Discrimination of speech-like contrasts in the auditory thalamus and cortex

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The neurophysiologic discrimination of acoustic contrasts was investigated as reflected by the mismatch negativity (MMN) response. Evoked responses were recorded from guinea pig thalamus (medial geniculate nucleus) and epidural surface in response to synthesized speech contrasts /ga/–/da/ and /ba/–/wa/. From the caudomedial portion of the medial geniculate nucleus, /ba/–/wa/ elicited a strong mismatch response, whereas /ga/–/da/ did not. Neither stimulus contrast elicited an MMN from the ventral, or primary, portion of medial geniculate. Both stimulus contrasts elicited an MMN from the midline surface. Neither contrast elicited an MMN from the surface over the temporal lobe. Results indicate a hierarchy of processing of the spectrotemporal changes which characterize formant transitions. Also, results indicate that the nonprimary portions of the auditory pathway contribute substantially to the MMN.

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INTRODUCTION

This study is part of a larger research effort in which the overall objective is to investigate the role of the thalamocortical pathways in the discrimination of speech-like signals. Speech perception is highly dependent on neuronal encoding of stimulus *change*. Current models of speech perception place special emphasis on the importance of patterns of stimulus change over time as the primary means of conveying linguistic information (Kewley-Port, 1983; Remez *et al.*, 1981; Van Tasell *et al.*, 1987; Gordon, 1988).

The measure of discrimination utilized is the mismatch negativity (MMN), an auditory evoked potential that reflects the neural processing of an acoustic change in a sequence of repetitive stimuli (Näätänen *et al.*, 1978). The MMN reflects a neuronal representation of the discrimination of numerous auditory stimulus attributes, having been obtained in response to changes in frequency, intensity, duration, spatial, and phonetic properties (Sams *et al.*, 1985; Näätänen, 1990; Näätänen *et al.*, 1987, 1989; Snyder and Hillyard, 1976; Novak *et al.*, 1990; Kaukoranta *et al.*, 1989; Paavilainen *et al.*, 1989; Nordby *et al.*, 1988; Ford and Hillyard, 1981; Aaltonen *et al.*, 1987; Sharma *et al.*, 1993; Kraus *et al.*, 1993a, b, c).

Particularly interesting is the suggestion that MMNs elicited by different stimulus attributes have different generators and are not produced by a unitary, nonspecific mismatch detector (Sams and Näätänen, 1991; Giard *et al.*, 1994; Tiitinen *et al.*, 1992). Aaltonen *et al.* (1993) showed that aphasics with posterior temporal lobe lesions had MMNs to pure tones but not to phonetic contrasts. Other data (Korpilahti *et al.*, 1992; Holopainen *et al.*, 1993) suggest that certain language-impaired children have abnormal MMNs to frequency contrasts, but normal MMNs to stimulus duration contrasts. These results could indicate separate MMN generators, but also could be explained by separate encoding areas which are monitored by a unitary MMN generator. More direct evidence for multiple MMN generators is suggested by electric and magnetic data showing systematic differences between mismatch fields elicited by frequency, intensity, and duration contrasts (Giard *et al.*, 1994; Sams, personal communication). Thus, different portions of the underlying neural network appear to be sensitive to changes in specific physical features.

These data suggest that a stimulus-related difference in the elicitation of the MMN at a particular brain location could indicate differences in site of processing of the stimuli. To investigate such a possibility, an animal model of MMN is required. The feasibility of an animal model is enhanced by the fact that the MMN is passively elicited, not requiring attention or a behavioral response (Näätänen, 1990; Novak *et al.*, 1992), and can even be obtained during sleep and under barbiturate anesthesia (Alho *et al.*, 1990; Nielsen-Bohlman *et al.*, 1988; Csépe *et al.*, 1987; Steinschneider *et al.*, 1992; Javitt *et al.*, 1992). MMN-like responses have been reported from guinea pig (Kraus *et al.*, 1994), cat (Csépe *et al.*, 1987; Karmos *et al.*, 1993), and monkey (Steinschneider *et al.*, 1992; Javitt *et al.*, 1992) in response to tone and intensity differences.

The characteristics of the MMN make it a singularly appropriate measure to investigate the processing of acoustic changes that characterize speech. In the current study, synthesized speech-like signals were used to elicit MMN responses from subdivisions of guinea pig auditory thalamus and the epidural surface. It is our goal to delineate central auditory pathway contributions to the generation of MMN evoked by various speech contrasts. It is also of interest to

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determine the relative contributions of primary and nonprimary regions of the thalamocortical pathway to the MMN. We hypothesize that MMNs to different acoustic stimulus contrasts have distinct generating systems, and that investigation of those distinctions will provide insight on the differential processing of stimulus contrasts utilized in speech perception.

A. MMN generating system

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

The postulation of primary auditory cortex involvement has been based on current source density data of MMN-like responses in the monkey (Steinschneider *et al.*, 1992; Javitt *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). In contrast, topographic data in cats and dipole source analysis of MEG data in humans implicate nonprimary auditory cortex (Csépe *et al.*, 1990, 1992; Scherg and Picton, 1990).

