ELSEVIER

Clinical Neurophysiology 116 (2005) 669–680

www.elsevier.com/locate/clinph

Auditory temporal processes in normal-hearing individuals and in patients with auditory neuropathy ☆

Henry J. Michalewski[a,*], Arnold Starr[a], Tin Toan Nguyen[a], Ying-Yee Kong[b], Fan-Gang Zeng[b]

[a]*Department of Neurology, University of California, 150 Med. Surge I, Irvine, CA 92697-4290, USA*
[b]*Department of Otolaryngology—Head and Neck Surgery, University of California, Irvine, CA 92697, USA*

Accepted 24 September 2004
Available online 25 November 2004

Abstract

Objective: To study objectively auditory temporal processing in a group of normal hearing subjects and in a group of hearing-impaired individuals with auditory neuropathy (AN) using electrophysiological and psychoacoustic methods.

Methods: Scalp recorded evoked potentials were measured to brief silent intervals (gaps) varying between 2 and 50 ms embedded in continuous noise. Latencies and amplitudes of N100 and P200 were measured and analyzed in two conditions: (1) active, when using a button in response to gaps; (2) passive, listening, but not responding.

Results: In normal subjects evoked potentials (N100/P200 components) were recorded in response to gaps as short as 5 ms in both active and passive conditions. Gap evoked potentials in AN subjects appeared only with prolonged gap durations (10–50 ms). There was a close association between gap detection thresholds measured psychoacoustically and electrophysiologically in both normals and in AN subjects.

Conclusions: Auditory cortical potentials can provide objective measures of auditory temporal processes.

Significance: The combination of electrophysiological and psychoacoustic methods converged to provide useful objective measures for studying auditory cortical temporal processing in normals and hearing-impaired individuals. The procedure used may also provide objective measures of temporal processing for evaluating special populations such as children who may not be able to provide subjective responses.

Keywords: Evoked potentials (EPs); Gap detection; Psychoacoustics; N100; P200

1. Introduction

The ability to make fine temporal discriminations of acoustic signals contributes to a number of auditory perceptions including speech discrimination and the localization of sound. A popular method in psychoacoustics for measuring temporal processes is the threshold for detecting silent gaps in noise (for example, see Phillips, 1999). Typically in gap detection broadband noise is interrupted (producing a gap or silent period) and measurements are made of the minimal gap interval that can be discriminated (gap threshold). In normal hearing subjects, gap durations of 3 ms, or less, have been measured with 'comfortably' loud noise levels (see, for example, Eddins and Green, 1995; Moore, 1997; Zeng et al., 1999), but can increase to 20 ms with noise levels near hearing threshold (Irwin et al., 1981; Zeng et al., 1999). Temporal processing deficits measured by gap detection have been reported for older listeners (Schneider and Hamstra, 1999), children with dyslexia (Ingelghem et al., 2001), patients with sensorineural hearing loss (Nelson and Thomas, 1997), and individuals with auditory neuropathy (Zeng et al., 1999).

Electrophysiological measures of brain events to gaps have been reported. For example, middle-latency magnetic fields (Rupp et al., 2002) and cortical potentials (mismatch negativity or MMN) (Bertoli et al., 2001, 2002; Desjardins et al., 1999) have been recorded. These physiological measures are sensitive to temporal gaps, but they have not received extensive use for the objective assessment of

☆ This research was supported by grant DC-02618 from the National Institutes of Health.

* Corresponding author. Tel.: +1 949 824 7604; fax: +1 949 824 2132.
E-mail address: hjmichal@uci.edu (H.J. Michalewski).

1388-2457/$30.00
doi:10.1016/j.clinph.2004.09.027

temporal processing in patient populations. We have examined procedures to quantify auditory temporal processes using cortical evoked potentials (N100, P200) to gaps in continuous noise. Two groups were studied: (1) a group of normal hearing subjects, and (2) a group of hearing-impaired individuals with auditory neuropathy (AN) (Starr et al., 1996). AN patients have particular problems with auditory temporal processes (Kraus et al., 2000; Starr et al., 1991) reflected by an elevation of gap detection thresholds to as much as 80 ms (Zeng et al., 1999). AN subjects have abnormalities of speech recognition scores (Starr et al., 1996; Zeng et al., 1999) beyond that seen in cochlear hearing loss (Yellin et al., 1989). Word recognition scores in AN subjects when adjusted for the pure tone threshold loss are beyond that seen in cochlear damage. The temporal bone pathology of a patient with AN has shown loss of ganglion cells and auditory axons whereas cochlear hair cells were preserved (Starr et al., 2003).

Even though auditory brain-stem responses (ABRs) are absent or severely abnormal in AN, cortical potentials (e.g. N100 to tones or speech sounds) are often present and frequently delayed in latency (Kraus et al., 2000; Rance et al., 2002; Starr et al., 2003). Here, we have utilized the cortical potentials evoked by gaps in noise to evaluate auditory temporal processing in normals and a group of individuals with AN. The results can be used to differentiate temporal processing deficits and, perhaps importantly, to evaluate temporal processing in special populations where reliable subjective responses are not available.

2. Methods

2.1. Subjects

Twelve healthy normal hearing adults (6 female, 6 male) ranging in age between 18 and 30 years (mean age females, 21.2; mean age males, 20.2) participated in the study. Hearing thresholds for pure tones at 0.5, 1.0, 2.0 and 4.0 kHz measured within a normal range (<10 dB loss) for all subjects. Three normal subjects (from the 12 above) performed the psychoacoustic gap detection test and were found to have gap thresholds between 2 and 3 ms, and are within the threshold norms (2–4 ms) established for our laboratory.

Fourteen AN subjects were tested ranging in age between 9 and 60 years. Table 1 sorts the AN subjects (AN1–AN14) by average speech perception ability, and gives their age at testing and average pure tone hearing. Hearing loss in the group of AN subjects ranged from mild to profound. Speech perception scores were abnormal for AN2–AN12; AN1 had normal scores; and the extent of deafness for AN13 and AN14 was consistent with their inability to recognize speech. ABRs were absent or showed only a delayed Wave V, whereas otoacoustic emissions (OAEs) and/or cochlear microphonics (CMs) were present. Psychoacoustic measures of gap detection were separately performed on AN subjects for comparison with electrophysiological measures of gap detection.

Table 1
Age, pure tone averages, and speech recognition scores for AN subjects

AN subjects	Age	PTA		Speech%	
		Left	Right	Left	Right
AN1	13	17	17	100	100
AN2	9	33	20	88	92
AN3	24	45	50	96	80
AN4	31	50	45	64	40
AN5	12	45	65	55	45
AN6	9	62	78	56	40
AN7	17	50	35	16	40
AN8	18	55	60	12	44
AN9	19	36	36	20	10
AN10	22	70	67	8	4
AN11	36	62	65	0	0
AN12	60	57	58	0	0
AN13	40	90	90	0	0
AN14	9	88	98	n.a.	n.a.

Subjects (AN1–AN14) were ordered by the average speech recognition score (speech% correct). AN, auditory neuropathy; PTA, pure tone average (threshold average for frequencies of 0.5, 1.0 and 2.0 kHz); n.a., not available.

Each normal and AN subject signed an informed consent following local IRB guidelines for testing human subjects and each was paid for participation in the study. Prior IRB approval for the research was obtained before any testing was conducted.

2.2. Audiological procedures in AN subjects

Pure tone audiograms, psychoacoustic gap detection, and speech recognition were measured in each AN subject. Testing was performed in a double-walled sound-attenuating chamber of an adjoining laboratory separate from electrophysiological testing. Pure tone thresholds were determined over a frequency range from 0.25 Hz to 8.0 kHz for each ear through Sennheiser HDA200 headphones. Pure tone averages (PTAs) were computed for frequencies of 0.5, 1.0, and 2.0 kHz. For psychoacoustic gap detection a 3-interval, 3-alternative forced-choice (2-down, 1-up) adaptive procedure was used to quantify performance (70.7% correct response). Broadband white noise bursts (20 Hz–14 kHz) of 500 ms duration (2 ms cosine-squared ramps) were used. A gap or silent interval was centered in the noise burst. Noise bursts were presented monaurally through headphones at a most comfortable loudness level. Trials consisted of 3 bursts with one burst containing a gap. Subjects registered their detection of the gap by pressing a button to a symbol on a computer screen representing one of the tone bursts. Gap stimuli were generated and controlled by a TDT system II (Tucker–Davis Technologies, Gainesville, FL). An on-line example of the psychoacoustic gap

detection procedure can be found at http://www.ucihs.uci.edu/com/hesp/Onlinetest/gapdetection/.

