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Effects of Identification Technique, Extraction Method, and Stimulus Type on Mismatch Negativity in Adults and Children

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Abstract

The overall aims of the study were to determine optimal methods and stimuli for eliciting mismatch negativity (MMN), extracting MMN from the deviant and standard waveforms, and identifying the response in children and adults. Several stimulus types were compared (pure tones, chords, and natural speech tokens) to determine which optimally elicit MMN. Deviant-alone and flip-flop MMN extraction methods that control for stimulus effects on MMN were compared for the speech stimuli (/da/ and /ga/). Visual identification, an area criterion, and integral-distribution techniques were used to identify MMN. Eight adults (20 to 28 years) and eight children (8 to 12 years) participated in the study. The deviant-alone method elicited bigger MMN area and duration than the flip-flop method for the speech stimuli. An area criterion of 110 µV x msec identified 90% of visually identified MMN compared to 62% identified using the integral-distribution technique. For both children and adults, speech stimuli and one of the chords most consistently elicited MMN.

Key Words: Area criterion, chords, event-related potentials, extraction method, integral distribution, mismatch negativity, speech stimuli

Abbreviations: ERPs = event-related potentials; ISI = interstimulus interval; MMN = mismatch negativity

Sumario

El objetivo global del estudio fue determinar los métodos y estímulos óptimos para generar una negatividad desigual (MMN), extrayendo la MMN de las ondas estándar y con desviación, e identificando la respuesta en niños y en adultos. Se compararon varios tipos de estímulos (tonos puros, acordes, y muestras de lenguaje natural) para determinar cuál generaba óptimamente una MMN. Se compararon métodos de extracción de la MMN, tanto de tipo desviación sola o de volteo alternante (flip-flop), ante sonidos de lenguaje como /da/ y /ga/. Técnicas como la identificación visual, un criterio de área y la distribución integral fueron utilizadas para identificar la MMN. Ocho adultos (20 a 28 años) y ocho niños (8 a 12 años) participaron en el estudio. Ante

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el estímulo de lenguaje, el método de desviación sola generó un área y una duración de la MMN mayor que el método de volteo alternante. El criterio de área de 110 µV por mseg, identificó el 90% de la MMN identificable, comparado con el 62% identificado usando la técnica de distribución integral. Tanto para los niños como para los adultos, los estímulos del lenguaje y uno de los acordes generaron una MMN más consistentemente.

Palabras Clave: Criterio de área, acordes, potenciales relacionados con el evento, método de extracción, distribución integral, negatividad desigual, estímulos de lenguaje

Abreviaturas: ERP = potenciales relacionados con el evento; ISI = intervalo inter-estímulo; MMN = negatividad desigual

Event-related potentials (ERPs) are measures of electrical brain activity time locked to an external event (Steinschneider et al, 1992). These include the obligatory and discriminative cortical auditory evoked potentials (Kurtzberg, 1989). Obligatory ERPs (e.g., P1-N1-P2) are elicited by the physical properties of a single stimulus such as intensity, duration, or pitch. Discriminative ERPs (e.g., mismatch negativity and P3a) reflect processing of a stimulus beyond its physical features (Stapells, 2001) and are typically obtained using an "oddball" paradigm in which a deviant stimulus occasionally replaces a repeating standard stimulus (Näätänen et al, 1978; Kraus et al, 1992).

Mismatch Negativity

Mismatch negativity (MMN) is elicited when the brain discriminates a sound or pattern from a different one stored in memory (Picton et al, 2000). The main determinant of MMN characteristics (latency, amplitude, duration, area) is the standard versus deviant stimulus contrast (see reviews by Näätänen, 1992 and Picton et al, 2000). MMN has been recorded using a wide range of stimulus types and durations, and interstimulus intervals. Interstimulus interval can vary widely with little effect on MMN (Ceponiene et al, 1998). Several cortical regions have been identified as sources of MMN, including the supratemporal plane in the auditory cortex, lateral posterior temporal cortex, and right frontal gyrus (Giard et al, 1990; Picton et al, 2000; Opitz et al, 2002). MMN generally occurs between 150 and 250 msec post stimulus presentation, with latency and amplitude varying depending on the stimuli used (Kraus and Cheour, 2000). MMN is passively elicited and hence does not require attention or a behavioral response (Näätänen, 1992; Kraus and McGee, 1994; Picton et al, 2000). MMN can be recorded using an oddball paradigm containing multiple deviant stimuli. Similar MMN results are obtained for single versus multiple deviant paradigms when tonal stimuli are used (Deacon et al, 1998).

