

Nonprimary Auditory Thalamic Representation of Acoustic Change

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SUMMARY AND CONCLUSIONS

1. The mismatch response, or mismatch negativity (MMN), is a neurophysiologic response to stimulus change. In humans and other animals, the MMN may underlie the ability to discriminate acoustic differences, a fundamental aspect of auditory perception.

2. This study investigated the role of the thalamus in the generation of a tone-evoked MMN in guinea pigs. Electrodes were placed in the caudomedial (nonprimary) and ventral (primary) subdivisions of the auditory thalamus (medial geniculate nucleus). Surface epidural electrodes were placed at the midline and over the temporal lobe. The MMN was elicited by a deviant stimulus (2,450-Hz tone burst) embedded in a sequence of standard stimuli (2,300-Hz tone bursts).

3. A tone-evoked MMN was present in nonprimary thalamus but was absent in the primary thalamus. Surface-recorded MMNs were measured at the midline but not over the temporal lobe. The correspondence between nonprimary thalamic responses and midline surface potentials, and between primary thalamic responses and temporal surface potentials, is consistent with data reported for the auditory middle latency responses in guinea pigs.

4. The results demonstrate that the nonprimary auditory thalamus contributes to the generation of a tone-evoked MMN in the guinea pig. Furthermore, the data indicate that the guinea pig is a feasible model for investigating central auditory processes underlying acoustic discrimination.

INTRODUCTION

This study examined, in an animal model, how portions of the primary and nonprimary auditory thalamocortical pathways contribute to the processing of stimulus contrasts, as reflected by the tone-evoked mismatch response, or mismatch negativity (MMN). The MMN is an evoked response that reflects the neurophysiologic processing of stimulus differences—an important aspect of auditory perception.

Neural responses to stimulus change as reflected by the MMN evoked response

The discrimination of acoustic change is fundamental to the categorization and recognition that are necessary for deriving meaning from sound. Change, in contrast to continuity, is representative of the natural acoustic environment, where variations in auditory signals are the salient features of meaningful stimuli.

The MMN is an event-related potential that is elicited by acoustic change. In humans, it occurs roughly 200 ms after stimulus onset. It is elicited by a physically deviant stimulus occurring in sequence with a series of homogenous stimuli (Näätänen et al. 1978). The MMN reflects the processing of differences in acoustic stimuli, occurring when a deviant signal differs from the standard by any detectable amount, including when the difference between the stimuli is near the psychophysical threshold for discrimination (Kraus et

al. 1993a; Näätänen 1986, 1990, 1992; Sams et al. 1985). MMN has been obtained in response to frequency, intensity, duration, spatial, and phonemic changes (Aaltonen et al. 1987; Ford and Hillyard 1981; Kaukoranta et al. 1989; Kraus et al. 1993a–c; Näätänen 1990; Näätänen et al. 1987, 1989a; Nordby et al. 1988; Novak et al. 1990; Paavilainen et al. 1989; Sams and Näätänen 1991; Sams et al. 1985; Sharma et al. 1993; Snyder and Hillyard 1976). Consequently, it appears that the MMN reflects a neuronal representation of the discrimination of numerous acoustic attributes.

The MMN is elicited passively, not requiring attention or a behavioral response (Näätänen 1990; Novak et al. 1992). It has been obtained during sleep in infants and adults (Alho et al. 1990; Nielsen-Bohlman et al. 1988) and during wakefulness, sleep, and barbiturate anesthesia in animal models (Csépe et al. 1987; Javitt et al. 1992; Kraus et al. 1994; Steinschneider et al. 1994). These studies suggest that the MMN is an automatic, preattentive response to stimulus change. As such, the MMN may provide a clinical tool for the objective evaluation of central auditory function. Consequently, it is important to understand the MMN generating system to use this response most effectively.

In humans, evoked potentials and magnetoencephalographic (MEG) studies utilizing tonal stimuli point to the existence of two major sources for the MMN—the supratemporal plane and the frontal cortex (Alho et al. 1992; Giard et al. 1990; Hari et al. 1984; Javitt et al. 1992; Kaukoranta et al. 1989; Näätänen and Picton 1987; Näätänen et al. 1978, 1980, 1989; Novak et al. 1990; Ritter et al. 1982, 1992; Sams et al. 1991; Scherg and Picton 1990; Simson et al. 1977; Vaughan et al. 1980). In addition, intracranial recordings in the cat suggest that the MMN may receive contributions from thalamus and hippocampus (Csépe et al. 1987).

