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Acoustic features and acoustic change are represented by different central pathways

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Abstract

The central processing of acoustic stimulus changes can be observed neurophysiologically in the mismatch negativity auditory evoked potential (MMN). Stimuli differing in interaural phase were used to investigate the contributions of the primary and non-primary auditory pathways to the encoding of binaural stimuli and to investigate passively elicited measures of binaural processing in experimental animals.

In guinea pigs, the MMN was obtained in response to 1000 Hz tones embedded in white noise (S:N = 2 dB). Using a modified oddball paradigm (that is, two stimuli presented in a series, each with a different probability of occurrence), stimuli were presented binaurally with both the tone and noise in-phase to the two ears (S_0N_0) as the standard stimulus and the tone 180° out-of-phase ($S_\Pi N_0$) as the deviant stimulus. The MMN, by definition, should occur only in response to a change, or 'mismatch,' between the standard and deviant stimuli. The response to the deviant stimulus in the oddball paradigm was compared to the response to the same stimulus when presented in a series alone. The responses to S_0N_0 and $S_\Pi N_0$ collected in a series alone, termed the intrinsic responses, were also compared. Responses were recorded from two surface epidural electrodes – one at the posterior midline and one over the left temporal lobe. AEPs from these locations have been shown to reflect the activity of primary and non-primary thalamo-cortical pathways respectively.

A significant MMN was observed at the midline electrode, but no MMN was observed over the temporal lobe. However, there was a significant difference in the intrinsic responses to the two stimuli over the temporal lobe while no difference in the intrinsic responses was seen over the midline. The results suggest that the primary and non-primary auditory pathways appear to provide distinctly different contributions to the encoding of changes in binaural phase. Additionally, the MMN to stimuli differing in interaural phase can be obtained in anesthetized animals and may provide a useful measure of binaural processing.

Keywords: Interaural phase difference; Binaural processing; Auditory evoked potentials; Mismatch negativity; Primary vs. non-primary pathways

1. INTRODUCTION

1.1. Binaural processing

Binaural processing is a fundamental aspect of the encoding of acoustic stimuli. It provides a means for localizing sound, for selective attention, and for extracting a signal from noise. A large body of literature concerning the binaural phenomenon of Masking Level Difference (MLD) (e.g., Hirsch, 1948; Webster, 1951) addresses the processing of interaural phase differences in tones. MLD is usually defined as an improvement in the masked threshold of a signal due to a phase difference between ears.

Auditory evoked potentials have been used to study interaural phase differences in humans. Several studies have demonstrated an increase in amplitude of the late potentials N1 and P2 when stimuli are presented out-of-phase vs. in-phase to the two ears (Butler and

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Klushens, 1971; Tanis and Teas, 1974). In addition, electrophysiologic correlations between behavioral MLDs and the cortical evoked potentials P1, N1, P2 and N2 have been demonstrated (Yonovitz et al., 1979; Fowler and Mikami, 1992a, Fowler and Mikami, 1992b). The present study draws from this literature conceptually but it is important to note that our paradigm makes no attempt to compare masked thresholds. Rather, we look at responses to changes in interaural phase at suprathreshold levels and we expect to be able to extract information about how binaural differences in stimulus phase are represented by central auditory pathway neurons.

While there have been several evoked potential studies that examined binaural processing in humans using stimuli with interaural phase differences, to our knowledge there have been no such studies using animals, although encoding of binaural phase has been examined extensively in single neurons (e.g., Rose et al., 1966; Brugge et al., 1969; Goldberg and Brown, 1969; Caird and Klinke, 1983; Yin and Kuwada, 1984; Caird et al., 1989; Reale and Brugge, 1990; Caird and Palmer, 1991; Palmer et al., 1992). A relatively non-invasive measure of binaural processing could be utilized in various animal preparations where binaural function is investigated, for example, in developing or experimentally reared animals who require ongoing monitoring. The mismatch response or mismatch negativity (MMN) is a passively elicited neurophysiologic index of the processing of stimulus differences (Näätänen et al., 1978; Kraus et al., 1993). The subject is not required to attend to the stimulus or provide a behavioral response, making the MMN an effective tool for studying neural response to an acoustic change in animal preparations. The MMN has been recorded in awake, asleep, and barbiturate-anesthetized animals (Csépe et al., 1987; Javitt et al., 1992, Kraus et al., 1994a, Kraus et al., 1994b), indicating that the response is present despite variations in attention levels. Using stimuli containing binaural phase differences, we investigated whether MMNs could provide a tool for assessing binaural processing in anesthetized guinea pigs.