Detectability of MMN

Two aspects of MMN make it an attractive clinical tool. One is that the test does not require active participation (subjects can watch TV or read a book). Secondly, MMN is sensitive to stimulus changes at the psychophysical discrimination threshold. Thus, MMN can provide an objective measure of auditory discrimination ability (Näätänen et al, 1978; Kraus et al, 1993, 1996). MMN detectability does seem to depend on the type of stimulus contrast used to evoke MMN. Dalebout and Fox (2001) identified MMN in only 29% of responses to a /da/-/ga/ contrast. Wunderlich and Cone-Wesson (2001) also only obtained MMN in some adult subjects, despite them being able to behaviorally discriminate the contrasting speech and tonal sounds. They found MMN in 25–32% of subjects for speech and 46–71% for tonal stimuli. This is in contrast to Kraus et al (1999), who reported that 75–83% of school-age children showed MMN to /da/ versus /ga/ and /ba/ versus /wa/. It appears that certain types of stimuli may be better at eliciting MMN, but there are inconsistencies across studies. Hence in the current study MMN detectability was compared for a range of stimulus types.

MMN Identification Technique

MMN is very small, with peak amplitudes varying between a fraction of a microvolt to several microvolts, and MMN typically occurs in high levels of background noise (Picton et al, 2000). Thus MMN can be very difficult to identify. Generally MMN is identified visually using the deviant-standard difference waveform. As an alternative to this, Ponton et al (1997) proposed an "integral distribution" technique for objectively identifying MMN. The integral distribution technique involves integration of the individual subject's waveforms for both standard and deviant stimuli. A distribution of integrated standard responses is created by making multiple subaverages from the pool of responses to the standard stimulus. The integrated deviant response is then compared to the distribution of integrated standard responses to determine whether MMN is present (Ponton et al, 1997; Wunderlich and Cone-Wesson, 2001).

Another technique that has been used to identify MMN is a simple area criterion. MMN area was recommended by McGee et al (1997) as the most useful single measure for identifying MMN. MMN is identified as present if the area under the curve of the deviant-standard difference waveform exceeds a predetermined normative criterion. Area criteria reported in the literature range from 110 µV x msec (Dalebout and Fox, 2001) to 225 µV x msec (McGee et al, 1997).

Although the integral distribution and area techniques appear to have some advantages over simple visual identification, they have been used relatively infrequently in MMN research. The current study compared these three techniques.

Stimulus Effects on MMN

MMN can be evoked by simple and complex acoustic signals differing in frequency, intensity, duration, or spatial location (Sams et al, 1985; Aaltonen et al, 1987; Näätänen et al, 1987; Kaukoranta et al, 1989; Näätänen, 1990; Novak et al, 1990; Kraus et al, 1992; Schroger, 1996; Winkler and Czigler, 1998; Wunderlich and Cone-Wesson, 2001). Wunderlich and Cone-Wesson (2001) used simple tones and reported larger MMN for frequencies below 1.5 kHz. Stimuli in the 1 to 2 kHz frequency range have been widely used in previous studies (Kropotov et al, 1995; Baldeweg et al, 1999; Schulte-Körne et al, 1999; Kropotov et al, 2000; Morr et al, 2002).

Schulte-Korne et al (1999) reported that MMN to tones presented in a serial pattern is more affected by auditory processing problems than MMN to simple tones. Thus, chords were included as stimuli in the current study to establish normative data that could be helpful in future work with clinical populations. Alho (1995) had previously studied MMN generators for simple tones, patterns (tones in sequence), and chords (simultaneous tones) using magnetoencephalography and found no difference between MMNm dipole locations for frequency changes within a chord versus a pattern. Alho (1995) concluded that a complex tone may be represented by the same neuronal population in the supratemporal region of auditory cortex irrespective of whether the frequencies are presented serially (pattern) or in parallel (chord).

