions, but did not attempt to reach thresholds. Tanis and Teas (1974) used N1-P2 amplitudes to compare to loudness percepts with stimuli used in MLD studies. They found that homophasic stimuli (SoNo and SπNπ) produced lower amplitudes than antiphasic stimuli (NπSo and NoSπ) throughout the range of signal-to-noise ratios tested (15–45 dB). Extrapolation from the lowest stimulus levels effectively demonstrated a 4-dB MLD between the homophasic and antiphasic conditions.

Yonovitz, Thompson, and Lozar (1979) recorded the N1-P2 amplitudes for low-frequency clicks and 1000-Hz tone bursts in the conditions of SoNo, SπNo, and SoNπ at 5-dB intervals from 5–45 dB SL relative to the behavioral threshold of SoNo. They extrapolated the data points to estimate a threshold for each of the conditions and calculated mean thresholds only from responses that were clearly above the noise levels. The extrapolated thresholds suggested MLDs for low-frequency clicks of 7 dB and 1000-Hz tonal signals of 9.8 dB. The study emphasized that the data estimated MLDs only for groups. Kevanishvili and Lagidze (1987) also used the N1-P2 to investigate the origin of the MLD. They used 580-Hz signals in SoNo and SπNo conditions to collect electrophysiological and behavioral responses. When SoNo responses were near threshold, the stimulus condition was flipped to SπNo and participants heard an increase in loudness. Using the same protocol with the evoked potential recordings, the researchers reported that the grand-averaged ABR and auditory middle latency response (AMLR) amplitudes were not different between conditions. Amplitude differences, however, were noted in the late cortical potentials; the amplitudes for P1, N1, and P2 SπNo were significantly larger compared with the amplitudes at the SoNo threshold. Threshold differences were not tested.

Thus, these early studies used only cortical potentials and (except Edwards, 1971) generally used grand-averaged waveforms for SoNo and SπNo, did not define thresholds, and did not comment on responses of individuals. Edwards (1971) used only two MLD conditions (NoSo compared with NoSm and NπSo), but found thresholds in both behavioral and electrophysiological recordings and MLDs in five individuals. Therefore, although the early studies did not show conclusive evidence for the electrophysiological MLD (eMLD) and did not search for origins, they provided the rationale for

further studies to identify and characterize the eMLD in individuals. This review covers subsequent human studies that sought the origins of the eMLD and its characteristics.

The MLD and Responses from the ABR

Because the brainstem was shown to be important in the generation of the behavioral MLD, the first evoked potential evaluated was the ABR. The first step of necessity was to determine if the behavioral MLD could be recorded with the short signals required for the ABR. The ABR was routinely run with 2-ms tonal signals (e.g., Fowler & Noffsinger, 1983), but the behavioral MLD had not been tested with comparable signals. R. H. Wilson and Fowler (1987) measured behavioral responses to 500-Hz signals with durations from 2–128 ms in the SoNo and SπNo conditions. The functions for SoNo and SπNo were essentially parallel for the signal durations and yielded MLDs ranging from a low of 10.4 dB at a 2-ms duration to a high of 13.0 dB at a 16-ms duration. With confirmation that behavioral MLDs were measurable with signals that were adequate stimuli for the ABR, the MLD trials with 2-ms signal durations could begin.

The ABR waves originate in the eighth cranial nerve and continue through the neural pathways up through the lateral lemniscus and inferior colliculus, but specific origins are complicated by multiple waveforms at intermediate generator sites (Moller, 2007; Moller, Jannetta, & Moller, 1981). The SOC is the primary origin for wave IV, and is the first site in the auditory system that processes binaural input. Before the Moller data, the origin of wave III was considered to be the SOC. Because of the binaural input, the SOC has been considered to be the origin of the MLD, a binaural phenomenon.

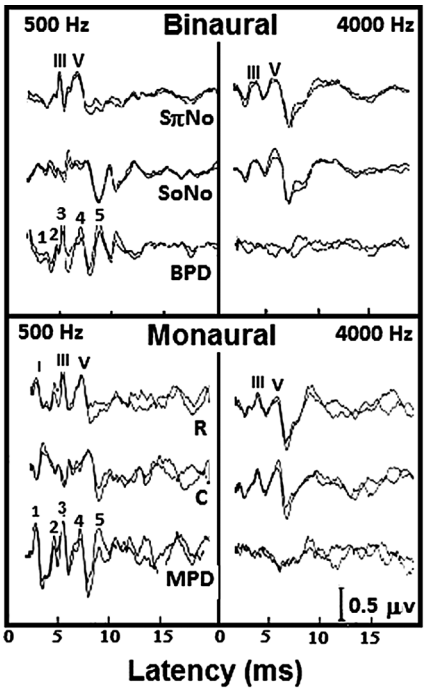
Three studies designed to confirm the locus for the MLD initially used individuals with brainstem lesions and compared results of behavioral and physiological tests. Jerger, Hannley, and Rivera (1980) reasoned that if the SOC function is necessary for a normal MLD, then the status of ABR wave III should be associated with the magnitude of the MLD. They recruited 20 volunteers with multiple sclerosis (MS), and divided them into three groups on the basis of the ABR findings. Group A had normal ABRs and normal MLDs, Group C had wave III absent in at least one ear and the smallest MLDs, and Group B had only delays of wave III in at least one ear and MLD magnitudes between those in the other two groups. Further, in three additional patients with only waves IV and V absent, the MLD was normal.