Speech recognition was measured by sentence materials (Bench and Bamford, 1979; Bench et al., 1979) presented through a speaker at the most comfortable loudness level. A total of 10 sentences were used for each condition and each sentence contained 3–5 key words. Percent correct scores were calculated based on the number of words correctly identified.

2.3. Gap stimuli for evoked potentials

A continuous broadband noise (50 Hz–10 kHz) was interrupted every 2.2 s by gaps (silence) of 50, 20, 10, 5, and 2 ms duration. The gap durations were ordered randomly in the sequence and at least 50 trials for each gap were collected for analysis. Fig. 1 shows a simulated section of the noise and gap sequence. The *offset* of the noise (i.e. start of the gap, silence) served as the trigger for averaging brain potentials. A PC-based Neuroscan Stim system was used to generate and control the presentation of stimuli. In normals, the noise and gap sequence was presented monaurally to the right ear from a shielded-transducer (Etymotic Type ER-3A) connected through a 25 cm plastic tube to a foam insert within the ear canal. The continuous noise was fixed at 90 dB SPL, approximately 60 dB above threshold (mean for normals, 29.4 dB SPL). A comparable stimulus procedure was followed for AN subjects. A noise intensity of 90 dB SPL was used in 10 AN subjects, but in 4 subjects, the 90 dB SPL signal was below their threshold for detecting gaps and intensity was increased to 100 dB SPL in two subjects (AN4, AN12), and 110 dB SPL in the other two subjects (AN5, AN11). AN subjects were tested monaurally in the ear with the better PTA, or the right ear if both PTAs were the same.

2.4. Experimental conditions (electrophysiology)

The noise-gap sequence was presented in two conditions for normal subjects. In the active condition, subjects listened to the interrupted noise and pressed a reaction time (RT) button as quickly as possible when a gap was detected.

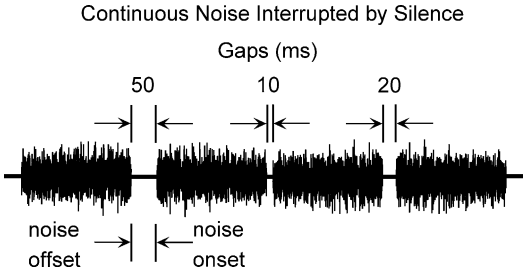

Fig. 1. A simulated segment of the stimulus sequence with gaps of different durations (not to scale) in continuous broadband noise is shown. Noise level was 90 dB SPL; gaps, or silent periods, were at zero. Evoked potential averages were triggered from noise offset.

In the passive condition, subjects were asked to listen to the interrupted noise, but not make a button press. The order of the active and passive conditions was counter-balanced among subjects. For AN subjects, we tested all 14 subjects in the passive condition, but only 9 subjects in the active condition. The 5 AN subjects (AN5, AN7, AN10, AN11, AN14) tested in only the passive condition were the first group tested. Subsequently, 9 AN subjects were tested in both the active and passive conditions.

Each subject was seated in a comfortable adjustable chair and was instructed to look at a fixation point directly ahead. Subjects were tested in a sound-attenuating chamber. Testing took approximately 10 min for each condition with a 3–5 min break between runs.

2.5. Recording and analysis

Scalp recordings were made with Ag–AgCl electrodes from midline sites Fz, Cz, and Pz and lateral placements C3 and C4 referenced to linked mastoids. Additional electrodes were located above and below the right eye to monitor ocular movements. A ground electrode was placed on the forehead. A PC-based Neuroscan recording system (Scan) with SynAmps (biological amplifiers) was used to collect the EEG data. Amplifier bandpass was set between DC and 100 Hz. Ongoing EEG was digitized (500 Hz) and stored to disk. Off-line, digitized EEG records were adjusted for DC drift (based on a polynomial fit) and were corrected for ocular artifact (eyeblinks) with Scan system software. Processed records were then epoched to include a 100 ms pre- and 800 ms post-stimulus analysis period. Separate averages were computed to each gap (2, 5, 10, 20 and 50 ms) in the passive condition, and to correct responses in the active condition.

Peak latency and amplitude were determined for N100 and P200 in the active and passive conditions, and a late positive peak, identified as P300, in the active condition. Evoked potential latencies were determined from the offset of the continuous noise to peak maximum; peak amplitudes were measured relative to the average of the pre-stimulus (before noise offset) baseline period to the peak voltage. Averages were lowpass filtered (Butterworth) with an upper corner frequency of 30 Hz (12 dB/octave slope) before peak measures were computed.

For the normal group, analysis of variance procedures (ANOVA) for repeated measures were used to separately evaluate peak latency and amplitude (N100, P200, P300), hearing threshold frequencies, noise thresholds, accuracy, and RTs. A 4-factor design (one between factor, 3 repeated measures) was used to analyze evoked potential measures (gender × condition × gap duration × electrode site). Only the midline sites (Fz, Cz, and Pz) were used in the analysis of electrode site. Post hoc tests of the means used the Tukey procedure. Correlation (r) procedures were used to examine the relationship between psychoacoustic and N100 gap thresholds, and the acoustic thresholds (continuous noise)

between males and females were evaluated by *t*-test. Differences of $P<0.05$ were considered significant. Test results for the AN subjects are considered separately relative to normal findings. Results for the normal hearing group are presented first followed by the results from the AN subjects.

3. Results

3.1. Normal subjects

3.1.1. Hearing

Normals showed no gender ($F(1,10)=<1$, $P=0.68$) or pure tone (0.5–4.0 kHz) threshold differences ($F(3,30)=1.5$, $P=0.23$). Thresholds for continuous noise were slightly lower for females (28.0 dB SPL) than for males (30.8 dB SPL), but the difference was not significant ($t(10)=-1.65$, $P=0.13$).

3.1.2. Accuracy and RT measures

Accuracy in the active condition was affected by gap duration ($F(4,40)=75.0$, $P<0.001$). Detection was approximately 99% for gaps of 50, 20, and 10 ms, but dropped to 73% and 17% for the 5 and 2 ms gaps, respectively. The accuracy for gaps at 5 and 2 ms was significantly reduced compared to the other gap durations (50, 20, and 10 ms); accuracy at 2 ms was significantly less than at 5 ms. Fig. 2A (top) shows both the average percent correct and the mean RT to the separate gap durations for normals. Reaction times were also affected by gap duration ($F(4,40)=10.7$, $P<0.001$). RTs were shorter to 50, 20, and 10 ms gap durations than to 2 ms gaps; RTs were shorter to 5 ms than to 2 ms gaps. No gender differences were indicated for either accuracy ($F(1,10)=1.76$, $P=0.21$) or reaction time ($F(1,10)<1$, $P=0.85$).

3.1.3. Evoked potentials

Grand averaged potentials in the passive and active conditions to the separate gap durations are shown for the midline sites Fz, Cz, and Pz sites in Fig. 3, and the measures of latency and amplitude for Cz are summarized in Table 2. The N100 and P200 components were evident for 50, 20, 10, and 5 ms gaps in both the passive and active conditions; potentials for 2 ms gaps, however, were not defined in either condition. A sustained, late slow wave (LSW) after P200 and a superimposed P300 peak were present in the active condition for all gap durations (and perhaps marginally at 2 ms).