MMN recordings from guinea pigs also supports a nonprimary generating site. The primary subdivision of the medial geniculate nucleus, the ventral division (MGv), is well-characterized morphologically and physiologically (Winer, 1992; Clarey *et al.*, 1992; Kraus and McGee, 1993, reviews). Considered here as "nonprimary" are the dorsal and medial subdivisions (Andersen *et al.*, 1980; Edeline and Weinberger, 1991b). In the guinea pig, the MGm has also been termed the caudomedial (MGcm) portion (Redies *et al.*, 1989a, b). A tone-evoked MMN can be obtained from guinea pigs at the thalamic level from MGcm (Kraus *et al.*, 1994). In contrast, no MMN was elicited from MGv in that study. Furthermore, in the surface recordings, MMN was only elicited from the midline recording site, a site that has previously been associated with nonprimary pathway generators (Kraus *et al.*, 1988; McGee *et al.*, 1991, 1992; Kraus and McGee, 1993, review).

B. Acoustic features underlying speech are processed distinctly by various processes along the auditory pathway

Studies in humans (patients with cortical lesions and PET data from normal subjects) have indicated, in general, that features like pitch and phonetic features are processed distinctively by specific brain regions and may show hemispheric specialization (Zatorre *et al.*, 1992; Auerbach *et al.*, 1982). Phonetic and suprasegmental aspects of speech may be mediated along different cortical pathways based on their temporal structure (Phillips and Hall, 1990; Phillips and Farmer, 1990). Acoustic changes associated with phonetic features occur rapidly within tens of milliseconds, while suprasegmental changes, such as intonation contours, are on the order of hundreds of milliseconds.

In this study, we investigated the guinea pig MMN to two acoustic contrasts that, in humans, are important for speech perception and are vulnerable to varying degrees when central auditory processing is impaired. One of the contrasts was /ga/ versus /da/, the other was /ba/ versus /wa/. There are various characteristics of the acoustic signals that lead human listeners to distinguish between these phonemes. Of the cues that have been reported, major and sufficient cues include the frequencies of word-initial formants to distinguish between /ga/ and /da/ (Stevens and Blumstein, 1978), and a difference in the rapidity of formant motion to distinguish between /ba/ and /wa/ (Miller *et al.*, 1984). Thus, /ga/ and /da/ can be discriminated primarily by a dynamic spectral difference and /ba/ and /wa/ can be distinguished by a duration difference.

There is now substantial evidence that many animal species are sensitive to the small acoustic distinctions that lead to the human perception of phonemes (Kuhl, 1978). Kuhl's work with chinchillas demonstrated that the patterns of voice onset time (VOT) discrimination were not unique to human speech perception. This finding, along with studies that showed that humans can perceive nonspeech sounds categorically (Pisoni, 1977), substantially changed the direction of the speech research that followed. Rather than investigating the properties of a hypothetical speech perception mechanism in the cortex, researchers began to study physiologic mechanisms that process perceptually important aspects of speech signals at various levels of the auditory pathway.

It is well documented that neurons along the auditory pathway are responsive to specific subcomponents of the speech signal. For example, neurons in cat auditory cortex (both AI and AII) are sensitive to the direction and rate of change of frequency transitions (Whitfield and Evans, 1965; Mendelson and Cynader, 1985; Phillips *et al.*, 1985; Makela *et al.*, 1987; Steinschneider *et al.*, 1982, 1990, 1992; Heil *et al.*, 1992a, b; Vranić *et al.*, 1993). Behavioral-ablation studies have indicated that the auditory cortex is essential for the discrimination of temporal sequencing and certain species-specific vocalizations (Diamond and Neff, 1957; Kelly and Whitfield, 1971; Heffner and Heffner, 1986, 1990; Phillips, 1993). Neural encoding of pitch and fundamental frequency is apparent at more peripheral levels of the auditory pathway (Blackburn and Sachs, 1990; Miller *et al.*, 1987; Delgutte and Kiang, 1984; Sachs *et al.*, 1983; Carney and Geisler, 1986).

Although the stimuli used in the present experiments are perceived as phonemes by human listeners, their differences are relatively simple acoustically. The distinction between /ga/ and /da/ is based entirely on a variation in the starting frequency of the third formant. The distinction between the /ba/ and /wa/ is based entirely on the duration of the first and second formant transitions. All other aspects of the stimuli were held constant. These stimulus specifications allow the use of stimuli which are natural sounding syllables to hu-

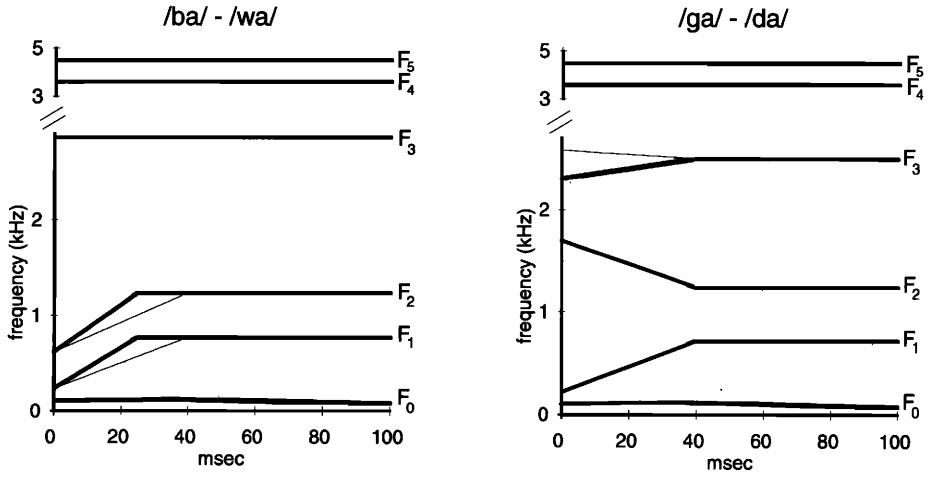

FIG. 1. Schematic spectrographic representation of acoustic contrasts. The /ba/–/wa/ contrast differs in formant transition duration. The /ga/–/da/ contrast differs in the frequency composition of the third formant transition.

mans and simply defined time-varying harmonic spectra to guinea pigs.