Noffsinger, Martinez, and Schaefer (1982) also recruited 20 individuals with MS to investigate the relations between ABR wave III, acoustic reflexes, and the MLD. Acoustic reflexes were included because their neural pathways include the auditory nerves up to the SOC. Thus, the expectation was that abnormal contralateral reflexes would correlate to abnormal wave III and abnormal MLDs. They reported that only individuals with abnormal ABR waves I, II, and III had absent or abnormal transbrainstem (contralateral) acoustic reflexes and absent or reduced MLDs. Individuals with only waves IV and V absent had normal MLDs. They therefore focused on the origin of MLD as the SOC given the relations with wave III and the contralateral acoustic reflexes, and its position as the lowest brainstem level for binaural interactions. Hannley, Jerger, and Rivera (1983) also evaluated patients with MS using ABR, acoustic reflexes, and MLDs. In this study, all participants had normal ABR wave I. Participants with abnormal contralateral reflexes (thresholds or decay) and abnormal wave III in one or both ears also had absent or reduced MLDs. Thus, these studies concurred on the importance of the SOC as the generator site for the MLD. The prevailing understanding at the time of these studies was that wave III was generated in the SOC. Moller et al. (1981), however, had just published new information suggesting that wave III originated in the cochlear nucleus. In deference to the new data, Noffsinger et al. (1982) acknowledged that abnormalities in the generators of waves I, II, and III could have a role in disruption of the input to the binaural system, and thus to the MLDs, even if they were not directly associated with binaural processing.

The acoustic reflex itself has been studied with MLD stimuli. Gorga, Abbas, and Lilly (1980) tested three participants with 550-Hz tones in So and Sπ conditions in a background of in-phase noise ranging from −20 to +20 dB SL regarding the reflex threshold. Although the participants perceived the antiphasic conditions louder than the homophasic conditions, there was no difference in the threshold or magnitude of the acoustic reflexes between these conditions. They concluded that the MLD was not reflected in the acoustic reflexes.

In a different approach, the ABR was recorded in the MLD paradigm in two experiments by Fowler and Mikami (1995). In the first experiment, binaural tone pips from 500–4000 Hz were presented in 103 dB peak SPL in 65 dB pressure spectrum density (PSD; dB SPL-10 log BW) of continuous noise in the MLD conditions of SoNo and SπNo. Responses to SoNo were subtracted from responses to SπNo, and results are shown in Figure 1 (upper panels) for the 500 and 4000 Hz signals. Within each panel are three responses: The top response is to SπNo, the second is to SoNo, and the third is the binaural phasic difference potential (BPD), which is the result of subtracting SoNo from SπNo. The BPD is large for 500 Hz but successively smaller for the higher frequencies and absent at 4000 Hz. Thus, BPD has the same frequency distribution as the behavioral MLD. These binaural ABRs, however, were similar to monaural ABRs that were recorded earlier to 500–4000-Hz tone pips in rarefaction and condensation modes in 65 dB PSD of noise (Fowler, 1992). In Figure 1, the lower panels show the monaural responses to 500 and 4000 Hz tone pips, which can be compared with the binaural responses in the upper panels. The top response is to rarefaction (R), the second is to condensation (C), and the third is the subtraction of the condensation from the rarefaction response, which gives the monaural phasic difference potential (MPD). Note the MPD is present for 500 Hz and absent for 4000 Hz, as was true for the BPD. Further note the nearly identical waveforms

Figure 1. Waveforms of the binaural (upper panels) and monaural (lower panels) auditory brainstem responses (ABRs) elicited by tone pips of 500 Hz (left panels) and 4000 Hz (right panels). For the binaural ABRs, the first waveform is the response to signals out of phase, noise in phase (SπNo), the second is the response to signals in phase, noise in phase (SoNo), and the third is the result of subtracting the SoNo from the SπNo waveform to form the binaural phasic difference potential (BPD), with the consistent peaks numbered. For the monaural ABRs, the first waveform is the response to rarefaction (R), the second is the response to condensation (C), and the third is the result of subtracting the condensation from the rarefaction waveform to form the monaural difference potential (MPD), with consistent peaks numbered. Note that the BPD and MPD are present only for the 500-Hz stimuli. Monaural: From "Effects of stimulus phase in the normal auditory brainstem response," by C. G. Fowler, 1992, *Journal of Speech and Hearing Research, 35,* p. 172. Copyright © American Speech-Language-Hearing Association. Adapted with permission. Binaural: From "Binaural phase effects in the auditory brainstem response," by C. G. Fowler and C. M. Mikami, 1995, *Journal of the American Academy of Audiology, 6,* p. 402. Copyright © American Academy of Audiology. Adapted with permission.



for the MPD and BPD at 500 Hz. The similarity is owing to the fact that the BPD actually includes the same response as the MPD as shown below for the tonal signals in the MLD conditions:

SπNo: rarefaction left ear + condensation right ear
SoNo: condensation left ear + condensation right ear

In this example, the left ear will show the phasic difference (rarefaction – condensation), but the right ear response will cancel (condensation – condensation). Each ear can be evaluated individually by choosing the ear that receives the out-of-phase signals.