The N100 component in the grand averages was broad in duration and was separated into two components for gap durations of 50 and 20 ms, best visualized at the frontal (Fz) recording site (Fig. 3) for both conditions. Two distinct N100 peaks were also evident in the overlayed individual averages for the frontal site at 50 ms in Fig. 4, and less so at the other gap durations. Examining either passive or active conditions, 8 of the 12 subjects showed two components at

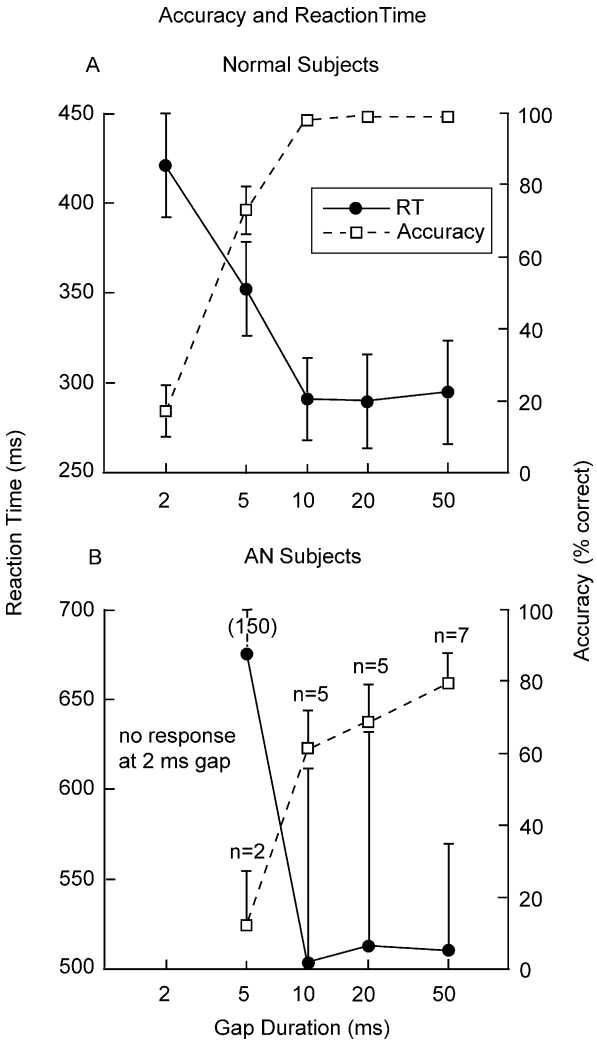

Fig. 2. Mean accuracy and reaction time to gap durations in the active condition are shown for normals (2A, top) and AN subjects (2B, bottom). AN subjects showed a similar pattern of behavioral responses, but were less accurate and had longer RTs than normals. Standard errors (SEs) are indicated. Note that SE bars for accuracy at 10, 20, and 50 ms gaps fall within the symbol (–□–) for normals.

Fz for the 50 ms gap duration; at the 20 ms gap, 5 of the 12 subjects showed two components; at 10 and 5 ms gaps, the separation of components was difficult to resolve. The second, and later of the two peaks, was usually the larger of the two components. For the 50 ms gap, a latency analysis indicated that the first N100 peaking at approximately 92 ms was significantly earlier than the peak of the second N100 component occurring at approximately 155 ms at Fz in the passive condition ($F(1,7)=175$, $P<0.001$).

3.1.4. Contribution of noise offset (gap onset) and noise onset (gap offset) to the N100

The appearance of two N100 peaks to gaps of 50 and 20 ms was unexpected. Typically substantially longer stimulus durations (e.g. 1–2 s tone bursts) are required to define separate clear onset/offset N100 components for

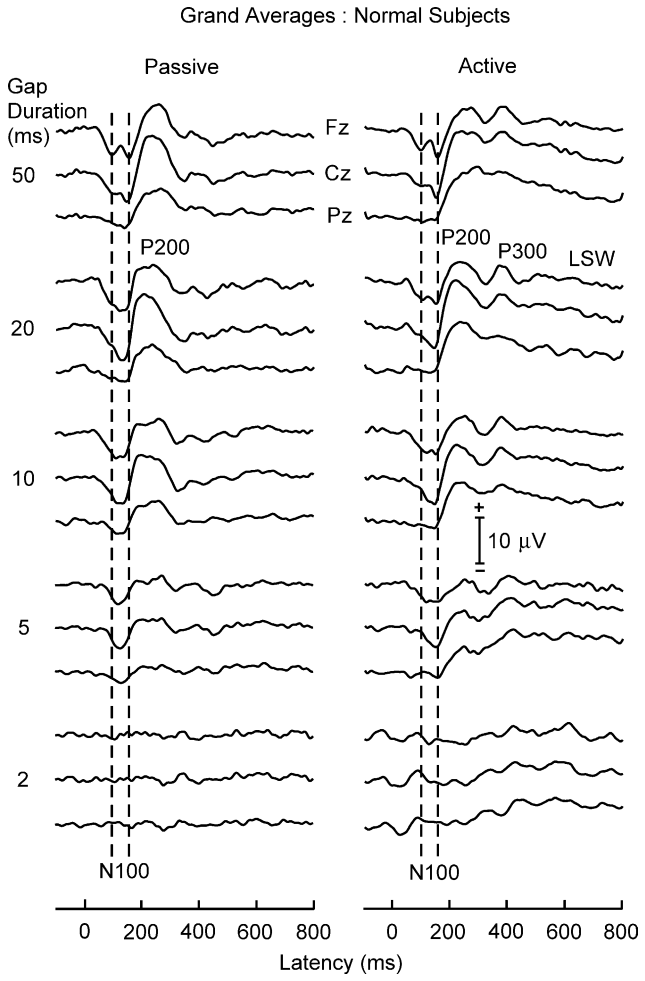

Fig. 3. Grand averaged potentials are shown for normal subjects as a function of gap duration in the passive and active conditions. N100/P200 potentials were present for both conditions for gap durations from 50 to 5 ms; at 2 ms, potentials could not be distinguished from background activity. Note the two negative peaks in both conditions at Fz for the 50 ms gap duration; at shorter gap durations (10 ms or less) a single peak was present intermediate in latency between the two negative components in the passive and active conditions (broken vertical lines drawn at the 50 ms gap).

scalp-recorded averages. Two possible alternative explanations for the two peaks are considered. First, there may be more than one peak generated at the offset of the continuous noise (gap onset). Second, the double N100 peaks may result from separate N100 responses to both the noise offset (at the beginning of the gap) and to noise onset (at the end of the gap).

To address the first alternative we tested 4 normal subjects with extended gap durations in order to temporally separate the cortical responses to noise offset and to noise onset. In addition to the regular gaps (50–2 ms), gaps of 100, 250, 500, and 1000 ms duration were randomly integrated into the stimulus sequence (and otherwise no different from the recording procedures used in the passive condition). A clear separation of offset N100 and onset N100 responses was apparent for the extended gap durations of 500 and

Table 2
Mean latency and amplitude for N100 and P200 in the passive and active conditions, and P300 in the active condition for normal subjects at Cz

Peak	Gap duration (ms)	Passive		Active	
		Latency (ms)	Amplitude (µV)	Latency (ms)	Amplitude (µV)
N100 (later peak)					
	50	140 (26)	−7.5 (3.6)	143 (24)	−6.1 (3.9)
	20	133 (12)	−8.0 (4.5)	136 (16)	−6.1 (2.7)
	10	131 (16)	−6.5 (3.5)	139 (13)	−6.7 (4.0)
	5	125 (14)	−5.3 (2.7)	144 (26)	−5.0 (2.5)
N100 (earlier peak)					
	50[a]	92 (6.0)	−5.1 (0.9)	83 (4.7)	−4.2 (.35)
	20[b]	83 (6.9)	−4.7 (0.9)	93 (11.9)	−4.9 (1.4)
P200					
	50	233 (24)	10.3 (3.6)	232 (30)	10.9 (4.5)
	20	220 (28)	9.0 (3.4)	219 (32)	12.1 (4.6)
	10	218 (35)	7.5 (3.3)	220 (18)	7.8 (4.2)
	5	208 (23)	3.0 (2.8)	231 (26)	4.9 (4.3)
P300					
	50			359 (50)	11.4 (6.1)
	20			373 (43)	9.1 (6.7)
	10			367 (31)	8.2 (6.1)
	5			387 (31)	7.6 (7.0)

The SD is indicated in parenthesis.
[a] Passive, $n=8$; active, $n=7$.
[b] Passive, $n=5$; active, $n=4$.