Primary/nonprimary auditory thalamo-cortical pathways

A fundamental organizing principle of pathways within the auditory system is that of primary and nonprimary systems (Galambos et al. 1950; Imig and Morel 1983, 1988; Winer 1992, reviews). That the auditory pathway involves at least two systems is a consistent finding not only in studies of neural connections but also in studies of cell morphology (Winer 1992; Winer and Morel 1983), single neuron physiologic responses (Calford 1983; Calford and Aitkin 1983; Morel 1964; Schreiner and Cynader 1984; Clarey et al. 1992, review), and evoked responses (Kraus et al. 1988; McGee et al. 1992; Kraus and McGee 1993, review). Terminology other than primary versus nonprimary also has been used to describe the subsystems including: specific versus nonspecific, extrinsic versus intrinsic, core versus belt, lem-

niscal versus extralemniscal, as well as the distinctively auditory terms of cochleotopic versus diffuse systems (Andersen et al. 1980; Winer and Morest 1983).

The primary pathway is characterized by neurons that respond only to auditory stimuli, show good frequency tuning, are tonotopically arranged, and time lock well to stimulus characteristics (Calford 1983; Clarey et al. 1992, review). It includes the ventral division of the medial geniculate body (MGv) and primary auditory cortex (AI and AAF). In contrast, nonprimary pathway neurons are sensitive to multimodality inputs, show broad tuning, are less time locked, and are more likely to demonstrate plasticity (Brugge 1992, review; Edeline and Weinberger 1992; Kraus and Disterhoft 1982; Rouiller et al. 1989). Considered here as "nonprimary" are the nontonotopic (involving MGd and AI) and polysensory (MGm and multiple cortical fields) thalamo-cortical systems described by Andersen et al. (1980). In the cat, this includes the magnocellular (MGm) and dorsal (MGd) divisions. In the guinea pig, it includes the caudomedial (MGcm) portion and the shell nucleus (MGs), (Redies et al. 1989a,b) and dorsal divisions (Edeline and Weinberger 1991). These regions project to areas outside AI, receive multisensory inputs, contain cells common to the reticular formation, and are thought to subserve integrative (not primary) processing functions (Morest 1964; Winer 1991). The nonprimary auditory cortical areas show reciprocal connections with tonotopic cortical areas and/or frontal, parietotemporal, and paralimbic areas (Irvine and Phillips 1982; Pandya and Yeterian 1985; Winer 1992). Recently, a similar dichotomy of pathways has been demonstrated in the rat (Simpson and Knight 1993a,b).

The relative roles of primary and nonprimary auditory pathways in the MMN generating system remain to be determined. The postulation of primary auditory cortex involvement has been based on recordings within AI of the monkey (Javitt et al. 1992; Steinschneider et al. 1992), MEG topography (Hari et al. 1984), and data indicating a polarity reversal of MMN over the Sylvian fissure (Alho et al. 1986). Topographic and dipole source analysis of MEG data in humans implicate nonprimary auditory cortex (Csépe et al. 1992; Scherg and Picton 1990; Scherg et al. 1989).

Guinea pig model of thalamo-cortical pathways

The relative contributions of subcomponents of the auditory thalamo-cortical pathways to auditory evoked potentials recorded within the first 100 ms after stimulus onset have been investigated previously using the guinea pig model (reviewed in Kraus and McGee 1993). Two distinct epidural auditory evoked potential morphologies have been identified, one recorded over the temporal cortex and the other recorded over the posterior midline. These waves, referred to as "temporal" and "midline" components, appear to be mediated by distinct generating systems that differ neuroanatomically, functionally, and developmentally (Kraus and McGee 1992; Kraus et al. 1988; Littman et al. 1992). Pharmacological inactivation of subdivisions of the medial geniculate body (ventral, MGv; and caudomedial, MGcm portions) has revealed that the primary sensory pathway (MGv) selectively contributes to the temporal re-

sponse, whereas the nonprimary afferent input (MGcm) contributes to both temporal and midline responses (McGee et al. 1991, 1992). The mesencephalic reticular formation appears to influence both components (Kraus et al. 1992).

In this study, we apply a previously developed experimental approach to investigate primary versus nonprimary auditory pathway contributions to the MMN generating system. The guinea pig model was used because the role of these pathways can be delineated with relative simplicity. Previous work on evoked potential generating systems suggests that this model, despite certain limitations, can be used effectively to examine the contributions of primary/nonprimary pathways to the generation of the mismatch response.