The second experiment in Fowler and Mikami (1995) measured thresholds for 500-Hz tone pips in the same MLD paradigm as in the first experiment (above); these ABR thresholds were identical for the SoNo and SπNo conditions. Therefore, the ABR did not indicate the threshold differences between conditions that are required for the MLD. Last, a case example shows that the temporal coding in the brainstem is crucial for the MLD (Fowler & Mikami, 1995). The ABR MLD paradigm using a 500-Hz tone pip was given to a participant with MS who did not have a behavioral MLD. Results are shown in Figure 2. The BPD in the bottom waveform in the left panel has only four peaks whereas the BPD in the middle panel has the full complement of five peaks (although Peaks 4 and 5 appear abnormally large). The right panel includes the responses from a healthy individual for comparison. The original monaural ABR waveform from the case with MS was missing wave V on the left side, whereas all waves were normal on the right side. This situation is interpreted as a loss of synchrony coding in the left auditory system, which made between-ear comparisons faulty at higher levels in the brainstem and ultimately resulted in an absent behavioral MLD.

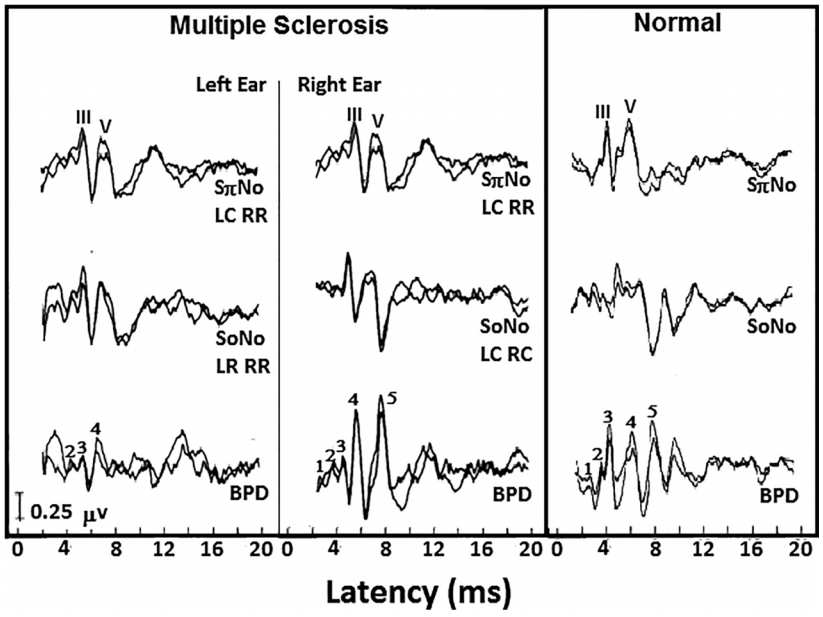
Auditory steady-state responses (ASSR) have also been evaluated as a possible physiological correlate for the MLD. Steady-state responses are evoked potentials elicited with amplitude-modulated (AM), frequency-modulated (FM), or a combination of AM and FM stimuli. The modulation rates can vary over a large range, producing responses that can be grouped into correlates of the transient early (> 70-Hz modulation), middle (20–69-Hz modulation), and late auditory (cortical) evoked responses (< 20-Hz modulation) (Herdman et al., 2002).

Wong and Stapells (2004) used the 80-Hz ASSR to search for the brainstem correlate and 7–13 Hz to search for the cortical correlate of the MLD. Discussed here are their findings for the brainstem response correlate. They obtained the ASSR with a carrier frequency of 500 Hz, 80-Hz amplitude modulation, and 100% modulation depth. The noise was 200 Hz wide and centered at 500 Hz. The signal was held constant and the masker was adjusted to mask the response. Behavioral MLDs were 8.5 dB for SoNo-SπNo and 10.5 dB for SoNo-SoNπ but only 0.9 dB for both conditions using the 80-Hz ASSR. These findings agree with those from the transient ABR.

Another response associated with the ABR is the frequency-following response (FFR), and that too has been used to test brainstem contributions to the MLD. The FFR is of interest because of its phase-locked response to low-frequency stimuli (Moushegian, Rupert, & Stillman, 1973). Generator sites for the FFR are still controversial, although long-held understanding is that the inferior colliculus is the predominant generator, at least with a vertical electrode montage (e.g., Bidelman, 2015; Smith, Marsh, & Brown, 1975). With the horizontal electrode montage, however, the FFR is predominantly from more peripheral generators, including the auditory nerve (Bidelman, 2015). In 2016, Coffey et al. (2016), using MEG, reported evidence of contributions to the FFR from the cochlear nucleus, inferior colliculus, medial geniculate, and auditory cortex.