1.2. Central auditory pathway encoding of complex stimuli

This study is part of a larger research effort in which the overall objective is to investigate the role of the thalamo-cortical pathways in the encoding of complex acoustic stimuli. Previous research has shown that the middle latency response recorded from the midline in guinea pigs is associated with the non-primary auditory pathway, while recordings from the temporal lobe are associated with the primary auditory pathway (Kraus et al., 1988; McGee et al., 1991; Kraus and McGee, 1993 review, 1993). Additionally, in response to tonal contrasts, a mismatch response was recorded from the non-primary (caudomedial) division of the medial geniculate body (MGcm) and from the surface midline, but was absent in the primary (ventral) division of the medial geniculate (MGv) and at the surface over the temporal lobe (Kraus et al., 1994a). Similar results were obtained for synthesized speech syllables (Kraus et al., 1994b). Those results support a non-primary pathway origin for the MMN. The current study uses the same surface recording locations to assess the response to binaural stimuli that differ in relative phase. By inference, the surface responses obtained in this study can be interpreted in terms of primary vs. non-primary auditory pathway contributions.

The concept of the auditory pathway having two subsystems has also been demonstrated in studies of cell morphology (Winer and Morest, 1983; Winer 1992) and single neuron responses (Calford, 1983; Calford and Aitkin, 1983; Clarey et al., 1992, review). Terms other than primary and non-primary have been used to describe these two subsystems of the auditory pathway, such as lemniscal vs. extralemniscal, core vs. belt, intrinsic vs. extrinsic and cochleotopic vs. diffuse (Andersen et al., 1980; Winer and Morest, 1983).

The purposes of this study were twofold. The first was to ascertain whether or not a neurophysiologic response could be elicited by stimuli differing in interaural phase and whether that response could be a useful measure of binaural processing. The second goal was to investigate the relative roles of the primary and non-primary auditory pathways in the neurophysiologic responses to binaural cues.

2. METHODS

2.1. Subjects and electrode placement

Six albino guinea pigs, each weighing approximately 350 grams, were used as subjects. Animals were initially anesthetized with intramuscular injections of ketamine hydrochloride (100 mg/kg) and xylazine (7 mg/kg). Smaller doses (15 mg/kg of ketamine; 3 mg/kg of xylazine) were administered as needed for the rest of the experiment, typically hourly. Anesthesia levels were closely monitored by noting the presence of the midline waves M + /M − and the temporal wave C which have been shown to be most sensitive to anesthetic effects (Smith and Kraus, 1987). Body temperature was maintained at 37° C (±1°) throughout the experiment.

A rostro-caudal incision was made along the scalp and the tissue was retracted to eliminate muscle artifact. Holes (1 mm diameter) were drilled in the skull and epidural silver bead electrodes (0.5 mm diameter) were used to record the surface AEPs as previously

described (Kraus et al., 1988). Recordings were made over the posterior midline, (10 mm caudal to bregma), and over the left temporal lobe contralateral to the ear receiving the phase-shifted 1000 Hz tone, (3 mm caudal to bregma and 10 mm lateral to the midline suture). These two recording locations are referred to as midline and temporal sites, respectively. The temporal electrode was positioned approximately over the dorsal portion of primary auditory cortex, as described by Redies et al. (1989). An electrode placed 15 mm rostral to bregma and 1 mm lateral to the sagittal suture served as the reference for both recording locations. A ground electrode was attached to the muscle tissue at the caudal end of the incision.