1000 ms. The averages for two subjects (with a good to signal-to-noise ratio) are shown in the left panel of Fig. 5 for the 500 ms gap duration for the midline sites. The offset N100 response was broader in duration than the sharply peaked N100 onset response. The offset response had a negative peak (or inflection) at Fz of 106 ms (A) and a later, larger negative peak at 152 ms (B); the onset response had a negative peak at 111 ms (C). We then superimposed 'offset' and 'onset' responses from the 500 ms gap aligned to stimulus change (offset/onset) shown in the right panel of Fig. 5. Note that the early offset N100 peak (A) is aligned with the onset N100 peak (C); the late offset N100 (B) remained distinct and separate from the earlier peaks. These records provide evidence that both early (100 ms) and late (150 ms) negative components can occur to noise offset.

To address the second alternative explanation for the double N100 peaks (i.e. that the double peak N100 results from the occurrence of both noise offset and noise onset components), we temporally shifted the gap potentials to align them to the onset of the noise occurring at the end of the gap. The averages aligned in this manner are shown for Fz in Fig. 6 for the passive and active conditions. Only a 300 ms portion of the average evoked potential is shown to emphasize the negative components. A dashed vertical line was drawn at 100 ms for both conditions. The late N100 potential at gap durations of 50 and 20 ms for both conditions aligns at 100 ms (gap offset), but not at the other durations. At least for the long gap duration (50 ms),

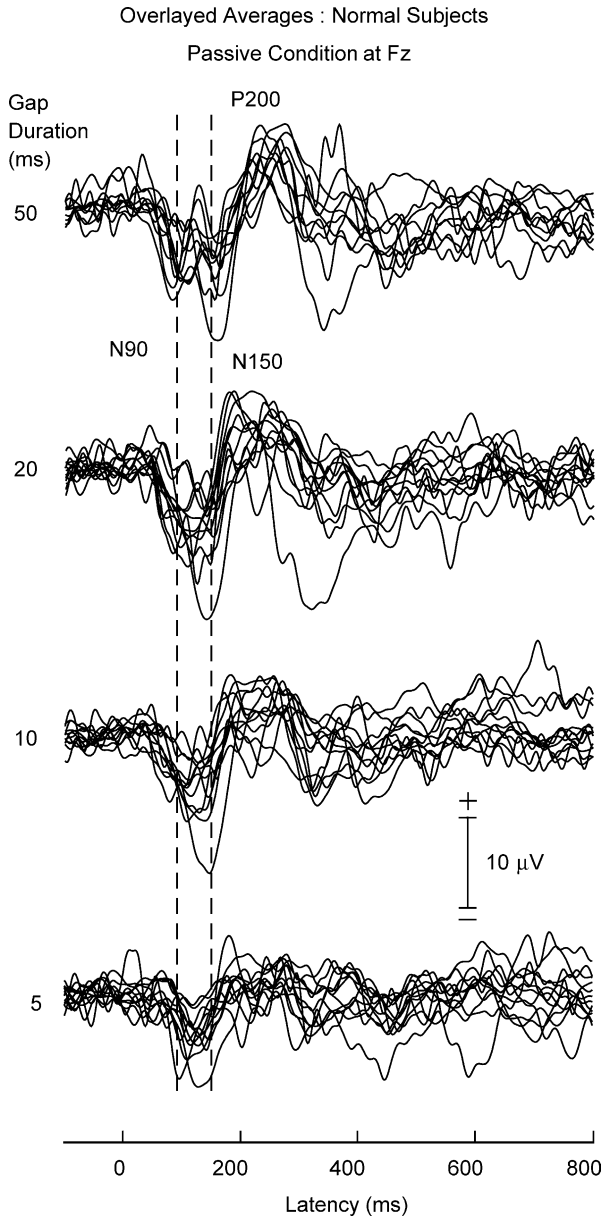

Fig. 4. Individual averages from normal subjects at Fz are shown overlayed to illustrate the occurrence of two peaks (N90 and N150) at the 50 ms gap duration in the passive condition. Eight out of 12 subjects clearly showed two peaks at the 50 ms gap. Broken vertical lines are drawn at the 50 ms gap for the two negative components.

shifting the waveforms to correspond to noise onset (gap offset) may account for the second peak of the double N100.

3.1.5. N100 latency

The largest negative peak in the interval between (90–190 ms) was used to define N100 measures of latency and amplitude in our analyses for gaps 5–50 ms. As indicated above (Sections 3.1.3 and 3.1.4), for some subjects this might be the second or later N100 peak, but for others the dual-component complex was not apparent and only the largest negative component was measured.

There were no latency effects for gap duration ($F(3,30) < 1$, $P = 0.70$), condition ($F(1,10) = 2.65$, $P = 0.13$), electrode site ($F(2,20) = 2.03$, $P = 0.16$), or gender ($F(1,10) < 1$, $P = 0.99$). N100 latencies were longer to the 50 ms gap than the other gap durations, but the differences were not significant (Table 2).

3.1.6. N100 amplitude

Significant effects for N100 amplitude were indicated for gap duration ($F(3,30) = 4.9$, $P < 0.007$), electrodes ($F(2,20) = 50.1$, $P < 0.001$), and gender ($F(1,10) = 6.6$, $P < 0.028$), whereas no differences between conditions were found ($F(1,10) = 2.12$, $P = 0.18$).

N100 amplitudes were significantly larger for 50 and 20 ms gaps than at 5 ms (Fig. 3). The electrode effect showed that Fz and Cz were larger than at Pz for all gap durations; differences between Fz and Cz were not significant.

Separate grand averages for females and males for gap duration in the passive and active conditions are shown in Fig. 7. The gender effect indicated that females overall had larger N100 amplitudes (by approximately 50%) than males, but gender did not interact with factors of gap duration, condition, or electrode site.

3.1.7. P200 latency

No significant P200 latency effects were found for gap duration ($F(3,30) = 2.3$, $P = 0.01$), condition ($F(1,10) = 3.04$, $P = 0.11$), electrode ($F(2,20) = 1.35$, $P = 0.28$), or gender ($F(1,10) = 3.5$, $P = 0.09$). P200 latencies were longer at the 50 ms gap duration than for the other gap durations (20, 10, 5 ms), but none of the differences attained significant levels (Fig. 3 and Table 2).

3.1.8. P200 amplitude

P200 amplitude increased ($F(3,30) = 44.9$, $P < 0.001$) with longer gap durations (Fig. 3). The amplitude of P200 for gaps of 50 and 20 ms were both larger than the 10 or 5 ms gaps; P200 was larger for the 10 ms gap than the 5 ms gap (Table 2). P200 amplitude was larger overall in the active condition (approximately 20%) than the passive condition ($F(1,10) = 6.19$, $P < 0.03$). Measures of P200 amplitude were not affected by gender ($F(1,10) = < 1$, $P = 0.46$).