J. R. Wilson and Krishnan (2005) used the FFR to investigate the contribution of brainstem generators to the

Figure 2. The auditory brainstem responses (ABRs) from an individual with multiple sclerosis (left and center panels) compared with the ABRs of a healthy control (right panel). The top waveforms resulted from the signals out of phase, noise in phase (SπNo) condition, the middle waveforms are from signals in phase, noise in phase (SoNo) condition, and the bottom waveforms are the binaural phasic difference potential (BPD) derived from the subtraction of SoNo waveforms from SπNo waveforms. For the individual with multiple sclerosis, the specific composition of the stimulus conditions is given, with the SπNo condition (LC RR = left condensation, right rarefaction) minus the SoNo condition (LR RR = left and right rarefaction for the left ear condition, and LC RC for the right ear condition) resulting in BPD. The left ear BPD is abnormal owing to the absence of Component 5. From "Binaural phase effects in the auditory brainstem response," by C. G. Fowler and C. M. Mikami, 1995, *Journal of the American Academy of Audiology, 6,* pp. 402 and 404. Copyright © American Academy of Audiology. Adapted with permission.



MLD. To be specific, they focused on the medial superior olive, which subserves location of low-frequency sounds via coincidence detector neurons that respond to interaural time/phase differences (Goldberg & Brown, 1968). They tested 15 young adults with normal hearing, but only nine participants met the criteria for the study. Signals were 90-ms (rise/fall = 10 ms) tone bursts presented at 56 dB SPL and 5.1/s in SoNo, SπNo, and SoNπ conditions. The noise masker was 1.5 kHz. In the behavioral study, the masker was manually controlled to mask the SoNo, SπNo, and SoNπ conditions. In the FFR study, the amount of noise from the behavioral SoNo condition was adjusted to reduce the FFR amplitude in the SoNo, SπNo, and SoNπ conditions to 50% of their initial amplitudes. Psychoacoustic MLDs tested in the nine participants averaged 6.74 dB for SoNπ and 9.53 for SπNo. For the corresponding FFR, only four participants had FFR MLDs averaging 5.00 dB in the SoNπ condition, and six participants had FFR MLDs averaging 2.58 dB in the SπNo condition. In this study, evidence for the FFR was weak at best, and did not correlate with the behavioral MLDs.

A second FFR study evaluated the FFR contributions to the behavioral MLD (Clinard, Hodgson, & Scherer, 2016). The researchers recruited 14 young adults with normal hearing and tested them with stimuli in SoNo, SπNo, and SoNπ conditions. The signal was 500 Hz embedded in 500-Hz narrowband noise. The electrode montage was vertical. Average behavioral MLDs for SoNo-SπNo were 10.03 dB and 8.29 dB for SoNo-SoNπ. Average FFR MLDs for SoNo-SπNo were −11.83 dB (a reverse MLD) and 1.83 dB for SoNπ. Analysis of the SoNπ and SπNo thresholds indicated that the larger amplitudes were associated with phase summation of the responses to the signal between ears, whereas the smaller amplitudes were associated with phase cancelation, and thus are peripheral effects. The responses to the noise (SoNπ) do not show this phase effect. This explanation likely also applies to J. R. Wilson and Krishnan's (2005) data.

In summary, the correlate to the behavioral MLD has not been found in the ABR using ABR, FFR, or ASSR at the high modulation rates that elicit brainstem responses. These three ways to stimulate the cochlear and brainstem neurons, however, all demonstrate the coding of temporal patterns that are prerequisite to the MLD. If confirmed, the contribution of the auditory cortex to the FFR-MLD will confound any purely brainstem interpretations of that particular response.

The Auditory Middle Latency Responses and the MLD

The next level in the auditory system to be investigated for evidence of the MLD is the AMLR, which occurs in the epoch from approximately 15–75 ms. The AMLR arises

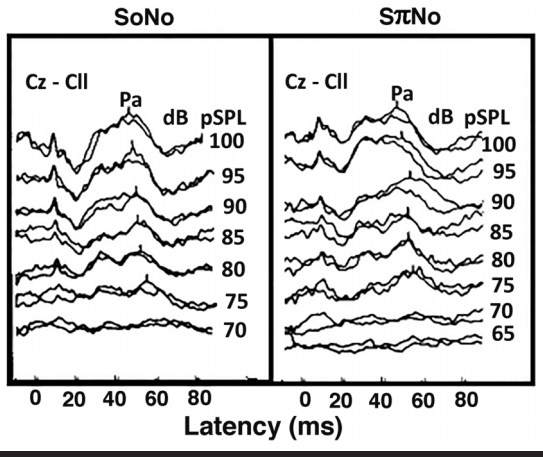
from the high brainstem, probably the midbrain or thalamus for Na, to the primary auditory cortex, with contributions from the reticular formation for Pa (Cacace & McFarland, 2009; Pratt, 2007). Fowler and Mikami (1996) evaluated the AMLR for evidence of the MLD using several vertical electrode arrays referred to CII (nape of neck), including Cz (vertex), T3 (left temporal area), and T4 (right temporal area), and also T3-T4 for a horizontal recording of the temporal areas. Thresholds among all these conditions were not different. Representative examples of threshold searches for one participant are shown in Figure 3. The top two panels show waveforms for Cz-CII with SoNo (left) and SπNo (right); both responses show thresholds at 75 dB SPL, as did the other conditions that are not shown. The T3-T4 horizontal condition had no response in most participants. The mean MLDs across all conditions ranged between −1–2 dB, except for the horizontal condition in which only two participants had responses; for the other participants, no waveforms were elicited. Hence, this study concluded that the MLD was not represented in the high brainstem to the primary cortex.