METHODS

Subjects and electrode placement

Twenty-two guinea pigs, weighing ~350 grams, were used as subjects. Animals were anesthetized with ketamine hydrochloride (100 mg/kg) and xylazine (7 mg/kg) and maintained at a body temperature of $37 \pm 1^\circ\text{C}$. Smaller doses (15 mg/kg of ketamine; 3 mg/kg of xylazine) were administered as needed for the rest of the experiment, typically hourly.

Epidural silver bead electrodes (0.5-mm diam) were used to record the surface responses as previously described (Kraus et al. 1988). Recordings were made over the posterior midline and from the temporal lobe contralateral to the stimulated ear (referred to as midline and temporal sites). The position of the temporal electrode was approximately over the dorsal portion of primary auditory cortex, as described by Redies and colleagues (1989a). An electrode placed 15 mm rostral to bregma and 1 mm lateral to the sagittal suture served as the reference.

Within the MG, a high-impedance (500 k Ω , 35- μ tip) microelectrode was positioned stereotaxically as described by McGee et al. (1991). Coordinates for the MGv were 4.8 mm rostral, 3.8 mm lateral, and ~7.5 mm ventral from the midpoint of the interaural line. Coordinates for the MGcm were 4.4 mm rostral, 3.5 mm lateral, and ~7.8 mm ventral. The ventral measurement was varied in each animal to obtain the best quality recordings.

Stimuli and response recording

Tone bursts (70-ms duration; 5 ms rise/fall times) were delivered monaurally to the right ear through insert earphones at 75 dB SPL, at a rate of 1.9/s. The recording window included a 70-ms prestimulus period and 180 ms of poststimulus time, with an A/D sampling rate of 2,048 points/s (0.488 ms/point). Evoked responses were analog bandpass filtered on-line from 0.1 to 100 Hz (12 dB/octave), and baseline adjusted to the prestimulus baseline.

MISMATCH CONDITION. The MMN was elicited by deviant stimuli (2,450 Hz) presented in a sequence of standard stimuli (2,300 Hz). Deviant stimuli occurred with a probability of 10%. Stimuli were presented in a pseudorandom sequence with at least three standard stimuli separating presentations of deviant stimuli. Although 2,500 standard stimuli were presented, only the responses to the standard just preceding the deviant were averaged into the standard response. Thus the same number of sweeps contributed to the averaged standard and deviant responses ($n = 250$).

ALONE CONDITION. By definition, the MMN is a response to stimulus change. It occurs only when the deviant stimulus is presented in the context of standard stimuli. The evoked response to the 2,450-Hz stimulus presented alone should not elicit a mismatch response (Alho et al. 1986; Kraus et al. 1992). Therefore, at each recording location, the response to the 2,450-Hz tone pre-

sented alone ($n = 250$) was compared with the response to that same stimulus when it occurred in the mismatch condition.

The MMN is best viewed in a difference wave computed by subtracting the average response to the standard stimulus from the response to the deviant stimulus. Likewise, a difference wave was computed by subtracting the response to the deviant-alone stimulus from the average response to the deviant stimulus when presented in the oddball paradigm. The morphologies of the standard, deviant, deviant-alone, and difference waveforms (deviant minus standard, deviant minus deviant-alone) were examined.

Data analysis

Grand averages were computed across animals for each recording location. Grand averages of the difference waveforms (deviant minus standard, deviant minus deviant alone) were calculated. Using the average responses of each animal as the data set, point-to-point t tests were performed comparing deviant versus standard responses and deviant versus deviant-alone responses (see Kraus et al. 1993a,b). In other words, using the individual grand average difference waves as a data set, one-tailed t tests were performed on corresponding points to determine whether the point was significantly less than the zero baseline.

The legitimacy of utilizing an interval of significance has been discussed by Guthrie and Buchwald (1991). Multiple t tests can result in spurious significant values and, because adjacent points in the waveform are highly correlated, spurious significant values may occur across short intervals. Using autocorrelation techniques on P300 waveforms, Guthrie and Buchwald (1991) concluded that a significance interval of ≥ 12 sampling points was required to be considered a significant response. Autocorrelations of guinea pig responses from the depth and surface sites showed that over an interval of 12 points (5.8 ms), regression coefficients among points fell to well below 0.6. Within 30 points (14.5 ms), regression coefficients were < 0.2 . A conservative criterion was imposed for this study: an interval of significance of ≥ 20 ms was required to be considered a valid mismatch response.

Histology

Medial geniculate recording locations were marked with electrolytic lesions ($35 \mu\text{A}$ for 10 s). Brains were cut in $17\text{-}\mu$ coronal sections and stained with Klüver stain, which permits visualization of cell bodies and fiber pathways.