Many studies have used speech stimuli to elicit MMN. Speech stimuli are of great interest for clinical applications because of the evidence for poor speech-evoked MMN in various clinical populations with speech and language difficulties (Bradlow et al, 1999; Picton et al, 2000). MMN studies have used either synthetic speech (Sams et al, 1990; Aaltonen et al, 1993; Sharma et al, 1993; Dehaene-Lambertz, 1997; Sharma and Dorman, 1998; Dalebout and Stack, 1999; Sharma and Dorman, 1999; Szymanski et al, 1999), semisynthetic speech (Pulvermüller et al, 2001; Ceponiene et al, 2002; Cheour et al, 2002), or natural speech tokens (Sandridge and Boothroyd, 1996; Muller-Gass et al, 2001;

Titova and Näätänen, 2001; Hahne et al, 2002; Kasai et al, 2002).

Picton et al (2000) recommended using natural speech tokens, as MMN is being used to study how speech is processed in real life and not just in the laboratory. The speech tokens /da/ and /ga/ were included in the current study based on Kraus et al's (1999) finding that just noticeable differences and MMN for these stimuli are already mature by six years and do not differ in 6 to 16 year olds. Furthermore, they found that stop consonants (/ba/, /da/, /ga/) elicit robust cortical responses. Previous studies have also shown that children with reading problems make more discrimination errors than average readers for minimal pairs of syllables (e.g., /ba/ versus /da/, /da/ versus /ga/) that differ in only one phonetic feature (Reed, 1989; Mody et al, 1997).

MMN Extraction Method

MMN can be extracted in three different ways. In each case an oddball paradigm is used in which a standard is presented with random deviant stimuli interspersed. The averaged response to the deviant stimuli contains the MMN. In the first method for extracting MMN, the standard response is simply subtracted from the deviant response. Different stimuli are used for the standard and the deviant, and hence this method assumes that there are minimal differences in the obligatory cortical responses to the standard and deviant, since these differences could affect MMN amplitude. This simple subtraction method is often used in studies involving similar tonal stimuli for which there are negligible differences in obligatory responses (Lang et al, 1995). The second and third MMN extraction methods both control for differences in the obligatory cortical responses to the standard and deviant and are often used in MMN studies using speech stimuli. For the second method the response to the deviant stimulus presented alone ("deviant alone") is subtracted from the response to the deviant when it is presented in the oddball paradigm. The third method involves running different trials with the standard stimulus in one trial becoming the deviant in the next (so-called flip-flop method). The response to the "deviant as standard" is subtracted from the response to the "deviant as deviant." Stimulus context and timing differ between the three methods. Despite this, Walker et al (2001) found that MMN detectability and area for tonal stimuli was similar across the three methods in adults, when interstimulus interval (ISI) of the standard stimuli was maintained at 500 msec. The current study further investigates the effects of MMN extraction method in both children and adults using speech stimuli.

Maturational Effects on MMN

Csepe (1995) found that, for frequency deviants, MMN latency did not differ between adults and children; however, MMN was larger in all age groups of children compared to adults. If MMN amplitude depends on the magnitude of the perceptual contrast, Csepe's results suggest that, for the same deviant, adults and children perceived the sounds differently, resulting in MMN differences. Consistent with Csepe (1995), Kraus et al (1992) did not find significant differences in MMN between adults and children for a speech contrast. More recently, Martin et al (2003) found significant differences in tone-evoked MMN scalp topography between children aged 4–11 years and adults. Differences in MMN between adults and children may be stimulus-dependent, and hence the current study investigated differences in MMN between adults and children for a range of stimuli.

Study Aims

The current study extended the previous investigation by Walker et al (2001) by comparing two MMN extraction methods using speech stimuli and both children and adults. The other aims of the study were to determine which stimuli optimally elicit MMN across age groups, to determine differences in MMN parameters between adults and children for a range of speech and simple versus complex tonal stimuli, and to compare different techniques for identifying MMN.