Two studies measured the ASSRs in MLD conditions. The 40-Hz ASSR is of interest because it has characteristics in common with the AMLR, including generator sites. Galambos and Makeig (1992) tested two listeners with 500 Hz modulated by 39.1 Hz at 35 dB SL. Their procedure had four steps: First, the stimulus was presented in quiet (Sm), and the listener reported hearing it. Second, ipsilateral noise was added (SmNm), and the listener no longer heard it. Third, the same noise was presented to the contralateral ear (SmNo), and the listener again reported hearing it. Fourth, the signal was added to the contralateral ear (SoNo), and the listener again no longer heard it. During this time, the 40-Hz ASSR was being recorded, but no response appeared in the recordings. The researchers concluded that the phase coherence measures were not related to the percept of the listeners, but rather to the physical stimulus.

In the second ASSR study, Ishida and Stapells (2009) tested 10 young adult listeners for evidence of the MLD in the 40-Hz ASSR. They used the same stimuli as for their previous study (Wong & Stapells, 2004), except that the modulation rate was 40 Hz. Behavioral MLDs were present in the listeners, but not in the 40-Hz ASSR. Neither the Galambos and Makeig (1992) nor the Ishida and Stapells (2009) studies, therefore, was able to demonstrate threshold differences for SoNo and SπNo with the 40-Hz steady-state response.

In summary, the three studies on the transient AMLR and the ASSR are consistent in supporting the lack of an MLD in the generators attributed to the high brainstem to the primary auditory cortex. Despite all listeners having behavioral MLDs, the eMLD was not elicited.

Figure 3. Representative examples of threshold searches for one participant for the auditory middle latency response. Pa. Both the signals in phase, noise in phase (SoNo; left panel) and signals out of phase, noise in phase (SπNo; right panel) conditions show thresholds at 75 dB pSPL. Cz = vertex; CII = nape of neck. From "Phase effects in the middle and late auditory evoked potentials," by C. G. Fowler and C. M. Mikami, 1996, *Journal of the American Academy of Audiology, 6,* p. 25. Copyright © American Academy of Audiology. Adapted with permission.



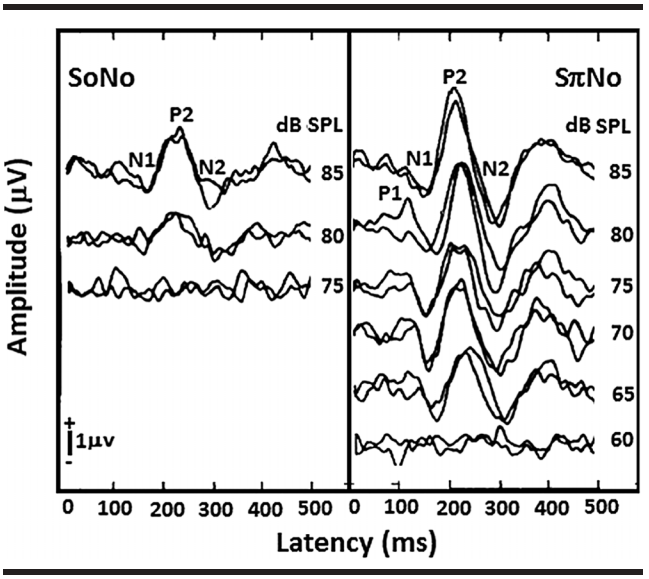
ALLRs and the MLD

The next higher level in the auditory system is the ALLR, which consists of waves P1, N1, P2, and N2 in the latency range of 50–250 ms. The origin includes the primary auditory cortex, auditory association area, frontal association area, and reticular formation (Stapells, 2009). Because of the origins, these potentials are also called cortical auditory evoked potentials. Presence of the potentials indicates that the representation of the sound has reached the areas that support cortical processing and perception, so they include more than just reflexive activity.

At the level of the ALLR, the eMLD is (finally) present. Fowler and Mikami (1992a) recorded the eMLD with 500-Hz tone bursts presented 0.5/s in quiet, narrowband (50 Hz) and wideband (600 Hz) noise. Thresholds for SoNo and SπNo were measured for P1, N1, P2, and N2, and MLDs were derived for each of these potentials by subtracting the thresholds for SπNo from SoNo. So and Sπ (in quiet) produced negligible differences for behavioral as well as electrophysiological responses, whereas MLDs were produced for both noise bandwidths. Figure 4 shows the SoNo (left panel) and SπNo (right panel) waveforms elicited by 500-Hz signals in the narrowband noise, and the potentials of interest are marked. Note that the SoNo threshold was 80 dB SPL and the SπNo threshold was 65 dB SPL, giving an eMLD of 15 dB. P1, seen on the SπNo waves, was shown to be the earliest evoked potential correlate of the eMLD. Of the late potentials, P1 also had the smallest eMLD by 2–4 dB. The generation site of the P1 has been identified as the primary auditory cortex (Reite, Teale, Zimmerman, Davis, & Whalen, 1988).