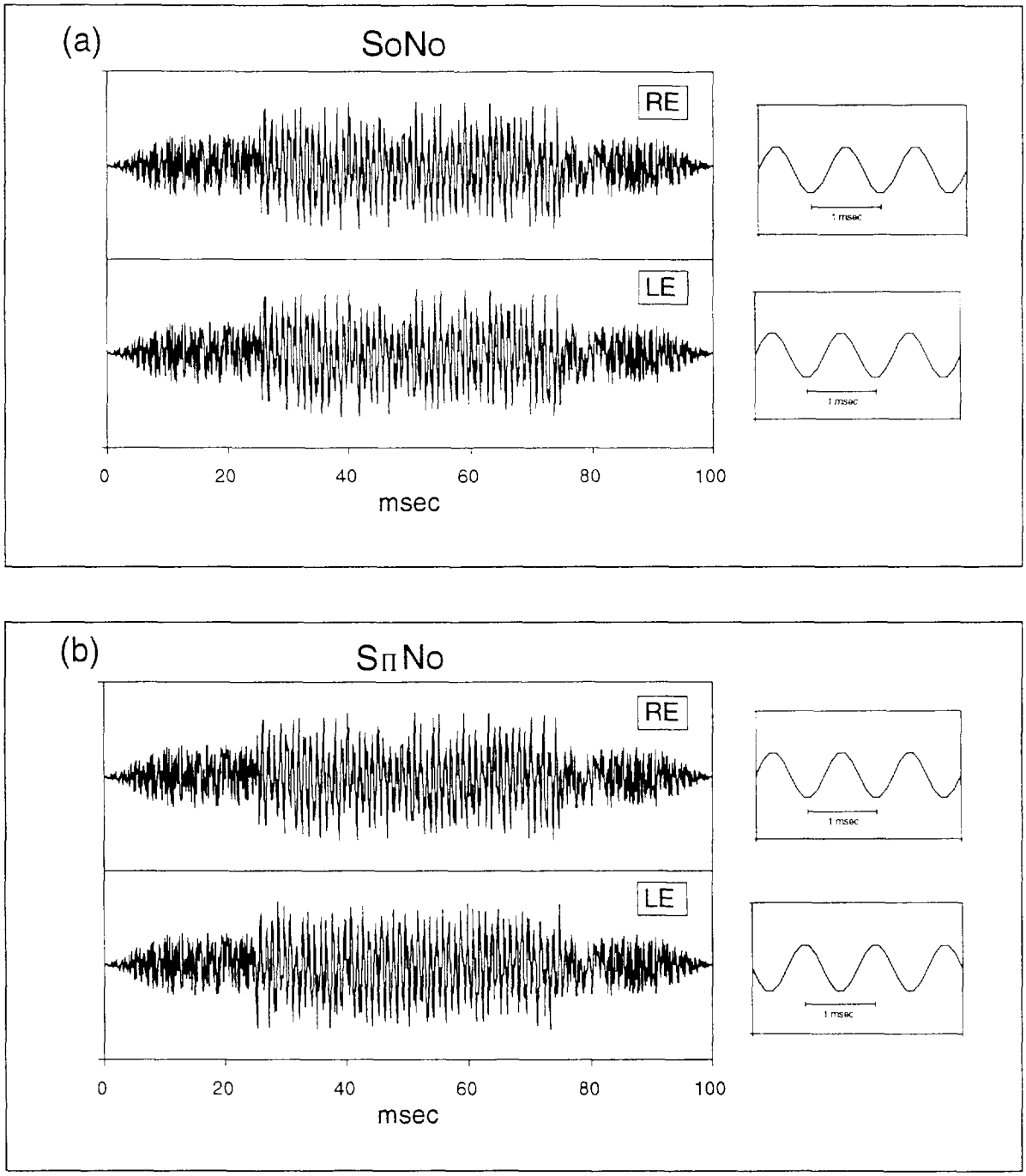

Fig. 1. (a) S_0N_0. A 50 ms 1000 Hz tone burst embedded in 100 ms of broadband noise, with the tone delivered in-phase to both ears. The insets show a magnified portion of the tones without the noise (1 waveform cycle = 1 ms). (b) $S_\pi N_0$. A 50 ms 1000 Hz tone burst embedded in 100 ms of broadband noise, with the tone delivered out-of-phase to both ears. The insets show a magnified portion of the tones without noise.

2.2. Stimuli and response recording

Tone bursts with a frequency of 1000 Hz and 50 ms in duration (74 dB SPL) were embedded in 100 ms bursts of white noise (72 dB SPL). The bandwidth of the noise was 100–4950 Hz. Tone and noise onsets were offset by 25 ms (Fig. 1). These stimuli were presented binaurally through insert earphones at a rate of 1.9/sec. The recording window included a 100 ms pre-stimulus period and 200 ms of post-stimulus time. Evoked responses were analog bandpass filtered on-line from 0.1 to 100 Hz (12 dB/octave), and baseline adjusted to prestimulus baseline.

The stimuli were presented with the tone and noise delivered in phase to both ears (S_0N_0) and with the tone delivered 180° out of phase to the two ears while the noise was in phase to the two ears ($S_\pi N_0$). $S_\pi N_0$ was obtained by shifting the phase of the 1000 Hz tone presented to the right ear. In humans, S_0N_0 gives a perception of a centrally fused sound and $S_\pi N_0$ gives a perception of diffusion of sound within the head.