3.1.9. P300 latency and amplitude (active condition)

No significant latency effects for P300 latency were found for gap duration ($F(3,39) = 1.29$, $P = 0.29$), electrode site ($F(2,20) < 1$, $P = 0.82$) or gender ($F(1,10) < 1$, $P = 0.57$). P300 latencies were longer to the 5 ms gap than the 50 ms gap (Fig. 3 and Table 2), but the differences were not significant. However, P300 amplitudes were affected by gap duration ($F(3,30) = 4.46$, $P < 0.01$) and electrode site ($F(2,20) = 11.3$, $P < 0.001$). P300 amplitudes were larger for 50 ms gaps than 10 or 5 ms gaps (Fig. 3). The electrode

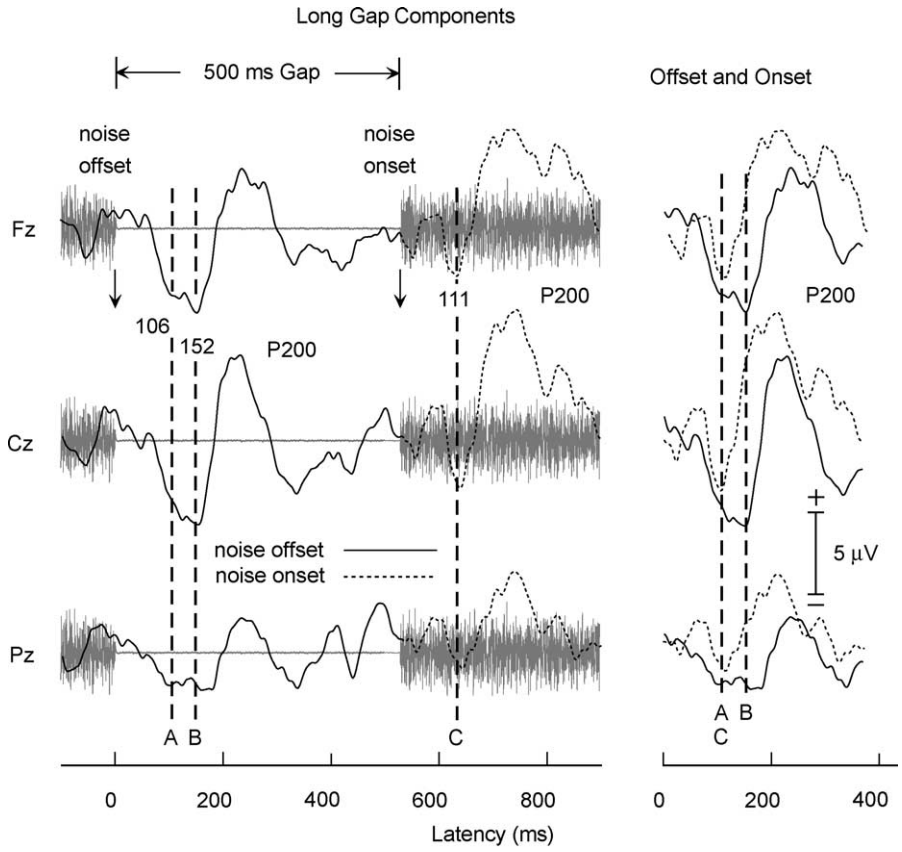

Fig. 5. Left panel shows the averages of two normal subjects to a gap of 500 ms duration. The offset and onset of the noise are indicated. Note the offset components at 106 ms (A, inflection) and 152 ms (B), and the onset component at 111 ms (C) at Fz. Right panel portrays the offset and onset components from the long gap aligned to stimulus change. Note that the early offset (A) and onset (C) are similar in latency whereas the later offset component (B) remains distinct.

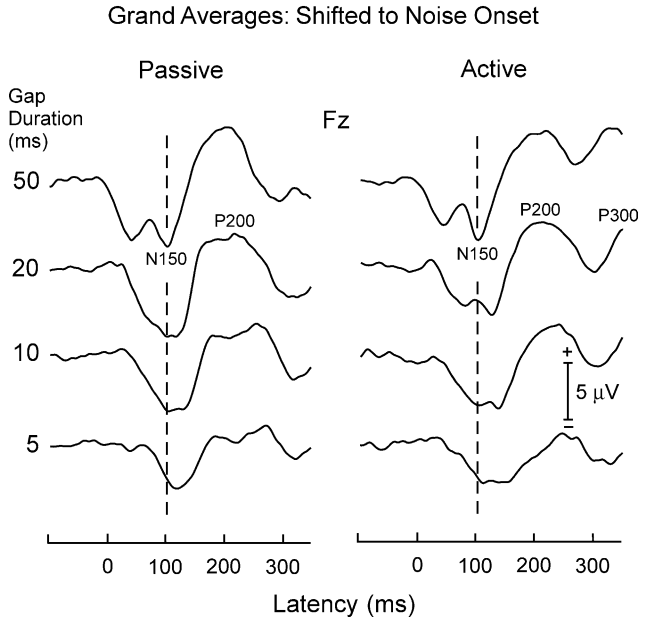

Fig. 6. Grand average waveforms shifted to equivalent gap noise onset. Note the alignment of the late N150 peak to the other gap durations. The vertical broken line is at 100 ms.

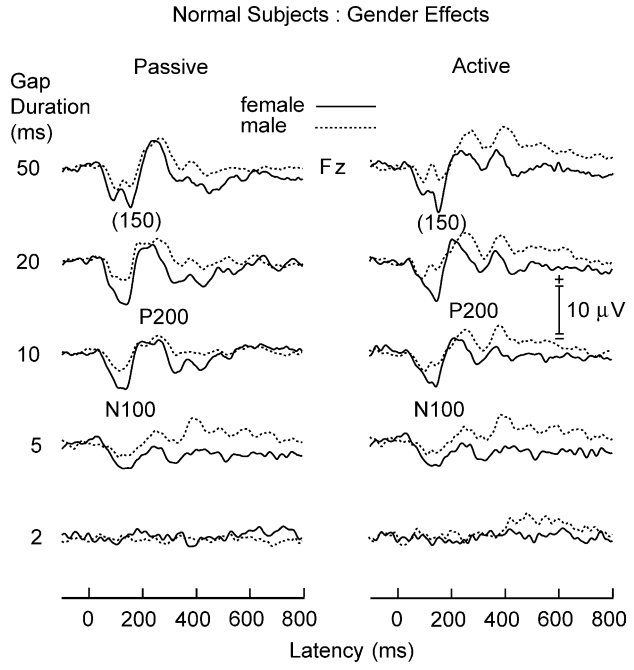

Fig. 7. Superimposed grand averages for females and males in the two conditions showing the N100 gender amplitude effect for gap durations over 50–5 ms. N100 amplitudes were larger for females than males by approximately 50% across gap durations and conditions.

Table 3
Thresholds for gaps defined by the presence of the N100 component evoked potential (Cz) and by psychoacoustic methods

Subjects	Condition passive/active	Noise dB SPL	N100 thresholds for gaps (ms)		N100 latency (ms) to threshold gaps		Gap (ms)
			Passive	Active	Passive	Active	Psychoacoustic
Normals	P/A	90	5	5	99–148	83–181	3 or less[a]
AN subjects							
N100 present to gaps in passive (n=7) and active (n=4) conditions							
AN1	P/A	90	10	10	118	136	5
AN3	P/A	90	10	10	139	143	5
AN4	P/A	100	10	10	**181**	**204**	8
AN6	P/A	90	20	20	**160**	151	10
AN7	P	90	20	n.t.	**179**	n.t.	10
AN10	P	90	20	n.t.	**158**	n.t.	30
AN11	P	110	30	n.t.	**230**	n.t.	30
N100 absent to gaps in passive condition but present in active condition							
AN2	P/A	90	n.r.	20	n.r.	177	5
AN8	P/A	90	n.r.	20	n.r.	**213**	21
AN9	P/A	90	n.r.	20	n.r.	**191**	20
AN12	P/A	100	n.r.	50	n.r.	**240**	40
N100 absent-profoundly deaf							
AN5	P	110	n.r.	n.t.	n.r.	n.t.	30
AN13	P/A	90	n.r.	n.r.	n.r.	n.r.	n.r.
AN14	P	90	n.r.	n.t.	n.r.	n.t.	n.r.

The ranges of N100 latencies to 5 ms gaps (threshold) for normals in passive and active conditions are indicated. Noise dB SPL (sound pressure level) refers to the stimulus level of the continuous noise. AN, auditory neuropathy; P, passive; A, active; n.t., not tested; n.r., no response. N100 latencies in bold were outside upper latency limits for normals.

[a] Psychoacoustic gap thresholds for normal hearing individuals (Eddins and Green, 1995; Moore, 1997).

effect indicated that P300 amplitudes (likely superimposed on the LSW) were larger at Cz and Pz than at Fz.

3.2. AN subjects

AN psychoacoustic gap detection thresholds ranged between 5 and 40 ms (Table 3) except for subjects AN13 and AN14 who were profoundly deaf and both did not have either button responses or have evoked potentials to the gaps.