I. METHODS

A. Subjects and electrode placement

Fifteen guinea pigs, weighing approximately 350 grams, were used as subjects. Animals were anesthetized with ketamine hydrochloride (100 mg/kg, i.m.) and xylazine (7 mg/kg i.m.) and maintained at a body temperature of 37 °C (±1°). 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 AEPs 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, respectively). The position of the temporal electrode was approximately over the dorsal portion of primary auditory cortex, as described by Redies *et al.* (1989a). An electrode placed over the olfactory bulb, 15 mm rostral to bregma and 1 mm lateral to the sagittal suture served as reference and ground. This site does not pickup any appreciable neural activity.

Within the MGB, a high-impedance (500 kΩ, 35 μm tip) microelectrode was positioned stereotaxically in the depth position, as described by McGee *et al.* (1991). Coordinates for the MGv were 4.8 mm rostral, 3.8 mm lateral from the interaural line, and approximately 7.5 mm ventral from the epidural surface. Coordinates for the MGcm were 4.4 mm rostral, 3.5 mm lateral, and approximately 7.8 mm ventral. The ventral measurement was varied in each animal in order to obtain the best quality recordings.

With regard to the intracranial electrode, it has been our observation that in the 7–40 ms time frame, volume conduction of remote potentials is not significant. As the electrode enters MG, depth penetration changes of 100 μm are sufficient to dramatically change response amplitude, with amplitude changes of approximately 25 μV/100 μm being noted in the most responsive areas. Likewise, if the electrode is driven too far, responses decrease precipitously. MGv rostral-caudal gradients in response properties have been noted, as well as response differentiation of MGv and MGcm (McGee *et al.*, 1994). Thus, the preparation allows recording from locally discrete areas.

B. Stimuli and response recording

The MMN was elicited by the speech contrasts /ba/–/wa/ and /ga/–/da/. The phonemes were generated with a Klatt (1980) digital speech synthesizer on a DEC VAX computer. The phonemes were composed of five formants and differed either in duration of the first and second formant transitions(/ba/–/wa/) or spectrum of the third formant transition (/ga/–/da/). For /ba/–/wa/, the spectral end-point frequencies were identical, but F_1 and F_2 transition durations differed. For /ba/, the transition was 25 ms; for /wa/, the transition was 40 ms. For /ga/–/da/, the F_3 formant transition had an identical duration, but a different spectral ramp. That is, for /ga/, F_3 began at 2580 Hz; for /da/, F_3 began at 2300 Hz. For both /ga/ and /da/, the 40 ms F_3 formant transitions joined the steady-state portion of the stimulus at 2500 Hz. Total stimulus duration was 100 ms. The frequencies used for F_2 and F_3 were selected based upon normal guinea pig auditory thresholds to ensure that contrasts were audible (Cheatham and Dallos, 1993; Prosen *et al.*, 1978; Heffner *et al.*, 1971; Makishima *et al.*, 1975, 1977). The acoustic specifications are shown schematically in Fig. 1.

Files from the Klatt synthesizer were transferred to a PC-based stimulus delivery system which output the signals through a 12-bit converter at a sampling rate of 10 kHz. That system controlled the time of delivery, the stimulus sequence, and stimulus intensity. It also triggered the PC-based evoked potentials averaging system at stimulus onset and indicated whether the trial contained a standard or deviant stimulus.

Stimuli were delivered monaurally through insert earphones at 75 dB SPL. A modified oddball paradigm was used

in which the deviant stimulus (probability of occurrence =10%) was presented in a series of standard stimuli (probability of occurrence=90%). For the /ga/–/da/ contrast, /da/ served as the deviant stimulus; for /ba/–/wa/, /wa/ was the deviant. Stimuli were presented in a pseudorandom sequence with at least three standard stimuli separating presentations of deviant stimuli. Evoked responses elicited by deviant stimuli and those elicited by standard stimuli were averaged separately. Only responses to standard stimuli immediately preceding deviant stimuli were included in the standard stimulus average. Averaged responses were the summation of responses to 250 deviant stimuli and 250 standard stimuli.

Stimulus presentation rate was 1.9/s. The recording window included a 50-ms pre-stimulus period and 200 ms of post-stimulus time, collected at a sampling rate of 2048 points/s. Evoked responses were analog bandpass filtered online from 0.1 to 100 Hz (12 dB/octave), and baseline adjusted to the prestimulus baseline.

As a control, responses were measured to 250 stimulus presentations (rate=1.9/s) of the deviant stimulus presented alone, that is, not in the oddball paradigm. This is referred to as the "alone" condition. The MMN should occur only when the auditory system discriminates between the standard and deviant stimuli. Therefore, the response obtained to the deviant stimulus presented in the oddball paradigm should be different from the response to the same stimulus when it is presented alone (Näätänen *et al.*, 1989; Kraus *et al.*, 1992).

Because the MMN is, by definition, elicited only by the deviant stimulus, 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 in the alone condition from the 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.