One of the characteristics of the behavioral MLD is the larger response to narrowband noise than to wideband noise, as shown in the Fowler and Mikami (1992a) study

Figure 4. Examples of the auditory late latency electrophysiological masking level difference recorded from a representative participant. The stimulus was 500 Hz in narrowband (50 Hz) centered at 500 Hz. SoNo responses are in the left panel, and SπNo responses are in the right panel. The masking level difference is the difference between the thresholds of signals in phase, noise in phase (SoNo; 80 dB SPL) and signals out of phase, noise in phase (SπNo; 65 dB SPL), or 15 dB. From "Effects of noise bandwidth on the late-potential masking level difference," by C. G. Fowler and C. M. Mikami, 1992a, *Electroencephalography and Clinical Neurophysiology, 84,* 57–163. Adapted with permission.



described above. The behavioral MLD with the narrow bandwidth was 9 dB and eMLDs from P1, N1, P2, and N2 were 9–13 dB, with the largest eMLD shown by P2. The behavioral MLD with the wideband noise was 6 dB and the eMLDs ranged from 4–5 dB, with the larger eMLDs shown by P2 and N2. This pattern of response was demonstrated in all individual listeners. The largest eMLDs for the narrow bandwidth of noise were consistent with the behavioral MLD data of Hall and Harvey (1985).

Other characteristics of the MLD were tested with similar stimuli, but this time using the only the 500-Hz narrowband noise in order to obtain the largest eMLDs. Fowler and Mikami (1992b) recorded SoNo and SπNo conditions with a 500-Hz signal in increasing noise levels from 0 to 60 dB PSD. At each noise level, 500-Hz signals were reduced in 10-dB steps at high levels and in 2-dB steps near threshold until no response appeared in two repetitions at a single level. The eMLDs were shown to increase linearly with noise level with a slope of approximately 2.3 dB/10 dB until an eMLD of 14 dB was recorded in 60 dB PSD of noise. The functions for SoNo and SπNo also were linear, with the SoNo function being steeper than the SπNo function. The values correspond well to the functions for the behavioral MLD data of Hall and Harvey (1985), although the functions were slightly shallower for the electrophysiological data. The electrophysiological functions did not reach the high-level plateau that was observed in Hall and Harvey. The electrophysiologic data, however, were consistent with the behavioral MLDs recorded in other studies (Durrant, Nozza, Hyre, & Sabo, 1989), which also did not reach a plateau for increasing levels of noise.

According to Hirsh (1948), the largest MLD is SoNo-SπNo, but other stimulus configurations produce smaller MLDs when referenced to SoNo. Some of these configurations include SmNo, SmNπ, SπNπ, SoNπ, and SπNo. Jeffress, Blodgett, Sandel, and Wood (1956) added the monaural condition (SmNm), which had the highest threshold. The same conditions were tested with the eMLD in order to compare the eMLD hierarchy with Hirsh's behavioral MLD hierarchy. The eMLDs were determined by the subtraction of thresholds of the different stimulus conditions from the SoNo threshold (Fowler & Mikami, 1996). The rank order of the MLD magnitudes was the same for both the electrophysiological and behavioral derivations in the Fowler and Mikami (1996) study and matched the rank order for the behavioral data from Hirsh (1948) and Jeffress et al. (1956). Table 1 shows the specific MLDs obtained in the same descending order thresholds that were obtained in the two behavioral studies. This study revealed that the smaller MLDs from the family of MLDs could be recorded with the eMLD in individual participants.

Another characteristic of the behavioral MLD is the suprathreshold loudness differences generated by SπNo and SoNo stimuli, with SπNo sounding louder than SoNo at equal signal-level conditions (Townsend & Goldstein, 1970). In a similar manner, for the eMLD, at equivalent SPLs, the P2 amplitude for SπNo was larger than for SoNo in each of the eMLDs recorded with the auditory late latency MLDs (e.g., Fowler & Mikami, 1996). These suprathreshold amplitude differences are consistent with the results of the behavioral loudness balancing tests.

The ASSR with low modulation frequencies (< 20 Hz) are thought to have cortical generators (Herdman et al., 2002). Therefore, Wong and Stapells (2004) used 500-Hz tones with 100% modulation depth and modulation frequencies of 7 and 13 Hz to search for the cortical MLDs. Eleven young adults were participants. The mean MLD for SoNo-SπNo was 9.3 dB for behavioral responses and 5.8 dB for the ASSR. In contrast, however, the SoNo-SoNπ MLD was 8.7 dB for behavioral responses, but only 1.5 dB for the ASSR. Hence, the cortical ASSR behaves differently from the transient ALLR. The authors conjectured that this finding may indicate that different neural pathways are involved for the transient and steady-state recordings. Further research will have to resolve this issue.