Responses were recorded when the stimuli were presented in an oddball paradigm and when presented in a series alone. The stimulation rate of 1.9/sec was maintained across both of these recording conditions.

2.3. The modified oddball paradigm

The MMN was elicited by deviant (also known as infrequent or rare) stimuli ($S_\pi N_0$) presented in a sequence of standard (also referred to as frequent) stimuli (S_0N_0). 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. Mismatch responses can occur to the standard stimuli immediately following each deviant stimulus. To avoid such contamination, only the responses to the standards just preceding the deviants were averaged into the standard response, even though 3750 standard stimuli were presented in the recording session. Thus, the same number of tracings contributed to the standard and deviant responses for each animal (n = 375).

2.4. Responses to stimuli presented alone

Because the MMN is, by definition, a response to stimulus change, it occurs only when the deviant stimulus is presented in the context of standard stimuli. Therefore, the evoked response to $S_\pi N_0$ when presented in a series alone ($S_\pi N_{0\ alone}$) should not elicit a negativity in the region of the mismatch response (Picton et al., 1985; Kraus et al., 1992). To assess whether a true MMN is present, the response to $S_\pi N_{0\ alone}$ (n = 375) was compared to $S_\pi N_{0\ deviant}$ at each recording location.

It is possible that differences seen in the waveforms collected in the oddball paradigm may be due to the differences in the acoustic features of the two stimuli used. Therefore, comparisons were also made between the responses to $S_0N_{0\ standard}$ and $S_\pi N_{0\ alone}$. Because only the responses immediately preceding $S_\pi N_0$ are used in the averaged response to S_0N_0 (see above), the response to $S_0N_{0\ standard}$ is equivalent to the response that would be obtained if S_0N_0 were presented alone. $S_0N_{0\ standard}$ and $S_\pi N_{0\ alone}$ are referred to as 'intrinsic' responses because they are determined by the basic differences in the acoustic features of each stimulus (rather than by acoustic changes in a stimulus sequence).

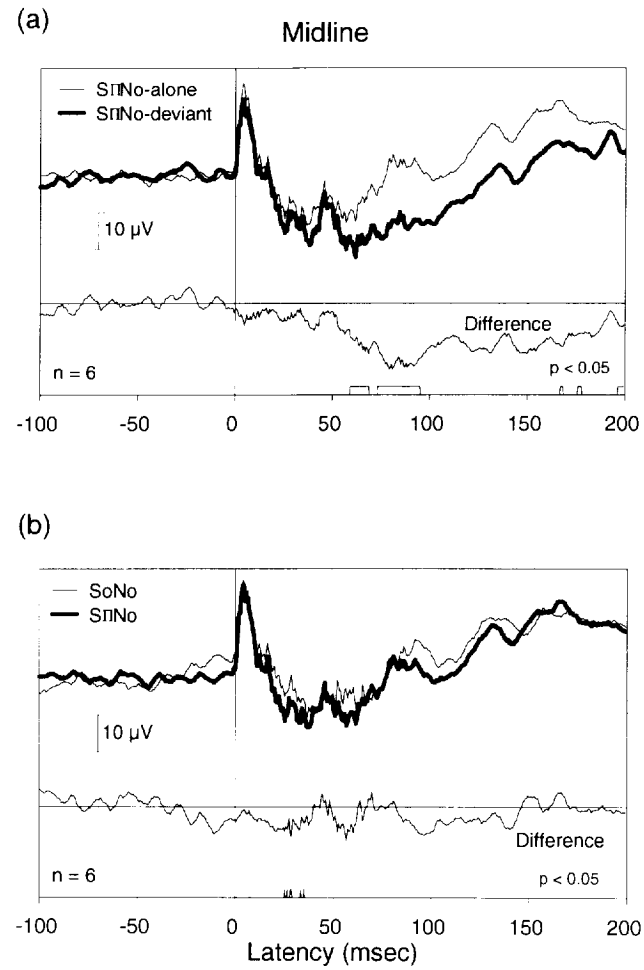

Fig. 2. (a) Averaged responses to $S_\pi N_{0\ alone}$ and $S_\pi N_{0\ deviant}$ recorded over the midline. There are negativities from 60 to 100 ms in the response to $S_\pi N_{0\ deviant}$ that are not seen in the response to $S_\pi N_{0\ alone}$. (b) Averaged responses to $S_0N_{0\ standard}$ and $S_\pi N_{0\ alone}$ recorded over the midline. No significant differences are seen in the two waveforms, indicating that the two stimuli elicit similar responses from brain regions contributing to the midline auditory evoked potential.