C. Data analysis

Grand averages were computed across animals for each recording location, for each stimulus pair, and for each waveform (standard, deviant, deviant-alone, and difference waves). Statistical tests were performed on group average responses. A point-to-point t test was performed using the individual grand averages of the standard and deviant waveforms as a data set. The t scores indicated whether a significant relative negativity occurred in the deviant waveform. A similar analysis was performed on the deviant (oddball paradigm) versus deviant-alone waveforms. The interval of significant t scores defined the MMN for each recording location.

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 at least 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 below 0.2. A conservative criterion was imposed for this study: an interval of significance of at least 20 ms was required to be considered a valid mismatch response.

D. Histology

At the end of the experiment, the recording locations were marked with an electrolytic lesion (35 μA for 10 s). Brains were cut in 17-μm coronal sections and stained with Klüver stain which permits visualization of cell body and fiber pathways.

II. RESULTS

A. Electrode sites

Histological results indicated that electrodes were placed into MGv in six animals and in MGcm in nine animals. Electrode sites are illustrated in the schematic drawings of Fig. 2. The sections are arranged rostral to caudal, spanning a total distance of 2.6 mm through the nucleus.

B. Medial geniculate responses

With the /ba/–/wa/ contrast, significant negative deflections (from 48- to 80-ms latency) were identified in the mismatch response from MGcm (Fig. 3, left-hand side). A longer duration (21–83 ms) and larger significant region for the mismatch negativity was apparent in the MGcm deviant-alone difference wave.

In response to /ga/–/da/, no mismatch was observed in the deviant versus standard comparison (Fig. 3, right-hand side). A brief mismatch interval (latency 76–93 ms) was apparent for MGcm in the deviant versus deviant-alone comparison. This interval was below the criterion duration of 20 ms. Thus there was little evidence of a mismatch response to /ga/–/da/ in the auditory thalamus.

No significant mismatch intervals were observed from MGv for the /ba/–/wa/ contrast (Fig. 4, left-hand side), nor were significant intervals present in the MGv deviant-alone difference wave. Similar to /ba/–/wa/, no mismatch response was recorded from MGv in either the mismatch or alone condition in response to the /ga/–/da/ contrast (Fig. 4, right-hand side).

C. Epidural surface responses

At the epidural surface, a significant mismatch response occurred in the midline surface waveform at a latency interval of 60–200 ms for /ba/–/wa/ and 30–200 ms for /ga/–/da/ (Fig. 5, top). The comparison of the deviant and alone conditions indicated a similar mismatch response (Fig. 5, bottom), with significant intervals of 50–200 ms for /ba/–/wa/ and 34–200 ms for /ga/–/da/. Differences in mean onset latencies between /ga/–/da/ and /ba/–/wa/ were not significant. Mean midline MMN amplitudes were similar for both contrasts for both conditions.

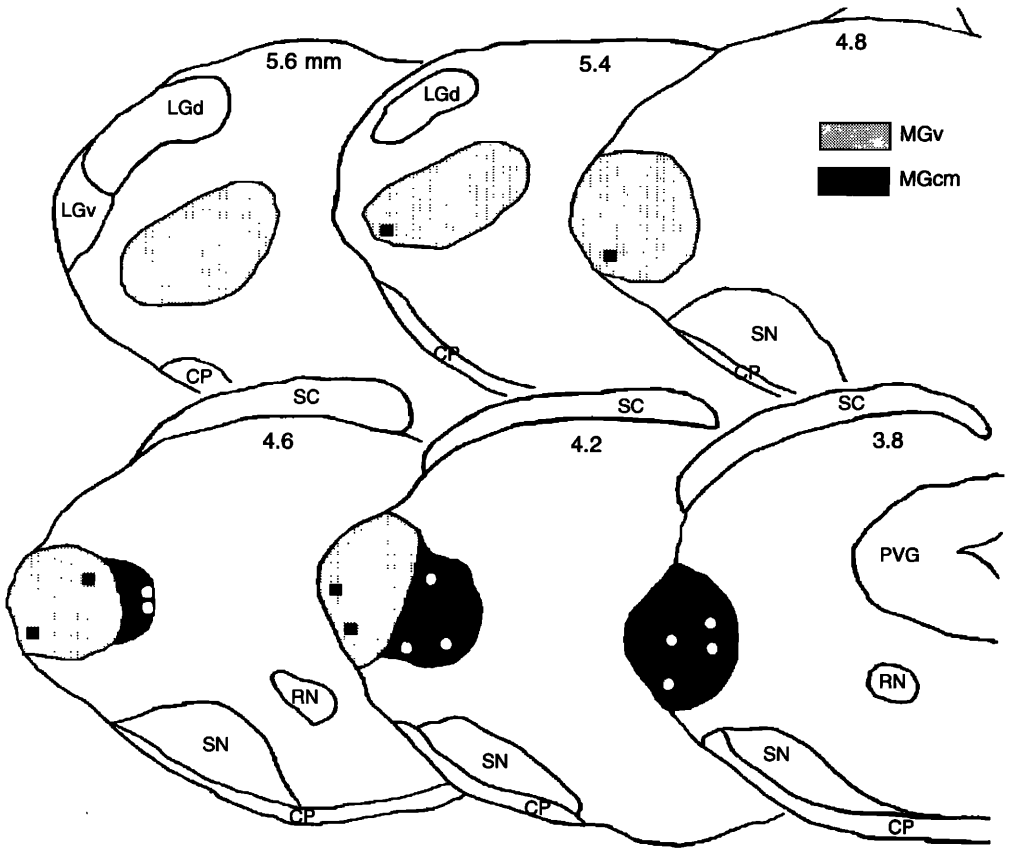

FIG. 2. Recording locations within the medial geniculate nucleus of thalamus, ventral (MGv) and caudomedial (MGcm) subdivisions (MGv, $n=6$; MGcm, $n=9$). Measurements are mm rostral to interaural line. Other abbreviations: LGd, dorsal division of lateral geniculate; LGv, ventral division of lateral geniculate: PVG, periventricular gray; SN, substantia nigra; RN, red nucleus; CP, cerebral peduncle.