Gap evoked potentials were present in 7 of the 14 subjects (AN1, AN3, AN4, AN6, AN7, AN10, AN11) in the passive listening condition at thresholds approximating those obtained in psychoacoustic measures of gap detection ($r=0.79$, $P<0.03$). The mean latencies of N100 to the gaps in 5 of these 7 AN subjects (AN4, AN6, AN7, AN10, AN11) were delayed beyond the upper range of control subjects (148 ms) and the extent of the delay ranged from 10 to 82 ms (Table 3, passive condition). For example, the N100/P200 components were present to the 10 ms gap in 3 subjects (AN1, AN3, AN4) with psychoacoustic gap thresholds of 5, 5, and 8 ms, respectively. The evoked potentials for AN4 with a mild temporal disorder (8 ms psychoacoustic gap threshold) are shown in the left panel of Fig. 8. The N100/P200 components to gaps of 50, 20, and 10 ms were present, but absent (or marginally present) to 5 ms. In contrast, evoked potentials from AN11 with an intermediate temporal processing disorder (30 ms gap threshold measured psychoacoustically) are shown in the right panel of Fig. 8; additional gap durations were provided (10 ms steps) in this one subject to more closely match the psychoacoustic threshold. For this subject N100/P200 components were present to the 50

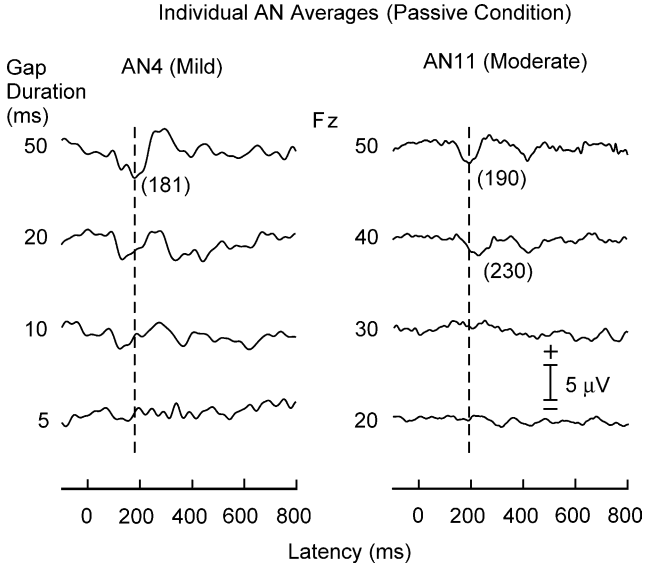

Fig. 8. Average cortical potentials for AN4 and AN11 classified by speech testing as mild and moderate, respectively, in the passive condition. A broken vertical line in the panels was positioned at the N150 component. The latency (ms) of this peak for each subject is in parenthesis. AN4 had a psychoacoustic gap threshold of 8 ms; cortical N100/P200 potentials were present to the 50, 20 and 10 ms gaps at delayed latency. AN11 had cortical potentials present at 50 and 40 ms, but delayed latency, with a psychoacoustic gap threshold of 30 ms.

Table 4
Mean reaction times (ms) and correct responses (percent in parenthesis) for AN subjects in the active condition

AN subjects	Gap duration (ms)				
	50	20	10	5	2
AN1	442 (80)	404 (66)	381 (74)	512 (12)	n.r.
AN3	268 (100)	269 (98)	339 (100)	818 (14)	n.r.
AN4	507 (80)	359 (56)	291 (50)	n.r.	n.r.
AN6	767 (38)	975 (33)	874 (32)	n.r.	n.r.
AN2	512 (88)	615 (88)	497 (52)	n.r.	n.r.
AN8	1760 (38)	1490 (34)	1360 (28)	n.r.	n.r.
AN9	451 (94)	n.r.	n.r.	n.r.	n.r.
AN12	678 (73)	n.r.	n.r.	n.r.	n.r.
AN13	n.r.	n.r.	n.r.	n.r.	n.r.

AN13 had a PTA of 90 db, profoundly deaf. n.r., no response.

and 40 ms gaps, but absent to the 30 and 20 ms gaps. Four of these 7 AN subjects (AN1, AN3, AN4, AN6), also performed the active version of the gap task and the evoked potential gap thresholds (10 ms in 3 subjects, and 20 ms in one subject) were similar between the two conditions for these subjects. Average percent correct and mean RTs are shown in Fig. 2B (bottom) for AN subjects performing the active condition, and individual values are shown in Table 4. An analysis of mean reactions times for gap durations of 50, 20, and 10 ms (excluding AN8 who had very prolonged RTs) were not significantly different from each other ($F(2,8)<1$, $P=0.67$); similarly, differences in the percent correct for the same gap durations were not significant ($F(2,8)=2.8$, $P=0.12$). AN subjects performing the active condition had P300 potentials that were delayed (approximately 50 ms) and of smaller amplitude (approximately 50%) than normals.

There were 7 AN subjects (AN2, AN8, AN9, AN12, AN5, AN13, AN14) without evoked potentials to any of the gap durations between 5 and 50 ms in the passive condition. The results were expected in two of these subjects (AN13, AN14) with a profound hearing loss (PTAs of 90 and 93 dB, respectively; Table 1). Since the noise signal in our system could not be made sufficiently intense to compensate for this loss, acoustic signals and psychoacoustic gap thresholds were not obtainable on these two subjects because of their hearing loss. There were 4 subjects (AN2, AN8, AN9, AN12), however, with a mild hearing loss (PTAs of 27, 58, 36, and 58 dB, respectively) and N100 gap potentials that were present in the active condition, but absent in the passive condition. Psychoacoustic gap thresholds ranged between 5 and 40 ms (AN2, AN8, AN9, AN12; Table 3). The EEG in these subjects did not show evidence of drowsiness that might affect attentional processes during the passive condition. In the active condition, 3 of the 4 subjects showed delayed N100/P200 components (N100 latencies of 213 ms [AN8], 191 ms [AN9], and 240 ms [AN12]) with evoked potential thresholds comparable to psychoacoustic gap measures. The gap potentials for AN2 with a latency of N100 at the upper limits of normal (177 ms) are shown in Fig. 9 for the passive and active conditions. Note the presence of N100 potentials to 50 and 20 ms gaps in the active condition (right) and their absence in the passive condition (left). Thus, it appeared that the combination of the requirements to 'listen' coupled with button press response in the active condition modulated the appearance of N100 in these 4 AN subjects in a manner qualitatively different both from other AN subjects and from normal hearing subjects.

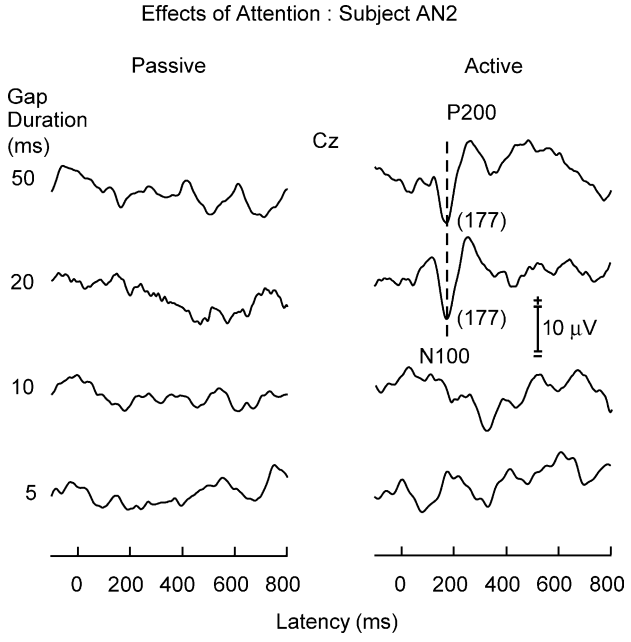

Fig. 9. Averaged cortical potentials for AN2 (age 9) are shown during the passive and active conditions. The broken vertical line in the right panel was positioned through the negative peaks at the 50 and 20 ms gaps; peak latencies (ms) are in parenthesis. In the passive condition no clear cortical components were identified; however, in the active condition N100/P200 potentials were present at gaps of 50 and 20 ms. The psychoacoustic gap threshold for this child was 20 ms. Note that all trials for the 5 ms gap were averaged in the active condition regardless of accuracy.