2.5. Data Analysis

Grand averages were computed across animals for each recording location. Grand averages of the difference waveforms were then calculated for each condition ($S_{\Pi}N_{0\ deviant}$ minus $S_0N_{0\ standard}$, $S_{\Pi}N_{0\ deviant}$ minus $S_{\Pi}N_{0\ alone}$ and $S_{\Pi}N_{0\ alone}$ minus $S_0N_{0\ standard}$). Using the individual average responses as the data set, point-by-point 2-tailed, paired t-tests were performed on the difference waves comparing the two intrinsic responses. Also, 1-tailed, paired t-tests were performed comparing $S_{\Pi}N_{0\ deviant}$ with $S_{\Pi}N_{0\ alone}$ and $S_{\Pi}N_{0\ deviant}$ with $S_0N_{0\ standard}$ (see Kraus et al., 1993a; 1993b). To meet the assumptions of normality for a t-test, waveforms were normalized by calculating the root mean square (RMS) of the average waveforms for each animal and dividing the waveform voltages by the RMS. Statistical tests were performed on normalized waveforms. Similar statistical analysis was performed on averages of the individual animal responses, using individual tracings as the data set.

3. RESULTS

3.1. Recordings from the midline

When the responses to $S_{\Pi}N_0$ collected in an oddball paradigm ($S_{\Pi}N_{0\ deviant}$) vs. $S_{\Pi}N_0$ collected in a series alone ($S_{\Pi}N_{0\ alone}$) are compared, a broad negativity is seen in the $S_{\Pi}N_{0\ deviant}$ waveform that is not seen in the response to $S_{\Pi}N_{0\ alone}$ (Fig. 2a). The difference waveform reveals regions of significance from approximately 60 to 100 ms, which we consider the 'true' mismatch response, in that it is not confounded by differences in the acoustic features of the stimuli used. A similar negativity was seen in the difference waveform of the responses to $S_0N_{0\ standard}$ and $S_{\Pi}N_{0\ deviant}$ presented in the oddball paradigm (not shown). In contrast, there were no significant differences in the intrinsic responses to $S_0N_{0\ standard}$ and $S_{\Pi}N_{0\ alone}$ recorded from the midline electrode (Fig. 2b), indicating that stimulus differences, per se, are not reflected in the midline response.