Brief significant intervals were observed in the standard versus deviant responses recorded over the temporal lobe. No significant differences were obtained in the deviant versus deviant-alone temporal responses (Fig. 6).

III. DISCUSSION

A. Roles of the thalamus and cortex: Relationship to single neuron and clinical studies

Obvious stimulus-specific effects are apparent at the thalamic level. From the thalamus, negligible mismatch activity was observed to /ga/–/da/. In contrast, /ba/–/wa/ elicited a robust MGcm response. Previously reported MGcm responses to tonal contrasts demonstrated a similar onset latency to the /ba/–/wa/ responses obtained here (Kraus *et al.*, 1994). However, the tonal MGcm MMN was of considerably longer duration (55.1 ms) and of larger amplitude (25.0 μV).

We suggest that these results are consistent with a hierarchy of processing for different acoustic parameters. For example, a tone-evoked mismatch can be detected easily at the thalamic level, thereby indicating that tone burst discrimination is encoded at a relatively low level in the system. Similarly, the /ba/–/wa/ contrast shows a significant, albeit smaller, thalamic response. On the other hand, the rapid spectral change of /ga/–/da/ shows virtually no mismatch activity at the thalamic level, even though the /ga/–/da/ midline surface MMN is equivalent to the tone and /ba/–/wa/ MMN. The surface midline MMNs suggest an equivalent discriminability among the three stimulus contrasts, while the MG response indicates that the processing of /ga/–/da/ occurs predominantly central to the thalamus.

This evidence of hierarchical processing of stimulus features in the guinea pig is consistent with clinical studies of persons with central auditory processing problems. In those individuals, the perception of certain acoustic contrasts is more likely to be impaired than the perception of other contrasts. For example, the perception of rapid formant transitions in stop consonants has been shown to be particularly vulnerable in clinical cases of processing disorders (Elliott *et al.*, 1989; Tallal *et al.*, 1980; Rosen, 1992), specifically with primary auditory cortex damage (Phillips and Farmer, 1990). In contrast, slowly varying spectral changes are more easily perceived and are less susceptible to primary auditory cortex impairment (Auerbach *et al.*, 1982; Phillips and Farmer, 1990).

Studies of neural encoding in single neurons have demonstrated poor representation of periodicity at the level of the auditory cortex. Those data have been interpreted to mean that the auditory cortex has poor temporal resolution (de Ribaupierre *et al.*, 1972; Eggermont, 1991; Langner, 1992, review; Steinschneider *et al.*, 1994). However, Phillips and Hall (1990) have demonstrated that cortical onset responses are remarkably precise indicators of acoustic change and, in that respect, have excellent temporal resolution. That

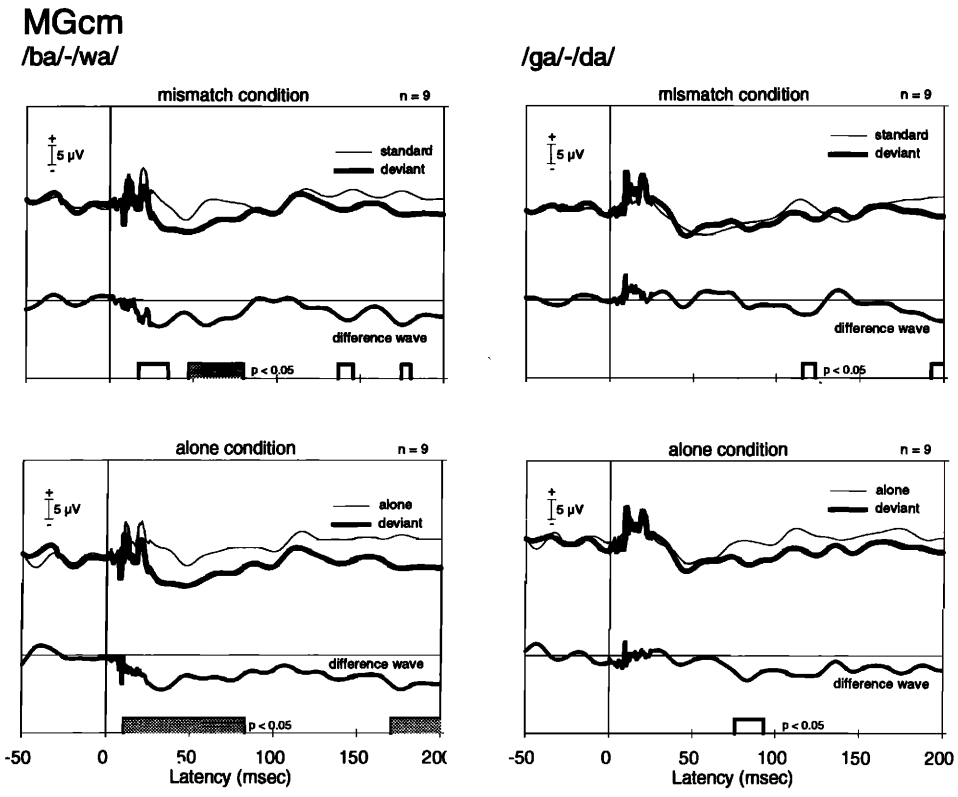

FIG. 3. Grand average responses to the contrasts /ba/–/wa/ (left-hand side) and /ga/–/da/ (right-hand side) recorded from the caudomedial subdivision of the medial geniculate nucleus. Mismatch activity was evident in response to /ba/–/wa/ in both the mismatch and alone conditions. In contrast, to /ga/–/da/, there were no significant differences between responses to standard and deviant stimuli. A very brief (17 ms) mismatch response was present only in the alone condition. Significant differences between the responses to standard and deviant stimuli (mismatch condition) or between the response to the deviant stimulus presented alone versus presented in the oddball paradigm (alone condition) are indicated by the shaded box under the difference waves.