RESULTS

Medial geniculate body

In the medial geniculate body of thalamus, recordings were obtained from MGv ($n = 13$) and MGcm ($n = 9$), contralateral to the stimulated ear. MG recording locations are shown in Fig. 1. Concurrently, surface responses were recorded from the temporal lobe contralateral to the stimulated ear and from the posterior midline.

Significant negativities were identified in the MGcm difference waves but not in the difference waves recorded from MGv. Grand average responses to standard and deviant stimuli recorded from the MGcm and MGv are shown in Fig. 2 (*top*). Significant differences between the responses to standard and deviant stimuli are indicated by the box under the difference wave. These deflections (at 30–80 ms and 135–170 ms) in the MGcm response were defined as the MG MMN.

The MG responses are shown for the alone condition in Fig. 2 (*bottom*). Grand average responses to the deviant stimulus (2,450 Hz) when it was presented alone are shown for comparison with the response to the same stimulus when it occurred in the mismatch condition. The negative deflection occurred in response to the 2,450 Hz stimulus only when it was the deviant stimulus in the mismatch condition. In the MGcm, there was a significant difference between the response to the 2,450-Hz stimulus in the mismatch and alone conditions. In the MGv, the response to 2,450 Hz was the same in both conditions, again indicating that a mismatch response was absent at this location.

Epidural surface responses

A significant mismatch negativity occurred in the midline surface waveform between 30 and 180 ms, whereas no significant mismatch response was evident in the surface temporal response until 150 ms. The deviation from baseline in the temporal response at ~ 20 ms was not significant. Grand average responses to standard and deviant stimuli recorded from the surface midline (*left*) and surface temporal (*right*) locations are shown in Fig. 3 (*top*).

Figure 3 (*bottom*) illustrates the alone condition. Grand average responses to the 2,450-Hz stimulus presented alone and in the mismatch paradigm are shown. The MMN occurs in response to the 2,450-Hz stimulus only in the mismatch condition. At the midline, there was a significant difference between the response to 2,450 Hz in the mismatch and alone conditions. Over the temporal lobe, the response to 2,450 Hz was essentially the same in both conditions ≤ 150 ms, again indicating that a mismatch response was absent until ~ 150 ms.

In summary, the MMN was seen in both the MGcm and the midline surface responses. No MMN was apparent in the MGv difference wave, and a mismatch response was observed in the temporal epidural response only at latencies > 150 ms.

DISCUSSION

These results establish the feasibility of the guinea pig model for investigation of the generating system underlying the processing of acoustic stimulus contrasts. A tone-evoked mismatch response was present in the nonprimary subdivision (MGcm) of the auditory thalamus and was absent in the primary subdivision (MGv). Similarly, there was a mismatch response in the surface potentials recorded at the midline at a latency corresponding to the MGcm response, but no mismatch response over the temporal lobe until 150 ms after stimulus onset. The correspondence between MGcm and midline surface responses, and between MGv and temporal surface responses, is consistent with correspondences seen in middle latency responses recorded from the same animal model (reviewed in Kraus and McGee 1993).

Generators of the mismatch response

Auditory thalamic contribution to the MMN is consistent with results reported in the cat (Csépe et al. 1987). New data provided by this study indicate that the thalamic contribution involves the nonprimary, not the primary subdivision of the MGB. The occurrence of a mismatch response