4. Discussion

4.1. Normal subjects

The results in the present study demonstrate that in normal hearing subjects auditory cortical-evoked potentials can be recorded to gaps in continuous noise in conditions that require either the detection of the gap (active), or listening to the stimuli without any instructions to identify the gaps (passive). In the normal subjects, evoked potentials (N100 and P200) to gaps as short as 5 ms were recorded whereas at 2 ms the potentials were absent, a close approximation to psychoacoustic measures of gap detection in normals (Eddins and Green, 1995; Moore, 1997; Zeng et al., 1999). Comparable cortical gap threshold results have been reported by others. For example, Desjardins et al. (1999) recorded mismatch negativity to measure gaps to short duration tones and estimated MMN thresholds at approximately 4 ms, comparable to 5 ms threshold we found for potentials to gaps in continuous noise. In another study, Bertoli et al. (2001) elicited MMN to gaps (in 1 kHz sinusoids with masking noise) at 3, 6, 9, and 15 ms and separately measured psychoacoustic gap thresholds. A MMN was recorded to gap durations longer (9 and 15 ms) than the mean psychoacoustic threshold at 6.4 ms. However, longer gap durations were required to elicit a clear MMN in older individuals although psychoacoustic gap thresholds between younger and older subjects were not different (Bertoli et al., 2002). Overall, the gap thresholds determined from these cortical measures are in good agreement given the methodological and stimulus differences among studies.

Psychoacoustic methods for determining gap detection thresholds use an adaptive procedure and are more sensitive than the 5-fixed gap durations used here. However, we altered gap durations in AN11 (Fig. 8) to provide a finer resolution between gap duration steps (e.g. 10 ms), a technique that may be useful in some patient testing situations.

Overall amplitudes for N100 were larger for females than males across conditions, gap duration, and electrode sites (Fig. 7). Gender effects for amplitude are generally not observed for N100 although found in other measures such as certain components of the auditory brain-stem potentials (for example, Michalewski et al., 1980). Baumann et al. (1991) reported that there was a difference in the location and orientation of dipole sources for the auditory evoked N100m for females compared to males. The differences recorded here between females and males cannot be directly attributed to pure tone hearing differences, noise threshold differences, or related to behavioral measures of accuracy or reaction time since no gender effects were indicated for any of these factors. It is speculative, however, to account for gender differences based on the present experimental variables and small sample size without further study.

A late positive peak, P300, was observed in the active condition, which progressively decreased in amplitude and was delayed in latency as gap duration shortened. This is a pattern of P300 associated with task difficulty or increasing perceptual demands (for example, Michalewski et al., 1988; Polich, 1986, 1987) and is reflected in the longer decision times of the shorter, more difficult, gap durations. Behavioral RTs complement P300 measures by providing evidence that the speed of response increased as gap duration decreased. The presence of P300 in the active condition and its absence in the passive condition affirms a distinction between the two experimental tasks.

4.2. AN subjects

In 7 of the 14 subjects with AN we found a close agreement between thresholds for gap duration using the evoked potential in the passive condition and psychoacoustic measures. However, there were 4 AN subjects who did not have evoked potentials in the passive listening condition, but did have psychoacoustically defined gap thresholds ranging between 5 and 40 ms. We were able to document in these 4 AN subjects that task condition (active listening, passive listening) was the key factor accounting for the discrepancy. Auditory EPs to gaps that were absent in passive listening in these 4 subjects, became clearly identifiable when they engaged in identification of the gaps in continuous noise. EP gap thresholds in the active condition for 3 of these 4 AN subjects were similar to their psychoacoustic gap thresholds. The role of attention in modulating auditory cortical responses was striking in AN in contrast to normal hearing controls who showed no significant difference in latency or amplitude of the N100 components between the passive and active conditions. AN subjects have altered auditory nerve input due to a decrease in the number of functioning fibers and their degree of synchrony (Starr et al., 2003). The profound effects of attention in auditory cortical potentials may represent the involvement of central auditory processes perhaps compensating for the sensory deafferentation. For instance, a change in the auditory environment has been associated with the appearance of a negative component that can range in latency up to 150 ms (Jones and Perez, 2002) with response features that differ from the typical onset N100 responses.

A prolongation of N100 latency of auditory cortical potentials to tone or speech onset has been noted in AN (Kraus et al., 2000; Rance et al., 2002; Starr et al., 2003) and in adults (N100m) with sensorineural hearing loss approaching threshold (Morita et al., 2003). A delay of N100 latency to gaps was identified in 8 of the 11 AN subjects in this study. The average latency was 182 ms in the passive condition (normals, 140 ms) and 212 ms in the active condition (normals, 143 ms), and extended in AN12 to 240 ms. Only a portion of the latency delay might be attributed to the elevated thresholds of hearing in AN since in normal subjects, N100 to tones may be delayed approximately 25 ms at threshold compared to suprathreshold intensities (Davis et al., 1966). However, AN subjects

have N100 latency delays as much as 70 ms to tones (Starr et al., 2003) and as much as 80 ms to gaps in the present study. The mechanisms underlying the prolonged latency of auditory evoked potentials in AN subjects is likely a central effect, again perhaps as a consequence of sensory deafferentation that occurs in the auditory system of AN subjects (Starr et al., 2003).

4.3. Cortical 'off' and 'on' responses

The cortical potentials recorded to gaps were triggered from the offset of the noise and can be distinguished from the onset N100 evoked to regular tones and noises. N100 *off* responses were broad and many times consisted of two separate components in most subjects when gap durations were longer than 20 ms: an early component peaking at 90 ms, similar in latency to an onset N100 and a later component peaking at approximately 150 ms. At gap durations of 20 ms or shorter, the N100 consisted of a single component approximately centered between the earlier 90 ms and the later 150 ms latency component (Fig. 3). Two possible explanations were advanced to account for the double peaks. First, when gap durations were extended so that clear and separable negative offset and onset potentials were apparent (e.g. 500 ms gap), as illustrated in Fig. 5, two components were present at the offset of the noise, an early peak at 106 ms (A) and a later peak at 152 ms (B); when noise was reinstated after the gap there was a narrow onset N100 peaking at 111 ms (C); the early offset peak and onset peaks (A and C, respectively) were almost coincident when aligned at stimulus change (Fig. 5). The two early and late N100 components were also evident at gap offset for the extended gap durations of 250 and 1000 ms (records not shown). The later negative peak to noise offset was frontally prominent and did not vary in latency among the extended gap durations. We are not certain of the identity of this second later component, but it might be related (a) to a separate perceptual distinction made by the subjects to longer gap durations (Phillips, 1999), (b) or a type of mismatch negativity representing stimulus change, given its scalp distribution (frontal) and timing (approximately 150 ms) (Näätänen, 1992), (c) or even a negative component related to auditory change, an 'acoustic change process' (Jones and Perez, 2002). Second, we cannot rule out that the double N100 peaks to noise offset may involve a combination of offset/onset responses, or the interaction of these responses in the averages. Neurophysiological data from single units in a subcortical site in experimental animals, the medial geniculate, has shown different latencies of discharge to the onset and offset of acoustic stimuli (He, 2001).