is, cortical neurons show excellent temporal precision in the representation of onsets of acoustic change. Based on these findings, it may be the case that the temporal information that represents onsets and transitions is processed at the cortical level and that temporal information typically associated with periodicity is not reproduced in the cortex.

Furthermore, in response to frequency modulated (FM) tones, neurons in cat primary auditory cortex exhibit an "onset" type firing that appears to be determined by the sweep of the frequency across the response area toward the CF (Heil *et al.*, 1992a, b). That FM topography is independent of tonotopicity (Heil *et al.*, 1992b; Mendelson *et al.*, 1993). These results, in combination with those of Phillips and Hall (1990), indicate that the response to formant transitions may be encoded by a succession of precisely timed onset responses sweeping across neurons that respond best to those frequencies and rates of frequency change within the formant transition. In that scenario, a pattern of responses from an ensemble of cortical neurons would underlie the encoding of formant transitions (Steinschneider, 1994, personal communication).

While temporal resolution is excellent in the thalamus, the presence of phase locking (which encodes steady-state signals) may obscure differences in fast transitions. For formant duration differences (/ba/–/wa/), there is a sufficient difference in the neural pattern to trigger an MMN despite the phase locking (albeit a smaller MMN than is seen for tones). When the formant transition duration is identical (/ga/–/da/), a cortical ensemble of neurons appears to be necessary to elicit an MMN. Thus, no thalamic MMN is apparent.

The results reported here are also germane to the issue of whether MMN is produced by a unitary generator or whether separate MMN generators exist for different stimuli. Because an MMN is recorded from the thalamus in response to some stimuli but not others, distinct generators for MMN responses to different stimulus contrasts may exist.

B. Role of habituation

The extent to which habituation may contribute to the MMN has been studied. Conclusions have been that the MMN is a response to change, not repetition and therefore is a reflection of a memory trace (Ritter *et al.*, 1992; Näätänen, 1990; Näätänen *et al.*, 1989). We acknowledge that neurons in the nonprimary pathway may habituate rapidly (Aitkin, 1973; Calford, 1983; Irvine and Huebner, 1979; Toros-Morel *et al.*, 1981). However, also present in MG nonprimary areas are novelty units (Calford, 1983) which do not respond even at slow rates of repetitive stimulation. Rather, they respond to small stimulus changes within a repetitive sequence.

This study does not speak directly to the issue of differentiating habituation from an MMN. Specifically, we did not compare the response to the deviant stimuli at different rates. However, there are two reasons why our results should not reflect simple habituation. First, this study revealed that the

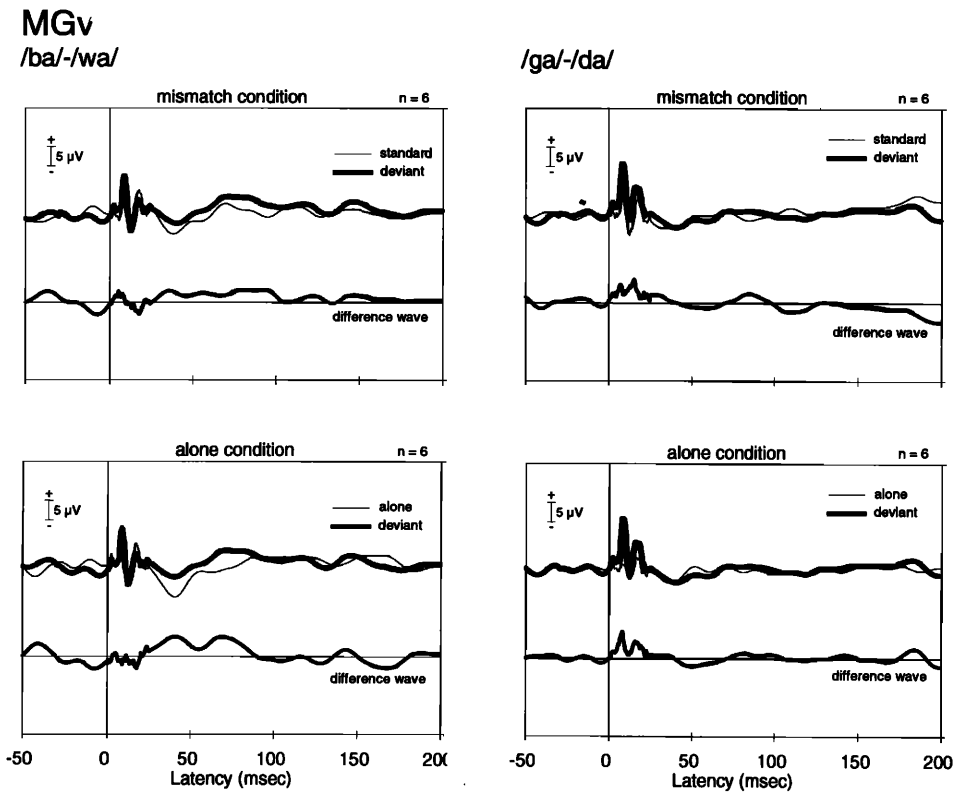

FIG. 4. Grand average responses to the contrasts /ba/–/wa/ (left-hand side) and /ga/–/da/ (right-hand side) recorded from the ventral subdivision of the medial geniculate nucleus. There was no evidence of mismatch activity in response to either stimulus.