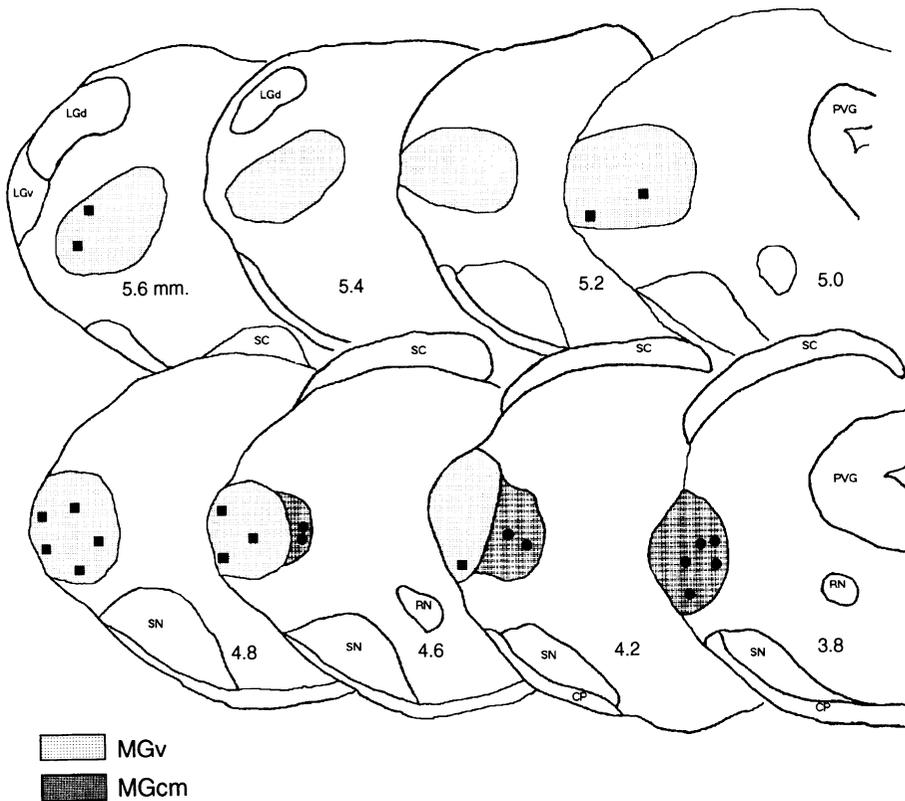


FIG. 1. Recording locations within the medial geniculate body of thalamus, ventral (MGv) and caudomedial (MGcm) subdivisions (MGv, $n = 13$; MGcm, $n = 9$). Measurements are millimeters rostral to interaural line. LGd, dorsal division of lateral geniculate; LGv, ventral division of lateral geniculate; PVG, periventricular gray; SN, substantia nigra; RN, red nucleus; CP, cerebral peduncle.

over the midline epidural site is also consistent with a nonprimary pathway origin (Kraus et al. 1988; McGee et al. 1992). Human studies on MMN generators (Csépe et al. 1992; Scherg and Picton 1990; Scherg et al. 1989) also have demonstrated nonprimary origins for the MMN. Mismatch responses recorded from the upper cortical layers of primary auditory cortex (AI) in the monkey (Steinschneider et al. 1992) and cat (Karmos et al. 1986) possibly reflect contributing input from nonprimary areas. Connectivity patterns linking these AI cortical layers with nonprimary auditory cortical and thalamic fields (Mitani et al. 1987; Niimi et al. 1984; Ojima et al. 1993; Rouiller et al. 1989) would seem to support this hypothesis.

How the MGcm mismatch response corresponds to the surface-recorded MMN is still at issue. Most human studies of the MMN generating system have pointed to a cortical origin for the response (Karmos et al. 1986; Scherg et al. 1989; Steinschneider et al. 1994; Tiitinen et al. 1992). The latency of the guinea pig thalamic MMN, which may be as much as 180 ms, would suggest that the underlying mechanisms incorporate cortical feedback. The likelihood of cortical involvement also is supported by the appearance of a mismatch response at the surface temporal location at 150 ms. Whether MGcm is an MMN generator site, whether it provides essential input to an MMN generator located in auditory cortex, or whether it simply reflects processing from more peripheral sites requires further investigation.

Previous investigations in humans have pointed to the existence of two MMN components (Giard et al. 1992; Novak et al. 1990; Paavilainen et al. 1991; Scherg et al. 1989). Based on dipole localization studies, Scherg et al. (1989) suggested that the origin of MMNa is from primary auditory cortex, whereas MMNb is localized to nonprimary auditory cortex. MMNa precedes MMNb in latency, but the

two overlap. Significantly, MMNa is observed in response to large differences between standard and deviant stimuli whereas MMNb is seen to small stimulus differences. Two components discussed by Novak et al. (1990) and Paavilainen et al. (1991) similarly are distinguished by degree of stimulus contrast. Paavilainen and associates specifically categorize the MMNa as an N1 enhancement possibly because of habituation effects. Our data indicate that the mismatch response involves the nonprimary auditory pathway and extends Scherg's findings to include the nonprimary auditory thalamus. The stimulus differences in the present study were close to what Scherg considered small (150 Hz), thus Scherg's MMNa should not be apparent. Whether a mismatch response would have been observed in MGv with larger stimulus differences remains, nevertheless, a possibility, and would be consistent with MMNa being an N1 enhancement.