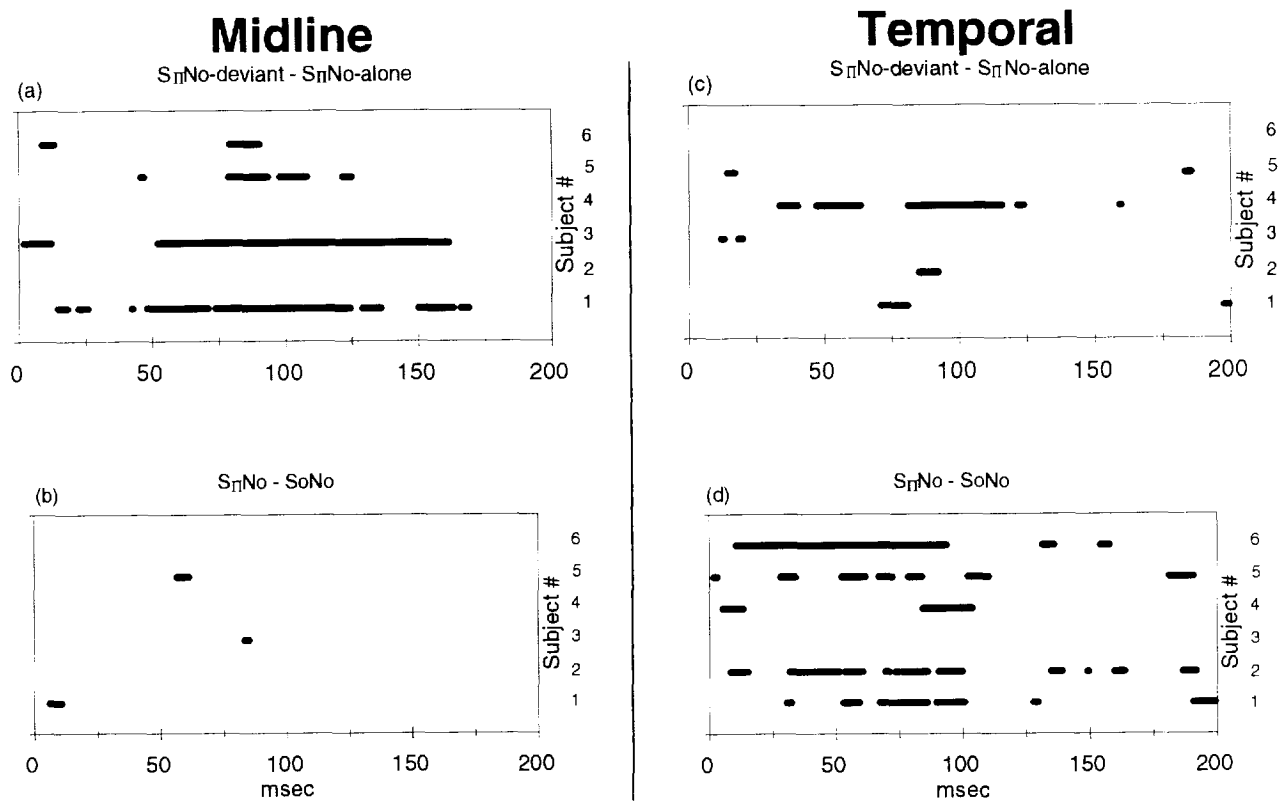

Fig. 3. Regions of significance seen in individual animal responses to $S_{\Pi}N_{0\ deviant}$ minus $S_{\Pi}N_{0\ alone}$ and $S_{\Pi}N_0$ minus S_0N_0 recorded from midline and temporal electrodes. Individual animal responses correspond well to the grand average responses seen in figures 2 and 4. (a) Subjects 1,3,5 and 6 show significant differences between $S_{\Pi}N_0$ collected in a series alone and as the deviant in the oddball paradigm over the midline. (b) There are essentially no regions of significant difference between the intrinsic responses recorded from the midline electrode. (c) Responses to $S_{\Pi}N_{0\ deviant}$ minus $S_{\Pi}N_{0\ alone}$ recorded over the temporal lobe. Averaged responses from subjects 1 and 2 have small regions of significance at approximately 80 ms, corresponding with the large negative peak seen in the grand averages to these responses. Responses from subject 4 show several broad regions of significance. Although these differences are not reflected in the grand average responses in Fig. 4a, these data suggest that there may be source(s) that contributes to the mismatch response that can be recorded from the temporal lobe, at least in some animals. (d) Responses recorded over the temporal lobe from five of the six subjects (1,2,4,5 and 6) revealed significant differences between $S_{\Pi}N_0$ and S_0N_0.

Fig. 3 shows the regions of significance for individual animals. These latencies reflect all areas of significance, including regions outside the latency range that were significantly different in the grand averages for all animals. In figure 3a, responses from four of the six animals showed significant differences between $S_\Pi N_{0\ \text{deviant}}$ and $S_\Pi N_{0\ \text{alone}}$. In comparison, there were virtually no significant differences between the intrinsic responses ($S_0N_{0\ \text{standard}}$ and $S_\Pi N_{0\ \text{alone}}$) in individual animals (Fig. 3b). These patterns correspond well with the responses seen in the grand average waveforms.

3.2. Recordings over the temporal lobe

There is essentially no difference in the response to $S_\Pi N_0$ over the temporal lobe when the stimulus was presented as the deviant stimulus in the oddball paradigm versus in a series alone (Fig. 4a). Thus there is no evidence of a mismatch response. However, responses to $S_0N_{0\ \text{standard}}$ and $S_\Pi N_{0\ \text{alone}}$, which reflect processing of the acoustic features of each stimulus, indicate that differences in the physical parameters of the two stimuli are, in fact, differentiated over the temporal lobe. This can be seen in the different waveform morphologies in response to the two stimuli (Fig. 4b) [1]. The latency ranges that are significantly different are small in comparison with recordings over the midline. However, it is important to note that the waveform morphology over the temporal lobe shows obvious differences between S_0N_0 and $S_\Pi N_0$. The narrow latency ranges over which these differences occur can account for the small regions of significance seen in the subtraction wave.