METHOD

Subjects

Eight young adults aged 20 to 28 years (mean 25.6, SD 2.2 years) and eight children aged 8 to 12 years (mean 10.7, SD 1.5 years) participated. All subjects had normal pure-tone air-conduction thresholds (less than 15 dB HL at octave frequencies from 0.5 to 4 kHz), no history of prolonged middle ear infections, normal immittance audiometry (Type A tympanograms and acoustic reflexes present at 1 kHz ipsilaterally), and present transient click-evoked otoacoustic emissions (OAE). The children had age-appropriate reading skills, and their parents reported no previous history of reading or learning problems. Adults reported no prior history of reading or learning problems.

Electrophysiology

Six stimuli (consisting of tones, chords, and speech) were used to elicit MMN. The standard tonal stimulus was 1 kHz, and the two deviants were 1.1 kHz (tone 1) and 1.5 kHz (tone 2). The tones were 80 msec long with 20 msec linear rise/fall times. The standard chord stimulus was a combination of simultaneously presented 1, 1.1, and 1.5 kHz tones, and deviant chords were 1 and 1.1 kHz presented simultaneously (chord 1), and 1 and 1.5 kHz presented simultaneously (chord 2). Chords were 160 msec long with 20 msec linear rise/fall times. Speech stimuli consisted of two natural tokens spoken in isolation, /da/ and /ga/ [as in the words dart and garden, respectively]. The stimuli were spoken by an Australian female with a background in linguistics. The two tokens were chosen because of their appropriate length and their clarity as judged by several trained listeners. After speech tokens were selected, they were shortened (from their original lengths of 250 msec) and normalized using Cool Edit 2000^{TM} software. The stimuli were shortened to 160 msec (±4 msec) using a zero crossing technique, which adjusts the beginning and end-points of the token to the nearest place where the waveform crosses the center line to avoid audible clicks. Both speech stimuli were ramped with 20 msec linear rise/fall times.

Stimulus onset asynchrony (SOA) (onset to onset duration) was 700 msec for all stimulus sequences. Stimuli were presented in a pseudorandom order within a block, so there were at least three standards between two deviants. Table 1 shows the combinations of test stimuli. In total there were 1200 standard tones and chords with 300 deviants. For speech stimuli there were 1350 standards with 150 deviants. Tone and chord stimulus sequences contained two deviant stimuli (150 each) whereas for speech there was only one deviant in a block. Each block took six minutes, and there were 18 blocks in total (three blocks each of tone sequence, chord sequence, /da/ deviant, /ga/ deviant, /da/ alone, /ga/ alone). For children there were two test sessions (nine blocks per session) undertaken on two separate days within ten days of each other. Adults were tested in one long session of around three to four hours with ten-minute breaks every half hour and a 20-minute break after around 20 minutes. None of the subjects showed signs of fatigue during the testing. Block presentation order was pseudorandomized (so that similar blocks were not presented sequentially) within and across sessions. Subjects had breaks within

Table 1. Details of the Stimulus Paradigm, Stimulus Type, and Duration and Number of Stimuli

Paradigm	Standard Stimulus	Deviant Stimuli	Duration	Number of Stimuli
1. Oddball	Tone (1 kHz)	T1 (1.1 kHz) T2 (1.5 kHz)	80 msec	1200 standard; 150 each deviant
2. Oddball	Chord (1, 1.1, 1.5 kHz)	C1 (1, 1.1 kHz) C2 (1, 1.5 kHz)	160 msec	1200 standard; 150 each deviant
3. Flip-Flop	/da/	/ga/	158.3 msec	1350 standard; 150 deviant
4. Flip-Flop	/ga/	/da/	163.7 msec	1350 standard; 150 deviant
5. Deviant alone	/da/		158.3 msec	1500
6. Deviant alone	/ga/		163.7 msec	1500

a session. During testing, subjects watched a self-chosen movie with the volume turned down (<35 dB SPL). Subjects were asked not to attend to the sounds being presented.

A NeuroScan and 8-channel SynAmps™ evoked potential system was used for evoked potential recording. Sounds were presented using Neuroscan STIM software and hardware to an ER-3A insert earphone in the subject's right ear at 75 dB SPL. Evoked potentials were recorded in continuous mode (gain 500, filter 0.1–100 Hz) using SCAN™ (version 4.2) via gold cup electrodes placed at F3, F4, Fz, and Cz with the reference electrode on the right earlobe and ground on the forehead. Eyeblinks were recorded via an active electrode above the eye, referenced to the right earlobe (Kraus et al, 1993).