Neuronal processes underlying the MMN

There has been considerable interest in determining the neural processes represented by the MMN. The "habituation" and "memory trace" hypotheses have been debated. Ritter et al. (1992) varied stimulus sequencing and concluded that the MMN is a response to change, not repetition, and therefore is a reflection of memory trace. Näätänen (1990; Näätänen et al. 1989) also concluded that the MMN is a memory process. Our study does not speak directly to this issue because sequencing was not varied. Neurons with habituating properties have been linked to the extralemniscal thalamus (Calford 1983) and nonprimary auditory cortex (Irvine and Huebner 1979). The fact that a mismatch response was observed in the nonprimary auditory pathway links it by inference to the habituation

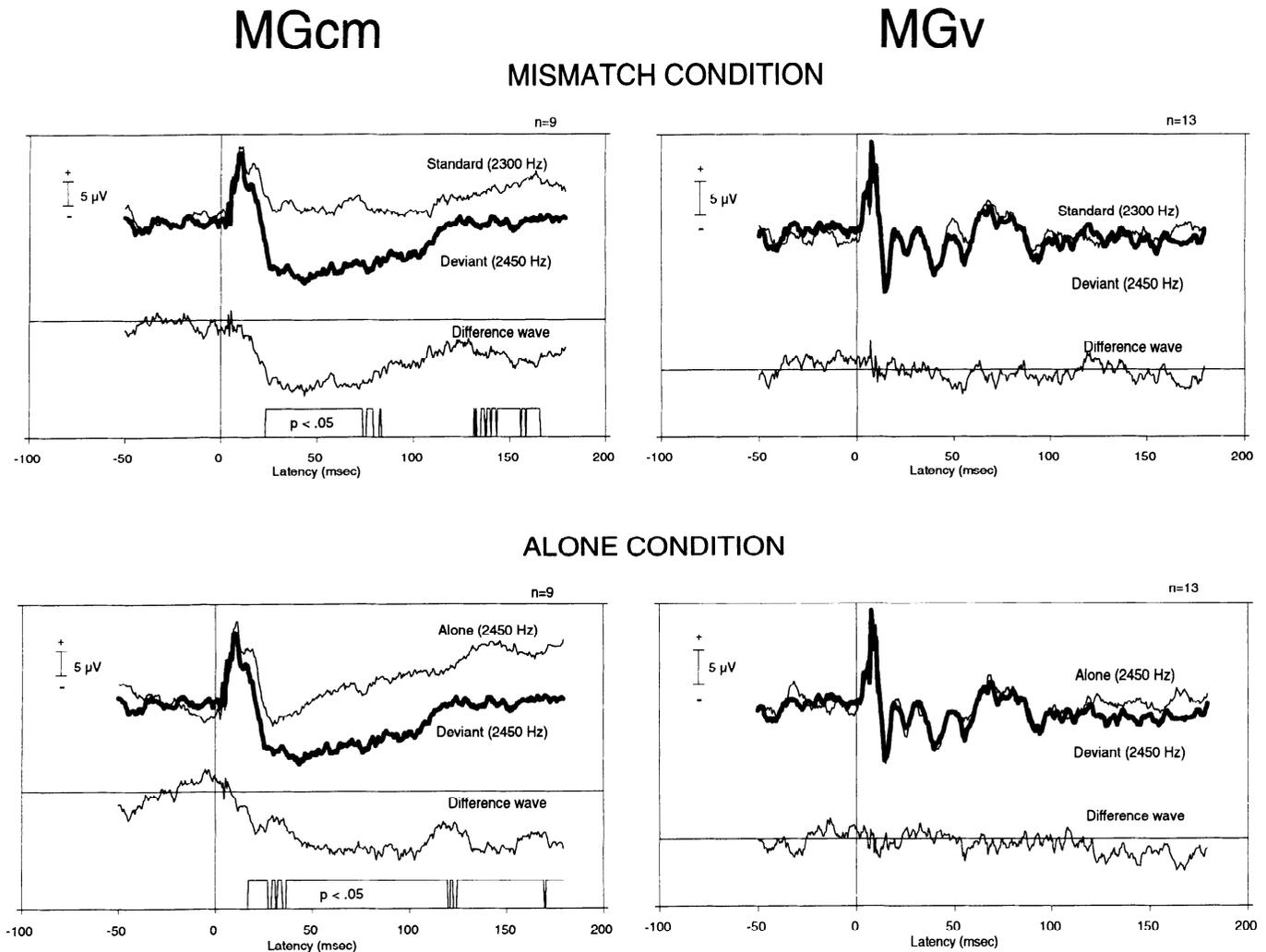


FIG. 2. Grand average responses (*top*) to standard (thin line) and deviant stimuli (thick line) recorded from MGcm (*left*) and MGv (*right*). Significant differences between the responses to standard and deviant stimuli are indicated by the box under the difference wave. Significant negative deflections (at 30–80 ms and 135–170 ms) were identified in the MGcm but not in the MGv. These deflections were defined as the MG MMN. Grand average responses (*bottom*) to the deviant (2,450 Hz) stimulus when it was presented alone (thin line) and when it was the deviant stimulus in the mismatch paradigm (thick line). The MMN occurred only in response to the 2,450-Hz stimulus in the mismatch condition. In the MGcm, there was a significant difference between the response to 2,450 Hz in the mismatch and “alone” conditions. In the MGv, the response to 2,450 Hz was the same in both conditions, again indicating that a mismatch response was absent at this location.