While no significant differences were seen between $S_\Pi N_{0\ \text{deviant}}$ and $S_\Pi N_{0\ \text{alone}}$ in the grand average waveforms, there were significant differences seen in three subjects' averaged responses (Fig. 3c). Two of the three animals (Subjects 1 and 2) had small regions of significance that corresponded with the large negative peak

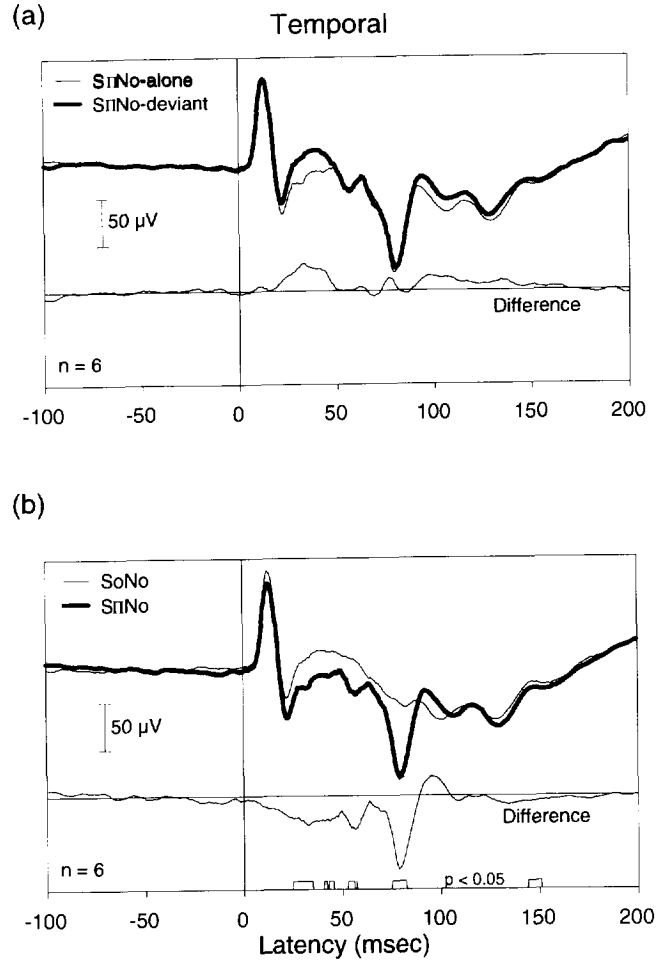

Fig. 4. (a) Averaged responses to $S_\Pi N_{0\ \text{alone}}$ and $S_\Pi N_{0\ \text{deviant}}$ recorded over the temporal lobe. The response to $S_\Pi N_0$ is the same regardless of the manner of presentation, indicating no mismatch response over the temporal lobe to changes in binaural phase. (b) Averaged responses to $S_0N_{0\ \text{standard}}$ and $S_\Pi N_{0\ \text{alone}}$ recorded over the temporal lobe. Significant differences, indicated by the boxes under the difference wave, are seen from 25–100 ms and at 150 ms. Thus, the two stimuli elicit distinct intrinsic responses over the temporal lobe.

seen in the grand average responses of $S_\Pi N_{0\ \text{deviant}}$ and $S_\Pi N_{0\ \text{alone}}$ at approxmiately 80 ms. Responses from Subject 4 showed several broad regions of significance. However, these differences were not reflected in the grand average data. Significant differences between the intrinsic responses were seen in the waveforms of five of the six subjects (Fig. 3d).

4. DISCUSSION

Kraus and colleagues (1994a,b; 1995, review) have demonstrated that an MMN can be recorded at the surface midline and within the MGcm to both tones and certain synthesized speech syllables. Those sites

[1] It should be noted that the difference waves of the responses to $S_0N_{0\ \text{standard}}$ and $S_\Pi N_{0\ \text{deviant}}$ collected in the oddball paradigm show negativites at **both** the midline and temporal electrode sites. However, no mismatch is seen when the temporal responses to $S_\Pi N_{0\ \text{deviant}}$ and $S_\Pi N_{0\ \text{alone}}$ are compared (refer to Fig. 4a). In fact, these responses are nearly identical. Thus, the negativities seen over the temporal area from stimuli presented in an oddball paradigm are actually a reflection of the encoding of intrinsic acoustic differences of the two stimuli, not a true mismatch response (refer to Fig. 4b). In contrast, the midline responses to $S_\Pi N_0$ reflect a characteristic negativity (the MMN) regardless of whether the stimulus is compared to the standard in the oddball paradigm or to itself when collected in a series alone (Fig. 2a). These results bear out the importance of examining not only the responses collected in an oddball paradigm, but also responses to the same stimulus presented in two different conditions, i.e., in a series alone and as the deviant in an oddball paradigm.

have been associated with the non-primary auditory pathway. In contrast, mismatch responses to these same stimuli were not as apparent from the surface over the temporal lobe and entirely absent within the MGv. Those sites have been associated with the primary auditory pathway. Those data provide evidence for a non-primary auditory pathway origin for the MMN. The current study uses the same surface recording locations. Therefore, the results from this study can be discussed in terms of primary vs. non-primary auditory pathway contributions to the MMN, even though recordings from the thalamus were not obtained.