Another stimulus used to elicit the behavioral MLD is speech, as described by Licklider (1948). He reported that 50 phonetically balanced words in binaural noise were more intelligible when the words were 180° out of phase as opposed to in phase between ears (SoNo vs. SπNo). Other combinations of speech and noise between ears also produced MLDs, but these MLDs were smaller than in the (SoNo-SπNo) condition. Licklider's article suggested that the central auditory system was critical to speech perception in noise, and so was critical to the generation of the speech

Table 1. Mean auditory late latency response (ALLR) electrophysiological masking level differences (eMLDs) and behavioral MLDs from Fowler and Mikami (1996) compared with the behavioral MLDs from Hirsh (1948) and Jeffress et al. (1956).

	Fowler & Mikami (1996)		Hirsh (1948)	Jeffress et al. (1956)
Stimulus	eMLDs (dB)	Behavioral MLDs (dB)	Behavioral MLDs (dB)	Behavioral MLDs (dB)
SoNo-SmNm	0	0	DNT	0
SoNo-SπNπ	–1	–1	–1	DNT
SoNo-SmNo	4	1	6	DNT
SoNo-SoNπ	9	5	9	DNT
SoNo-SπNo	11	7	11	DNT

Note. SoNo = signals in phase, noise in phase; SmNm = signals monaural, noise monaural; SπNπ = signals out of phase, noise out of phase; DNT = did not test; SmNo = signal monaural, noise in phase; SoNπ = signals in phase, noise out of phase; SπNo: signals out of phase, noise in phase. From "Phase effects in the middle and late auditory evoked potentials," by C. G. Fowler and C. M. Mikami, 1996, *Journal of the American Academy of Audiology, 6,* p. 25. Copyright © American Academy of Audiology. Adapted with permission.

MLDs. In a similar manner, threshold measures of the ALLR to speech signals (nonsense syllables) in the SoNo and SπNo conditions have been shown to produce a speech evoked eMLD (Fowler & Wilson, 2016), which is smaller than the 500-Hz tone evoked eMLD (Leigh, Fowler, Ireland, & Spencer, 2014). These newest findings confirm Licklider's statement of the necessity of cortical input for the behavioral speech MLD, although it is not clear if the precise cortical generators are different for the tone and speech evoked MLDs as tested in these studies.

The MLD is clinically applied to determine the condition of the auditory nervous system in cases of eighth nerve/brainstem lesions and central auditory deficits. Noffsinger, Schaefer, and Martinez (1984) showed eMLD results for a patient with MS who had no behavioral MLD. The eMLD for this patient showed equal thresholds for SoNo and SπNo, and those thresholds were equal to the SoNo thresholds of normal participants. Unfortunately the researchers were unable to complete other tests to determine where in the auditory system the disruption occurred.

A psychophysical phenomenon that is related to the MLD is the comodulation release from masking. In this situation, if both a target signal and noise are coherently modulated, a release of masking will occur that yields thresholds that are lower than if the noise is not modulated. Androulidakis and Jones (2006) measured auditory late latency potentials (N1 and P2) to 1000 Hz in four conditions. The tone was first presented in quiet, second with random noise, and third and fourth with two bandwidths of comodulated noise. The N1 and P2 were present to 1000 Hz in quiet and in the two comodulated conditions but not in the random noise, demonstrating a release from masking in the comodulated conditions. Thresholds were not measured. Ernst, Uppenkamp, and Verhey (2010) replicated the comodulation release from masking, and used functional magnetic resonance imaging (fMRI) to document the cortical area involved. They reported that the difference in audibility in the signal-to-noise ratio between modulated and unmodulated signals was localized specifically to the antero-lateral part of Heschl's gyrus.

In summary, the eMLD is evoked with the ALLR and has been confirmed as equivalent to the behavioral MLD in all the ways that have been investigated. Both behavioral and eMLDs require noise, and higher levels of noise produce larger MLDs. Both types of MLDs are larger for low-frequency signals than for high-frequency signals. Both types of MLDs are larger with narrowband noise than with wideband noise, and both have the same hierarchy of size with various alternate combinations of signal and noise between ears. Both MLDs are disrupted with pathological conditions that reduce the synchrony of responses in the ABR pathways. The full MLD phenomenon, however, requires cortical processing as indicated by the eMLD.

Auditory Evoked Magnetoencephalography and Functional Magnetic Resonance Imaging Studies

Attempts have recently been made to localize the origin of the MLD using other techniques, specifically auditory MEG and fMRI. MEG records dendritic electrical field responses in time frames similar to the ALLR waves and uses similar terminology (with the addition of an "m") for the elicited waves. Unlike AEP, the MEG recordings are not distorted by passing through tissues, skull, and scalp. Because MEG collects data from sources tangential to the plane of the cortex, it is sensitive to sources in sulci, including the auditory cortex. The magnetic fields are small, with minimal spread, allowing recordings from the individual cortices (Jacobson, 1994). Sasaki et al. (2005) studied the MLD with MEG to characterize the late potential correlate, N1m. Behavioral and MEG responses were recorded to SoNo and SπNo conditions for stimulus frequencies 250, 1000, and 4000 Hz. In both types of recordings, MLDs of 20 dB for 250 Hz and smaller MLDs for the higher frequencies were recorded. They also reported that the right hemisphere produced larger responses than the left hemisphere, which has not been reported in the ALLR recordings. The N1m was localized to the auditory cortex for all conditions in which the participants were able to hear the signals (Sasaki et al., 2005).