Data Analysis and MMN Identification

EEG files with a -50 to +550 msec time window were obtained from the continuous files. The first standard after each deviant was rejected before averaging. Based on the eyeblink channel recordings, any responses on the scalp electrodes exceeding ±50 µV for adults and ±100 µV for children were rejected. With these criteria, around 80% of eye blinks were rejected, and no more than 400 stimuli were discarded out of 1500. Prior to averaging, EEG files were baseline corrected using the pre-stimulus period. Averages were digitally low-pass filtered at 30 Hz (24 dB/octave slope).

In order to use Ponton et al's (1997) integral-distribution technique, the time point where the difference waveform returned to baseline was identified for adults (as a group) and children (as a group) for each stimulus and each extraction method. Time points for calculating the integral value were selected prior to applying the integral technique to reduce tester bias. The integrated response for any time point is the sum of amplitude values for all preceding points. At the point where the difference waveform returns to baseline, the integrated MMN is maximal. Time points for the integral calculation were determined using the grand average difference waveforms obtained by subtracting the response to the stimulus as a standard from the response to the deviant, for /ga/ and /da/, for the adults and children. After selecting the time points, a distribution of responses to the standard was created. For each subject and stimulus a random subaverage of about 150 responses was created from all accepted responses to the standard. This subaverage included about the same number of responses as the deviant average. (Exact number varied, depending on the number of accepted trials.) This process was repeated 100 times to create multiple subaverages of responses to the standard. The 100 standard subaverages and the single deviant average were then integrated. The integrated MMN amplitude for the deviant waveform at the pre-selected time point was then compared to the values obtained for the 100 standard subaverages. MMN was identified as present if the integral of the deviant response was below the 5th (Ponton et al, 1997) or 10th percentile of the standard integral distribution (Wunderlich and Cone-Wesson, 2001).

Two experts judged the waveforms independently to visually identify MMN. The standard, deviant, and difference waveforms were first superimposed. A negativity in the difference waveform was then identified as MMN if (1) it occurred in the 80 to 250 msec latency range, (2) it started after P1 and before or at P2 (if P2 was present), (3) its duration was 100–250 msec, and (4) it extended beyond the early N1 in the deviant waveform. If the negativity was present across electrode montages, then the latency and morphology of MMN was expected to be consistent across montage. This was used to verify MMN visual identification. The negativity also had to be bigger (greater amplitude, longer duration) than other variations in the same waveform due to noise. MMN onset, offset, and peak latencies, peak amplitude, area, and duration (difference between the onset and offset) were determined using the deviant-standard difference waveforms. MMN onset and offset were identified visually in the difference waveforms as the positive peaks immediately preceding and following, respectively, the negativity identified as MMN (Sharma et al, 1993; Dalebout and Stack, 1999). If the negativity continued throughout the difference waveform or returned to the baseline after 250 msec, the offset was taken as 250 msec, to avoid including the late negativity (N2b) that can be elicited in a passive oddball paradigm (Näätänen, 1992; Ritter et al, 1992). The Neuroscan SCAN™ analysis software was used to calculate MMN area between the onset and offset. For the speech stimuli, MMN was identified using both deviant-alone and flip-flop extraction methods. Standard and deviant responses were superimposed to help identify the obligatory cortical responses P1-N1-P2 in the standard waveform. P1 was defined as the most positive peak occurring earlier than 100 msec after stimulus onset. N1 was defined as the most negative peak around 70–200 msec, and P2 as the positive peak at 120–300 msec. N1 and MMN latency ranges overlap, and hence the measured MMN could include some N1 enhancement.

The third technique used to identify MMN was an area criterion. An area criterion was established by assuming that the visual identification of MMN by independent observers was correct. Hit rates (% MMN correctly identified using area criterion) and false alarm rates (% MMN incorrectly identified using area criterion) were calculated for a range of criteria. A criterion of 110 msec x μV, which is the same as the value used by Dalebout and Fox (2001), had the highest hit rate of 90% and a low (<5%) false alarm rate and thus was accepted.