hypothesis. Arguing against this interpretation is that the stimulus differences used here were small and intrinsic responses to the standard and deviant stimuli are likely to have involved overlapping neuronal pools.

Our results do indicate that MMN is a result of a process that can occur at lower levels of the auditory system. If this is an auditory echoic memory process, then the definition of memory must incorporate processes that can occur in the thalamus in an anesthetized animal. If “memory” is defined as any neural activity that is preserved after stimulus offset and influences neural responses to a sequence of events, then there is no conflict. Using that definition, a “memory trace” could be automatic, preattentive and could occur at low levels as well as cortically.

MMN and behavioral discrimination

The guinea pig MMN may relate to behavioral acoustic discrimination. The human MMN has been linked to perceptual discrimination of acoustic change (Kraus et al.

1993a,c; Lang et al. 1990; Sams et al. 1985). The encoding of changes in acoustic properties, reflected by the MMN, may be a precursor of conscious discrimination. Because behavioral discrimination was not measured, our animal data do not directly indicate that the MMN reflects discrimination.

Other studies support the notion that discrimination processes can occur at fairly low levels of the auditory pathway. Many behavior-ablation studies have shown that some behavioral discriminations survive large cortical lesions (and likely retrograde degeneration into thalamus), (Cranford 1979; Heffner 1978). On the other hand, other behavior-ablation studies requiring fine discrimination of acoustic cues and species-specific vocalizations have shown that the auditory cortex is required for some discriminations (Diamond and Neff 1957; Heffner and Heffner 1986, 1990; Kelly and Whitfield 1971; Phillips 1993). It is likely that the neural elements underlying discrimination differ depending upon the difficulty of the task and the specific acoustic stimuli eliciting the responses.