Another approach to document origins of the MLD was described in fMRI studies. Uppenkamp, Uhlig, and Verhey (2013) reported MLD correlates with fMRI, which demonstrated activation of the lateral Heschl's gyrus in response to the audibility of signals in noise. Wack et al. (2012), also using fMRI, demonstrated brain areas involved with the MLD by subtracting activation in diotic conditions from activation in dichotic conditions. Thus, the MLD was shown to involve activation of the pulvinar thalamus, insula, and corpus callosum. Therefore, Wack, Polak, Furuyama, and Burkard (2014) used fMRI and diffusion tensor imaging to show fiber connectivity during MLD tasks. They found both excitatory and inhibitory activity in the auditory cortex, and showed involvement as low as the inferior colliculus. Although they did not record at threshold levels for the MLD conditions, they noted that increasing neural activity was associated with lower level signals.

Some studies have attempted to document the areas of the brain underlying the MLD using naturally occurring lesions and MEG recordings. Hughes et al. (2014) used MEG to test 13 individuals with progressive supranuclear palsy with atrophy in the midbrain beginning at the level of the inferior colliculus. Overall, the N1m and P2m responses in the patients were smaller and delayed compared with the responses of controls, but these reductions occurred in both SoNo and SπNo conditions, and the MLD phenomenon was preserved.

Epilepsy is a cortical disorder that also may affect the MLD. Gascoyne (2015) used MEG to evaluate 10 individuals with epilepsy originating from various areas of the brain, including temporal, parietal, frontal, and occipital lobes. Because they did not actually record SoNo and SπNo thresholds, results were described qualitatively in terms of degree of binaural unmasking. Nine of the 10 patients had abnormalities in unmasking, ranging from small responses bilaterally to hemispheric asymmetries; the results, however, were not correlated with the site of lesion (Gascoyne, 2015).

In summary, the MEG, MRI, and lesion studies have generally supported auditory cortical activation by the MLD. Sasaki et al. (2005) specifically localized the MLD in the right hemisphere. Results from lesion studies have not been consistent, primarily due to the nature of the lesions. One study found abnormalities in the MEG MLD in individuals with epilepsy, but the abnormalities were not related to the site of the lesion.

Spatial Hearing and Cortical Input

The requirement for cortical input for the MLD puts it in the company of other psychophysical phenomena that are known to have cortical connections. *Spatial hearing,* a binaural function that occurs in complex auditory environments, incorporates the MLD as one component. Kotelenko, Fed'ko, and Shustin (2000) studied spatial localization in 29 patients with cortical epilepsy, including 13 who had lesions in the temporal lobe, seven in the frontal lobe, and 12 with underlying space-occupying lesions. All patients had disorders of spatial hearing, with the degree of impairment depending on the location and extent of involved tissue. Zatorre and Penhune (2001), however, recruited 13 patients with excised focal lesions, five with left focal hemisphere lesions and eight with right focal hemisphere lesions. All patients participated in tests of spatial localization. Results demonstrated that the individuals with right hemisphere lesions had bilateral spatial localization deficits, whereas the individuals with left hemisphere lesions had virtually no localization deficits. The difference between epileptic lesions with broader effects compared with focal lesions may explain the different results from the two studies. Medication to control the epileptic seizures may also have affected the results of the first study.

The MLD, supported by the studies on spatial localization, suggests a role for the corpus callosum. The Sasaki et al. (2005) MEG MLD study indicated that the right hemisphere has greater responses than the left hemisphere for the MLD. That study is substantiated by the Zatorre and Penhune (2001) study that also showed the dominant role of the right hemisphere in spatial localization. Further, Wack et al. (2012) in their fMRI MLD study, noted corpus callosum activity in the response to the dichotic stimuli. These studies suggest a dominant role for the right hemisphere in both the MLD and spatial location. They also hint at a role for the corpus callosum, which has not yet been studied. All stimuli were click or tonal stimuli, which undergo processing in the right hemisphere. Given that speech signals undergo processing in the left hemisphere in most individuals, MEG and MRI studies on the MLD elicited by speech signals are needed to determine if the task or the type of signal is responsible for the cortical place for processing.

Conclusions

According to the electrophysiological data, the MLD includes auditory processing from the periphery to higher cortical areas. The ABR functions to code temporal aspects of the signals and transmit them to higher centers. In the brainstem, any lesion that disrupts the neural synchrony *before* the input to the binaural system can reduce or eliminate the MLD. This finding corroborates the importance of the healthy brainstem in the generation of the MLD. The brainstem, however, is not sufficient for the threshold differences that define the MLD; for that, cortical function, including the primary auditory cortex, is necessary. Newer techniques, including MEG and fMRI, are shedding new light on the MLD. Several studies using these techniques have already been published, and others undoubtedly are on the horizon. More studies using participants with normal brain function and cortical lesions are needed to clarify the specific cortical areas involved in the MLD, and what reorganization occurs with recovery. Both evoked potential and imaging tests can build upon the studies already in the literature. With various techniques tracing the pathways of excitation and suppression through the auditory neural system, the full course of the MLD may finally be realized.

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