RESULTS

Obligatory Cortical Responses to Standard Stimuli

Figure 1 shows grand average waveforms for the 1 kHz standard tonal stimulus across the four electrodes for adults and children. For all stimuli, adults had smaller and earlier P1 and N1 peaks than children (see Table 2). The adults had a robust P2 with similar amplitudes and latencies for the tone and speech stimuli, but not for the chord. The children's grand averages show a robust P1 and a late negativity, which we refer to as N1. There was a small peak following N1; however, the amplitude was negative, and hence P2 was not identified in the children's waveforms.

The effects of group, stimulus, and electrode on P1 and N1 latencies and amplitudes were examined using repeated-measures ANOVA. All standard stimuli were included in this analysis (chord, tone, speech) including /da/ and /ga/ standard stimuli for both deviant-alone and flip-flop methods. P1 latencies were significantly longer in children than adults ($F_{1, 14} = 20.8$, $p < 0.001$). Children had more robust P1 amplitudes than adults ($F_{1, 14} = 24.8$, $p < 0.001$). N1 was later ($F_{1, 14} = 140.9$, $p < 0.001$) and more negative ($F_{1, 14} = 10.2$, $p = 0.007$) in children than adults. There were no electrode effects, but there were stimulus effects on N1 latencies ($F_{5, 70} = 3.4$, $p = 0.008$) and amplitudes ($F_{5, 70} = 5.7$, $p < 0.001$). Newman-Keuls post hoc testing showed that N1 latency for the tone was significantly shorter than N1 for /da/ and /ga/, for both methods ($p < 0.05$). N1 latency was shorter for the chord than for both speech stimuli, for the deviant-alone method. Smallest N1 amplitudes were obtained for

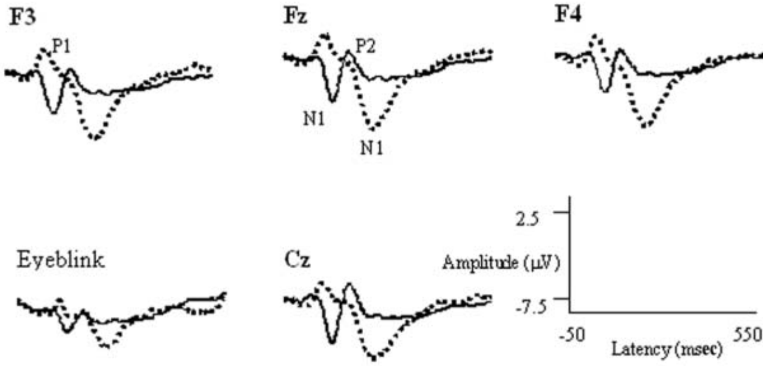

Figure 1. Grand average cortical response waveforms for the standard 1 kHz tonal stimulus recorded at the F3, Fz, F4, and Cz electrodes for adults (thick line) and children (dotted line). A response is also evident in the eyeblink channel, for which a noninverting electrode was placed on the supraorbital region (above the eye) with a right ear reference (Kraus et al, 1993). There is a prominent P1, a late N1, and absent P2 for children. In adults P1 and N1 are earlier and smaller than the children's P1 and N1. P2 is present in the adult waveforms.

Table 2. Average Cortical P1, N1, and P2 Peak Latencies (msec) and Amplitudes (μV) of Adults and Children at the Fz Electrode for All the Standard Stimuli (including two different stimulus paradigms for /ga/ and /da/)