In the present study, the intrinsic responses to S_0N_0 and $S_\Pi N_0$ were very similar at the midline electrode, suggesting that the non-primary auditory pathway response does not reflect the differences in the acoustic features of these two stimuli, i.e., the difference in interaural phase. However, the intrinsic responses recorded from the temporal electrode are significantly different, indicating that the differences in the acoustic features produced by shifting the phase of a 1000 Hz tone in noise 180° are represented in the primary auditory pathway. Steinschneider et al. (1994) reported a related finding, in that the differences in the acoustic stimulus features of the speech-like syllables /da/ and /ta/ (i.e., differences in voice-onset-time) were reflected in different evoked responses from the primary auditory cortex in the awake monkey.

In contrast, the midline response to $S_\Pi N_0$ differed depending on the context in which the stimulus was presented. The negativity seen in the response to $S_\Pi N_{0\ \text{deviant}}$ was not evident in the midline response to $S_\Pi N_{0\ \text{alone}}$ (see Fig. 2a). By inference, we draw the conclusion that the non-primary auditory pathway is predominantly responsive to the change in the stimulus sequence, reflected by the MMN seen in response to $S_\Pi N_0$ only when it is the deviant stimulus in the oddball paradigm. In contrast, the temporal lobe response to $S_\Pi N_0$ is relatively independent of the stimulus context, at least for stimuli differing in interaural phase. This is reflected by the similarity of the responses to $S_\Pi N_{0\ \text{deviant}}$ and $S_\Pi N_{0\ \text{alone}}$ (Fig. 4a).

It is interesting to note that although no significant difference was found between the grand averaged responses to $S_\Pi N_{0\ \text{deviant}}$ and $S_\Pi N_{0\ \text{alone}}$ over the temporal lobe, individual averages of three subjects revealed regions that were significantly different between the two responses. Although the latency ranges were small, a pattern of significant latencies at approximately 80 ms was evident across the three animals. This suggests that there may be some contribution to an MMN from non-primary regions near the temporal recording electrode or from the primary pathway itself. It has been demonstrated that different complex signals can evoke different topographic maps of the MMN, including responses recorded over the temporal lobe to some stimuli (Kraus et al., 1995). Possibly, individual variability in acoustic signal processing could account for why some animals have this response while others do not.

Considered together, the results support the hypothesis that midline and temporal responses reflect different aspects of the encoding of sound. While the representation of intrinsic stimulus properties seems to be reflected principally in the primary auditory pathway, the representation of stimulus change appears to have a strong non-primary auditory pathway contribution. Because the intrinsic responses differ only over the temporal lobe and the MMN is seen primarily over the midline, at least for these stimuli, it is likely that the information needed for coding both basic stimulus properties and stimulus change is shared by the primary and non-primary pathways. Therefore, it seems likely that both pathways are necessary, but neither is sufficient alone, to detect the stimulus differences reflected in the MMN.

This study adds to previous results that demonstrate that the epidural midline is likely to reflect non-primary pathway activity and that this pathway's role is key in the detection of stimulus change, not just with stimuli differing in interaural phase, but with a variety of acoustic stimuli including tones and different synthesized speech syllables. The current findings further suggest that, for interaural phase differences, one of the roles of the primary auditory pathway is the representation of differences in acoustic stimulus features. Because intrinsic responses to stimuli differing in phase are already clearly evident over the temporal lobe, it does not appear to be necessary to use the more complex oddball paradigm to investigate coding of binaural phase differences in guinea pigs. A comparison of the intrinsic responses recorded over the temporal lobe to stimuli differing in phase could provide basic information about the presence or absence of binaural processing. This provides a quick, relatively non-invasive means of assessing binaural processing in developing or experimentally reared animals. However, these experiments represent a 'best case scenario' where the signals are 180° out-of-phase and there is a good signal-to-noise ratio. With 'poorer' listening conditions, the differences seen in the evoked potential recorded over the temporal lobe may not be so obvious, but a mismatch response may still be seen over the midline. In such a case, the MMN may be a better tool for assessing binaural function.

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