Several studies have reported 'on' and 'off' responses using magnetic responses. Joutsiniemi et al. (1989), for example, recorded magnetic responses to noise bursts (10–160 ms) and noise pauses of equivalent durations (i.e. gaps) in continuous noise. Three distinct components were evident in the response to noise burst onsets (P40m, N100m, P200m) at the 40 ms duration; in contrast, noise pause onsets were similar in waveform, but lacked the earlier P40m peak. Source locations for N100m to offsets were anterior to N100m for onsets in agreement with earlier findings by Hari et al. (1987). In a later, but related study of on and off auditory responses, Pantev et al. (1996) recorded magnetic responses to tones of 2 s duration. Several responses were recorded and included P1on, N1on, P2on, a sustained potential (between tone onset and tone offset), an N1off and a P2off. Statistically, N1on and N1off, P2on and P2off source locations were not different. However, estimated 3D source locations (based on 10 subjects) indicated separate locations for the on and off responses of N1 and P2, and the sustained response. A study of the early activation of the auditory cortex measuring middle-latency magnetic responses was provided by Rupp et al. (2002). They reported middle-latency responses to gaps centered in 600 ms noise bursts; short gap durations of 3, 6, and 9 ms were used. A prominent early onset response at approximately 37 ms (P37m) appeared at the start of the noise burst and a negative N45m response at the end of the burst. Positive middle-latency responses to all 3 gaps (in the noise burst), when aligned to the onset of the noise (gap offset), had a similar morphology and peak latency (approximately 40 ms) as the on response (P37m). The adjustment of cortical N100 responses to noise onset was reported as showing an alignment for the 3, 6, and 9 ms gaps, a much smaller gap range than we used in the present study (2–50 ms).

Additional studies are needed (1) to characterize the neural mechanisms underlying brain activity to the prolonged potentials after continuous noise offset, (2) to describe the offset/onset changes related to the processing of varying temporal gaps, and (3) to unravel the variety of negative potentials that may be involved (Näätänen and Picton, 1987).

4.4. Significance and importance

The electrophysiological procedures used here are relatively brief, requiring approximately 10 min of recording time to obtain objective measures of cortical temporal processing and complement psychoacoustic measures. This may have an advantage over other methods (e.g. MMN) where more trials and additional testing time are required to define potentials to gaps. By including passive and active conditions there is also the opportunity to examine the role of attention and cognitive processing (e.g. P300, RT, accuracy). We have demonstrated the utility of these methods in a group of 14 subjects with AN with psychoacoustic gap detection thresholds ranging from 5 to 40 ms. Further application of these methods may be useful to assess temporal processing in (1) testing special populations such as children with developmental disorders (e.g. autism, delayed language acquisition) and (2) provide,

in applied settings, objective cortical measures of the fitting and the performance of auditory prostheses (Busby and Clark, 1999).

Acknowledgements

The authors thank Dr Hillel Pratt for valuable discussions of the issues related to evoked potentials and gap detection.

References

Baumann SB, Rogers RL, Guinto FC, Saydjari CL, Papanicolaou AC, Eisenberg HM. Gender differences in source location for the N100 auditory evoked magnetic field. Electroencephalogr Clin Neurophysiol 1991;80:53–9.

Bench J, Bamford J. Speech-hearing tests and the spoken language of hearing-impaired children. London: Academic Press; 1979.

Bench J, Kowal A, Bamford J. The BKB (Bamford–Kowal–Bench) sentence lists for partially-hearing children. Br J Audiol 1979;13: 108–12.

Bertoli S, Heimberg S, Smurzynski J, Probst R. Mismatch negativity and psychoacoustic measures of gap detection in normally hearing subjects. Psychophysiology 2001;38:334–42.

Bertoli S, Smurzynski J, Probst R. Temporal resolution in young and elderly subjects as measured by mismatch negativity and a psychoacoustic gap detection task. Clin Neurophysiol 2002;113: 396–406.

Busby PA, Clark GM. Gap detection by early-deafened cochlear-implant subjects. J Acoust Soc Am 1999;105:1841–52.

Davis H, Mast T, Yoshie N, Zerlin S. The slow response of the human cortex to auditory stimuli: recovery process. Electroencephalogr Clin Neurophysiol 1966;21:105–13.

Desjardins RN, Tainor LJ, Hevenor SJ, Polak CP. Using mismatch negativity to measure auditory temporal resolution thresholds. NeuroReport 1999;10:2079–82.

Eddins DA, Green DM. Temporal integration and temporal resolution. In: Moore BCJ, editor. Hearing. San Diego, CA: Academic Press; 1995. p. 207–42.

Hari R, Pelizzone M, Mäkelä JP, Hällström J, Leinonen L, Lounasmaa OV. Neuromagnetic responses of the auditory cortex to on- and offsets of noise bursts. Audiology 1987;(26):31–43.

He J. On and off pathways segregated at the auditory thalamus of the guinea pig. J Neurosci 2001;21:8672–9.

Ingelghem M, Wieringen A, Wouters J, Vandenbussche E, Onghena P, Ghesquiere P. Psychophysical evidence for a general temporal processing deficit in children with dyslexia. NeuroReport 2001;16: 3503–7.

Irwin RJ, Hinchcliff LK, Kemp S. Temporal acuity in normal and hearing-impaired listeners. Audiology 1981;20:234–43.

Jones SJ, Perez N. The auditory 'C-process' of spectral profile analysis. Clin Neurophysiol 2002;113:1558–65.

Joutsiniemi S-L, Hari R, Vilkman V. Cerebral magnetic responses to noise bursts and pauses of different durations. Audiology 1989;28: 325–33.

Kraus N, Bradlow AR, Cheatham MA, Cunningham J, King CD, Koch DB, Nicol TG, Mcgee TJ, Stein LK, Wright BA. Consequences of neural asynchrony: a case of auditory neuropathy. J Assoc Res Otolaryngol 2000;1:33–45.

Michalewski HJ, Thompson LW, Patterson JV, Bowman TE, Litzelman D. Sex differences in the amplitudes and latencies of the human auditory brain-stem potential. Electroencephalogr Clin Neurophysiol 1980;48: 351–6.

Michalewski HJ, Kamel AW, Starr A. Brain potentials during mental distance judgments. Int J Psychophysiol 1988;6:221–9.

Moore BCJ. An introduction to the psychology of hearing. San Diego, CA: Academic Press; 1997 p. 148–76.

Morita T, Naito Y, Nagamine T, Fujiki N, Shibasaki H, Ito J. Enhanced activation of the auditory cortex in patients with inner-ear hearing impairment: a magnetoencephalographic study. Clin Neurophysiol 2003;114:851–9.

Näätänen R. Attention and brain function. Hillside, NJ: Lawrence Erlbaum Associates; 1992.

Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987;24:375–425.

Nelson PB, Thomas SD. Gap detection as a function of stimulus loudness for listeners with and without hearing loss. J Speech Lang Hear Res 1997;40:1387–94.

Pantev C, Eulitz C, Hampson S, Ross B, Roberts LE. The auditory evoked 'off' response: sources and comparison with the 'on' and the 'sustained' responses. Ear Hear 1996;17:255–65.

Phillips DP. Auditory gap detection, perceptual channels, and temporal resolution in speech perception. J Am Acad Audiol 1999;10:343–54.

Polich J. Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. Electroencephalogr Clin Neurophysiol 1986;63:251–9.

Polich J. Task difficulty, probability, and inter-stimulus interval as determinants of P300 from auditory stimuli. Electroencephalogr Clin Neurophysiol 1987;68:311–20.

Rance G, Cone-Wesson B, Wunderlich J, Dowell RC. Speech perception and cortical event related potentials in children with auditory neuropathy. Ear Hear 2002;23:239–53.

Rupp A, Gutschalk S, Hack S, Scherg M. Temporal resolution of the human primary auditory cortex in gap detection. NeuroReport 2002;13: 2203–7.

Schneider BA, Hamstra SJ. Gap detection thresholds as a function of tonal duration for younger and older listeners. J Acoust Soc Am 1999;106: 371–80.

Starr A, McPherson J, Patterson JV, Don M, Luxford W, Shannon R, Sininger Y, Tonakawa L, Waring M. Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. Brain 1991; 114:1157–80.

Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. Auditory neuropathy. Brain 1996;119:741–53.

Starr A, Michalewski HJ, Zeng F-G, Fujikawa-Brooks S, Linthicum F, Kim CS, Winnier D, Keats B. Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145→Ser). Brain 2003;126:1604–19.

Yellin MW, Jerger J, Fifer RC. Norms for disproportionate loss in speech intelligibility. Ear Hear 1989;10:231–4.

Zeng F-G, Oba S, Garde S, Sininger Y, Starr A. Temporal and speech processing deficits in auditory neuropathy. NeuroReport 1999;10: 3429–35.