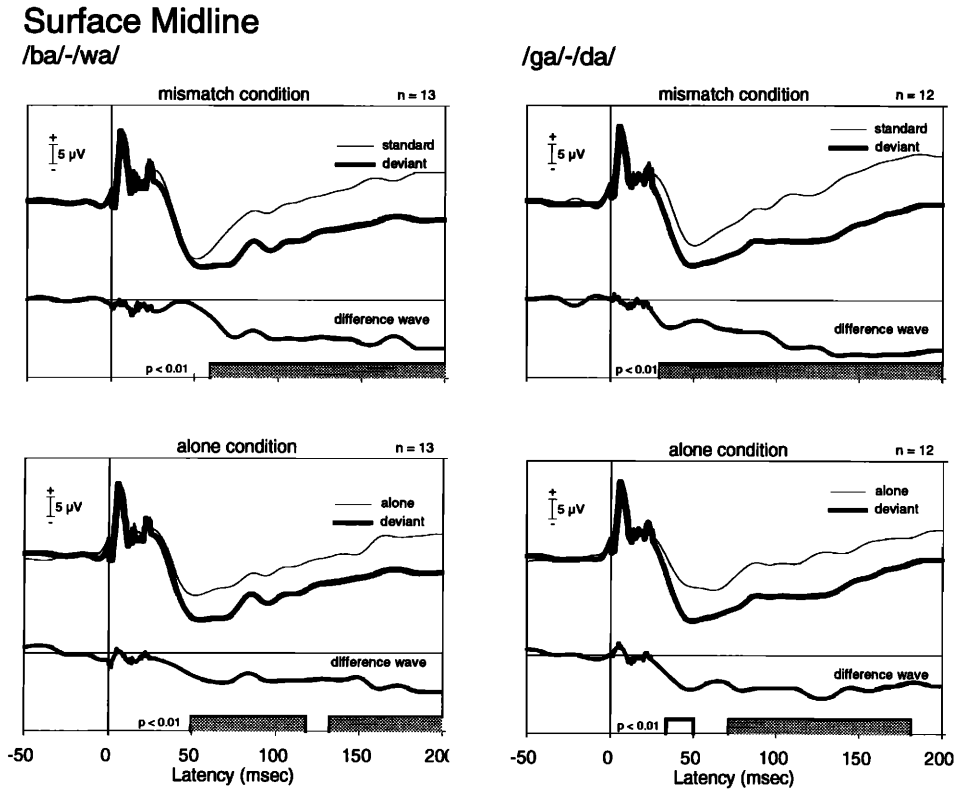

FIG. 5. Grand average responses to the contrasts /ba/–/wa/ (left-hand side) and /ga/–/da/ (right-hand side) recorded from the epidural midline. Significant mismatch activity was evident in response to both contrasts in the mismatch and alone conditions. Significant differences between the responses to standard and deviant stimuli (mismatch condition) or between the response to the deviant stimulus presented alone versus presented in the oddball paradigm (alone condition) are indicated by the shaded box under the difference waves.