		P1		N1		P2	
		Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
/ga/ Flip-flop	Adult	74.81 (17.76)*	0.94 (0.55)	135.88 (24.25)	-1.04 (0.73)	189.53 (34.39)	0.70 (0.36)
	Child	95.31 (16.18)	2.44 (1.79)	266.75 (59.45)	-2.93 (2.15)		
/da/ Flip-flop	Adult	71.18 (19.41)	0.91 (0.64)	118.38 (13.11)	-1.27 (0.75)	181.00 (21.42)	0.82 (0.66)
	Child	93.63 (16.68)	2.47 (1.77)	253.75 (58.00)	-4.21 (2.22)		
/ga/ Deviant-alone	Adult	71.25 (17.76)	0.93 (0.50)	146.38 (41.50)	-1.31 (0.64)	201.11 (29.11)	0.38 (0.31)
	Child	89.75 (17.56)	2.35 (1.31)	263.25 (55.46)	-2.98 (1.83)		
/da/ Deviant-alone	Adult	71.5 (18.48)	0.92 (0.52)	124.25 (16.88)	-1.25 (0.86)	189.85 (20.53)	0.49 (0.34)
	Child	92.25 (23.29)	2.47 (0.98)	281.5 (30.50)	-3.84 (1.97)		
Tone (1 kHz)	Adult	52.25 (10.56)	0.30 (0.32)	103.00 (6.41)	-2.66 (1.90)	165.72 (33.92)	0.95 (0.55)
	Child	92.06 (24.15)	1.91 (1.25)	232.15 (12.16)	-4.23 (2.84)		
Chord (1, 1.1, 1.5 kHz)	Adult	66.19 (15.25)	0.43 (0.43)	140.25 (22.38)	-3.00 (1.22)		
	Child	89.69 (10.08)	2.02 (0.80)	244.75 (57.07)	-4.35 (1.77)		

Note: There are no P2 values for children as P2 was not readily identifiable in their cortical waveforms.
*Values shown in parentheses are standard deviations.

/ga/. Tone and chord standards both produced significantly larger N1 amplitudes than /ga/.

To determine whether there were differences in P1-N1 evoked by the two speech stimuli and two methods (deviant-alone versus oddball/flip-flop), /da/ and /ga/ were examined separately. The only significant finding was that, for the flip-flop method, N1 latency for /da/ was significantly earlier than /ga/ ($F_{1, 14} = 7.3$, $p = 0.017$).

An ANOVA of adult P2 amplitudes and latencies for the stimuli that produced a positive P2 in at least some subjects (/da/, /ga/, tone) showed that the tone produced shorter P2 latencies than both speech stimuli ($p \leq 0.006$). P2 amplitude showed a stimulus by electrode montage interaction effect ($F_{6, 18} = 2.7$, $p = 0.046$). For /da/ and the tone, P2 was biggest at Cz, whereas /ga/ elicited similar P2 amplitudes across montages. P2 was larger at Cz than at frontal electrodes (Fz, F4) for /da/ ($p \leq 0.032$) and was larger at Cz than all other montages for the tone ($p \leq 0.007$). P2 for /ga/ was smaller than tone-evoked P2 across montages ($p \leq 0.007$) and was smaller than P2 for /da/ at two of the four montages (F3, Cz, $p \leq 0.027$).

Table 3. Agreement between Subjective and Objective Techniques for Identifying MMN

Visual Identification	Integral distribution ($p < 0.05$)	Integral distribution ($p < 0.10$)	Area criterion (≥ 110 msec x μV)
MMN present (N = 395, 77%)	N = 200, 50.6% present	N = 243, 61.5% present	N = 355, 89.9% present
MMN absent (N = 117, 22.9%)	N = 0, 0% present	N = 0, 0% present	N = 5, 4.3% present

Note: A total of 512 waveforms were examined to determine if MMN was present (16 subjects x 4 electrode montages x 8 stimuli). The 4 montages were F3, F4, Fz, and Cz. The 8 deviant stimuli were tones 1 and 2, chords 1 and 2, and /da/ and /ga/. The speech stimuli were derived using both deviant-alone and flip-flop extraction methods.

MMN Identification and Extraction Method

There was 90% agreement between the observers when they independently identified MMN. For the 10% of waveforms where they did not agree, MMN presence was determined after reconsidering the criteria for MMN identification and reaching a consensus. MMN was identified visually in 77% of waveforms (see Table 3). If one assumes that this process produced the "truth," then Table