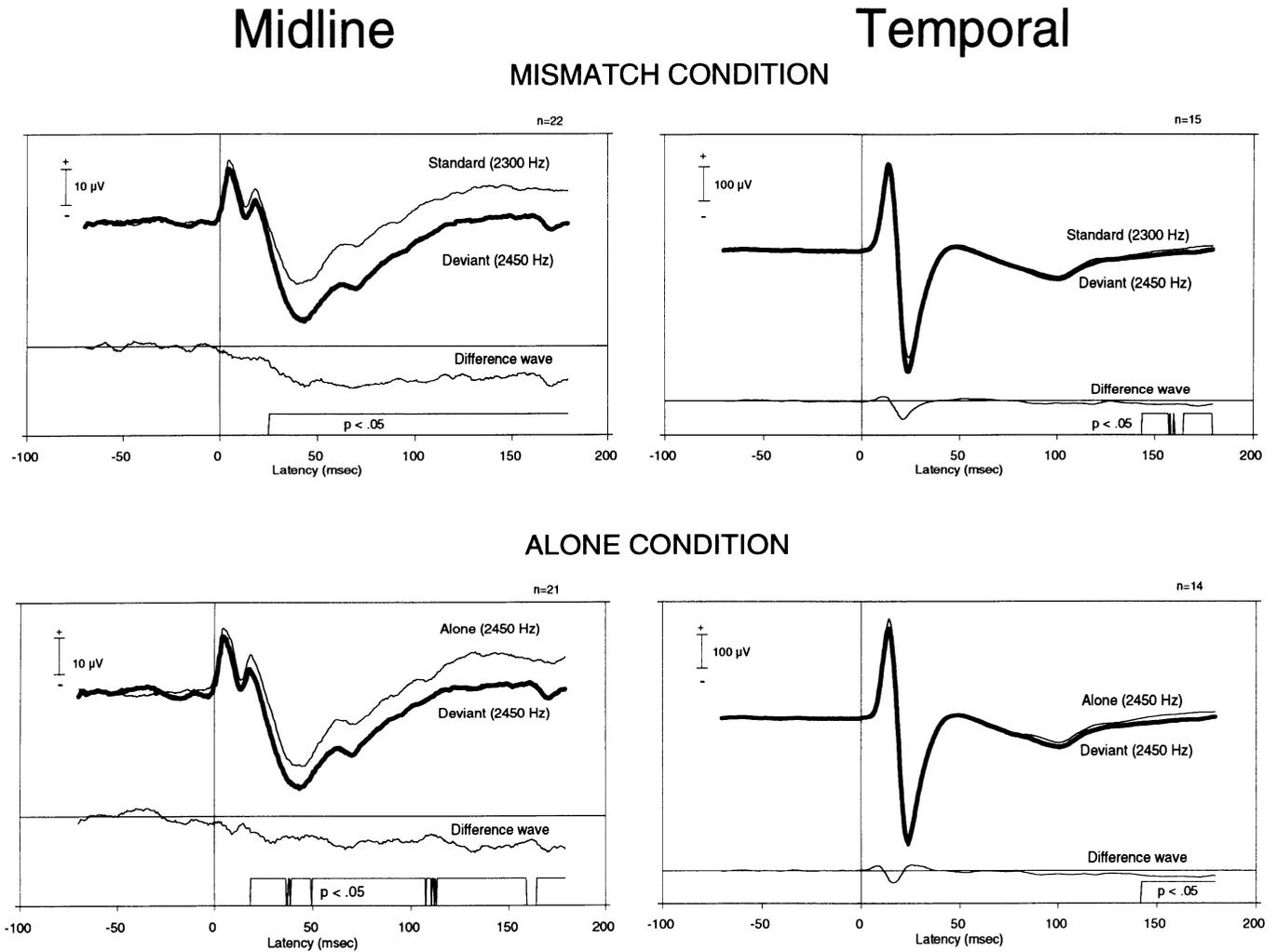


FIG. 3. Grand average responses (*top*, mismatch condition) to standard (thin line) and deviant stimuli (thick line) recorded from the surface midline (*left*) and surface temporal (*right*) locations. Significant differences between the responses to standard and deviant stimuli are indicated by the box under the difference wave. A significant mismatch negativity occurred in the midline surface waveform (between 30 and 180 ms). No mismatch activity was evident in the surface temporal response until 150 ms. Grand average responses (*bottom*, alone condition) to the deviant (2,450 Hz) stimulus when it was presented alone (thin line) and when it was the deviant stimulus in the mismatch paradigm (thick line). The MMN occurs only in response to the 2,450-Hz stimulus in the mismatch condition. At the midline, there was a significant difference between the response to 2,450 Hz in the mismatch and “alone” conditions. Over the temporal lobe, the response to 2,450 Hz was essentially the same in both conditions, again indicating that a mismatch response was absent until ~150 ms. (The deviations from baseline in the temporal response at ~20 ms were not significant). Also note that these deviations are not symmetrical in the mismatch (*top*) and alone (*bottom*) conditions.

MMN and other acoustic contrasts

Our data demonstrate that the tone-evoked MMN is observed in nonprimary auditory thalamus. However, the thalamus may or may not contribute to the MMN elicited by other stimuli. Interestingly, it appears that MMNs elicited by various acoustic parameters have different generators and may not be produced by a unitary, nonspecific mismatch detector. For example, topographically distinct regions have been described for MMN elicited by frequency contrasts, stimulus duration changes, and intensity differences (Giard et al. 1994; Paavilainen et al. 1991). Furthermore, MMNs to frequency, duration, and intensity differences were modeled by significantly different equivalent current dipoles, thereby suggesting activity in separate areas of the auditory cortex (Tiitinen et al. 1992). MEG data also show systematic differences between mismatch fields elic-

ited by frequency, intensity and duration. Our data also indicate distinct contributing sources for tonal stimuli and for various speech contrasts (Kraus et al. 1994). Specifically, a mismatch response was recorded from MGcm to a formant duration contrast ($|ba| - |wa|$), whereas there was no response to a spectral difference in formant transition ($|ga| - |da|$) at this location. Both contrasts elicited an MMN at the surface midline.

Summary

In conclusion, the robust MMN obtained in the anesthetized animal—and the clear delineation of pathways involved in the tone-evoked MMN—indicate that the guinea pig is a good model for investigating the neural mechanisms underlying acoustic discrimination. Further research will focus upon studying the generating system underlying the

MMN elicited along the auditory pathway by a variety of acoustic contrasts that simulate those that occur in the natural environment.

We thank Roxanne Edge for histologic expertise.

This work was supported by National Institute on Deafness and Other Communication Disorders Grant RO1 DC-00264 and National Organization for Hearing Research.

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Received November 1993; accepted in final form 9 May 1994.

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