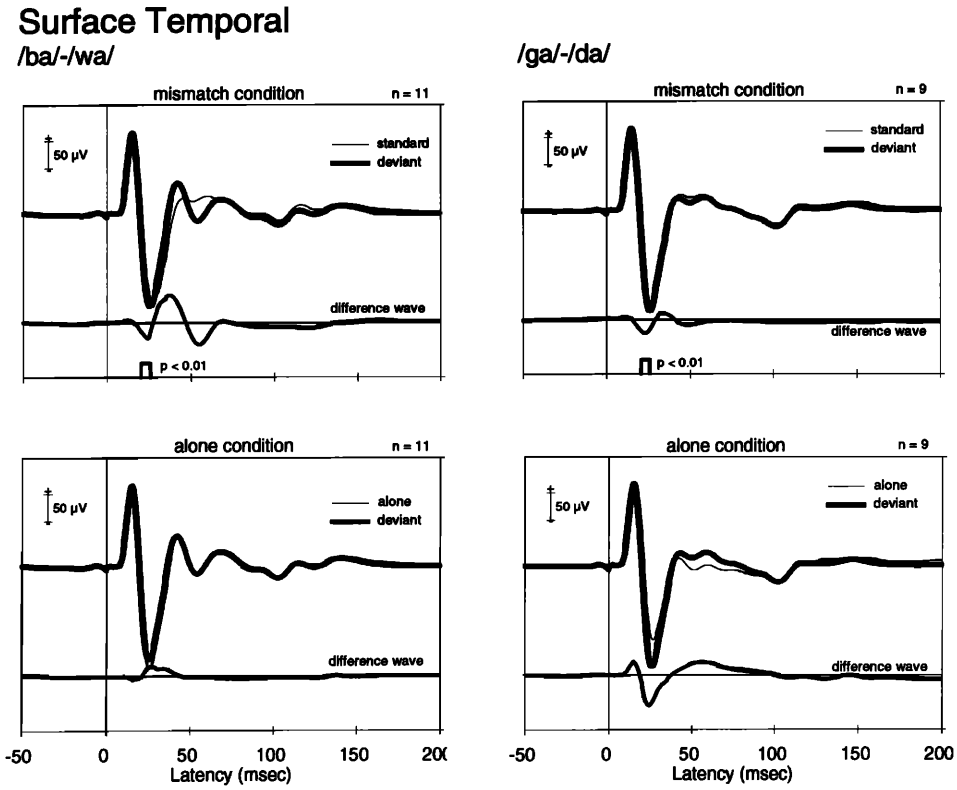

FIG. 6. Grand average responses to the contrasts /ba/–/wa/ (left-hand side) and /ga/–/da/ (right-hand side) recorded from the epidural temporal area. Although the responses to each stimulus within each contrast were different, there is no evidence of mismatch activity at this location. This is clearly seen in response to /ba/–/wa/ in which the responses to /wa/ are identical in the mismatch and alone conditions, indicating that this region does not reflect the processing of stimulus change.

mismatch response was present in the thalamus to /ba/–/wa/ but not to /ga/–/da/. Habituation effects would not be expected to occur in response to one stimulus pair and not to the other. That is, it is unlikely that there would be selective habituation for an F_2 transition duration difference but not for a spectral F_3 ramp difference. Second, the characteristics of the standard and deviant stimuli used in this study were identical in most respects (F_0, total duration, steady-state portions, much of the formant transition information). Moreover, the stimulus differences between the standard and deviant stimuli were small. Thus, the intrinsic responses to the standard and deviant stimuli are likely to have involved overlapping neuronal pools. One would expect that habituation effects would already be occurring in response to the standard stimuli, such that the negativity in response to the deviant stimulus would reflect neuronal processes over-and-above any ongoing habituation effects.

C. Role of primary versus nonprimary pathways

These results give insight to the relative contributions of the primary and nonprimary portions of the auditory pathway to the MMN. Consistently, the auditory pathway can be segmented into two systems with respect to neural connections, cell morphology (Winer and Morest, 1983; Winer, 1992), single neuron physiologic responses (Calford, 1983; Calford and Aitkin, 1983; Morest, 1964; Schreiner and Cyander, 1984; Clarey *et al.*, 1992, review), and evoked responses (Kraus *et al.*, 1988; McGee *et al.*, 1992; Kraus and McGee, 1993, review). Specifically, primary pathway neurons 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). 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; Rouiller *et al.*, 1989; Kraus and Disterhoft, 1982; Edeline and Weinberger, 1992, 1991a, b).

Response properties associated with single neurons in nonprimary thalamus and cortex are consistent with their involvement in the observed mismatch response. For example, response latencies are longer in nonprimary than in primary auditory thalamus (Calford, 1983) and cortex (Reale and Imig, 1980; Schreiner and Cynader, 1984). In the cat, mean latencies in MGv are on the order of 12 ms while in nonprimary subdivisions mean onset latencies range from 18 to >100 ms (Calford, 1983; Aitkin *et al.*, 1981; Imig and Morel, 1985). In the cortex, primary cortex responses occur at <20 ms, whereas nonprimary auditory cortex responses occur at >50 ms. The nonprimary pathway latencies are consistent with the latencies at which a mismatch response is observed. Moreover, nonprimary pathway neurons have a greater proportion of inhibitory and sustained response patterns as well as neurons that respond to novel stimuli (Calford, 1983).

The absence of an MMN to /ba/–/wa/ from MGv and the presence of a mismatch response in MGcm point to in-

volvement of the nonprimary auditory pathway in the generation of the MMN. Surface responses showed a similar differentiation, with a robust MMN being apparent in the midline but not the temporal lobe response. At the temporal lobe, considering the lack of significance in the deviant versus deviant-alone temporal responses, the limited intervals of significance in the standard versus deviant responses may indicate differences in encoding of each individual stimulus, not a mismatch response (King *et al.*, 1994). This result is seen clearly in the temporal response to /ba/–/wa/ where the responses to /wa/ are identical in the mismatch and alone conditions, indicating that the response from this region does not reflect the processing of acoustic change in a stimulus sequence. In contrast, the midline response shows extensive intervals of significance in both the mismatch and alone comparisons for both stimulus pairs, indicating considerable mismatch activity at that location.

In studies of the guinea pig MLR, the midline response has been associated with the nonprimary auditory pathway, while the temporal lobe response appears to be generated in the primary auditory cortex (Kraus *et al.*, 1988; McGee *et al.*, 1992; Kraus and McGee, 1993, review). Similar results were noted with a tone-evoked MMN, that is, that the nonprimary thalamic area (MGcm) and the nonprimary surface response showed mismatch activity, while the primary area (MGv) and the primary surface response did not (Kraus *et al.*, 1994).

IV. SUMMARY AND CONCLUSIONS

(1) At the thalamic level, no mismatch response was apparent in response to the stimulus contrast /ga/–/da/, a contrast which depends on the processing of a rapidly changing spectral difference. On the other hand, thalamic mismatch responses are apparent to /ba/–/wa/ and to tones. These results are consistent with the notion that speech features are differentially processed, and that certain acoustic features require processing at the cortical level. Surface mismatch responses were equivalent for both stimulus pairs.

(2) Mismatch responses were associated only with nonprimary areas of the auditory pathway, thereby indicating a nonprimary pathway origin for the processing of acoustic stimulus change.

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