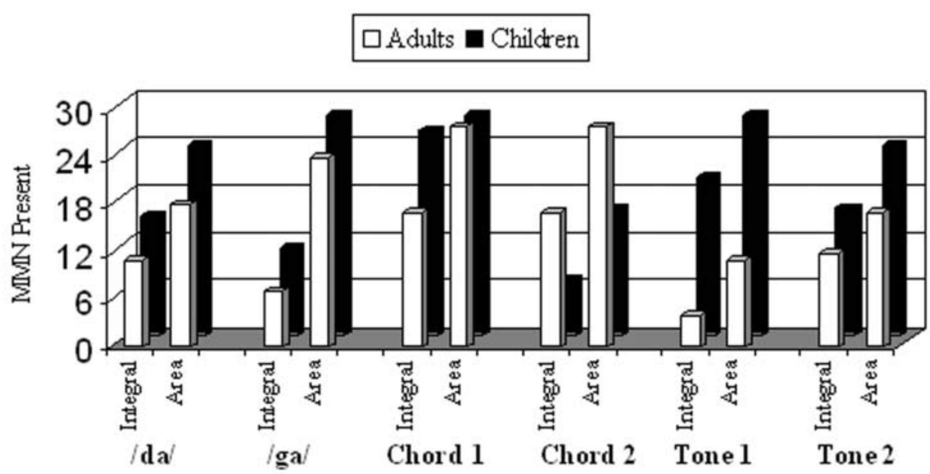

Figure 2. Presence of MMN summed across subjects and across electrode montages, as determined by integral-distribution ($p < 0.05$) and area criterion (≥110 μV x msec) techniques. The maximum MMN value is 32 (8 subjects, 4 electrode montages). White boxes show the total number of MMN identified in adults, and dark boxes show the total number of MMN identified in children. The deviant-alone MMN extraction method was used for the speech stimuli.

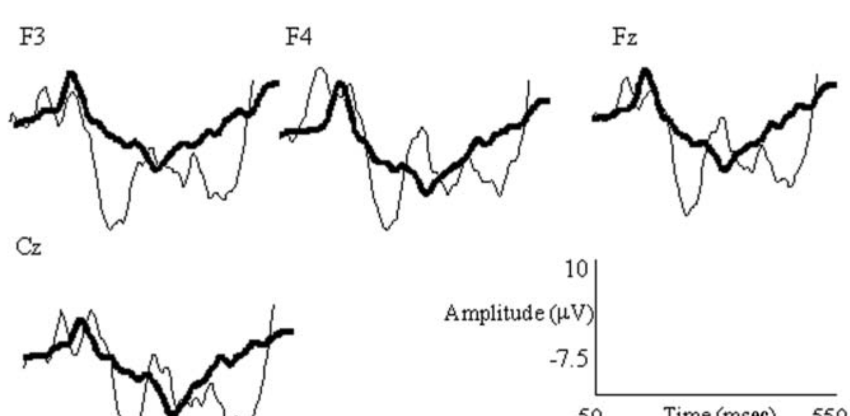

Figure 3. An example of MMN to /ga/ identified visually in a child that also exceeded the area criterion of 110 μV x msec that was classified as absent using the integral technique ($p = 0.3$). The thick line is the response to /ga/ as standard, and the thin line is the response to /ga/ as deviant in flip-flop paradigm.

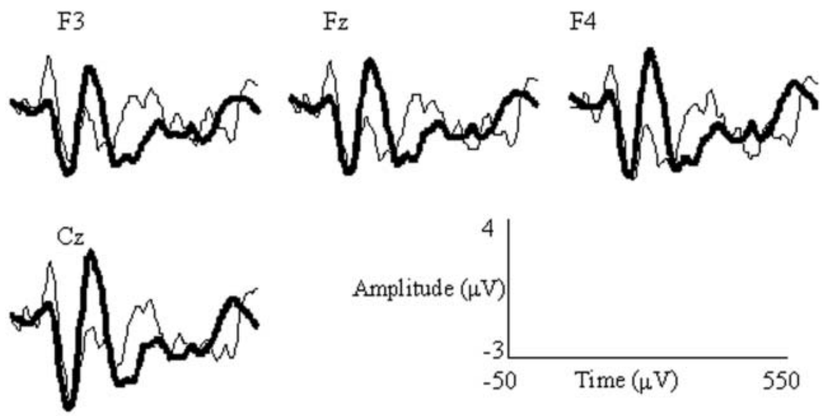

Figure 4. An example of MMN identified visually in an adult that was classified as absent using the area criterion of 110 μV x msec. The thick line is the response to the 1 kHz standard, and the thin line is the response to the 1.1 kHz deviant.

3 shows that the integral-distribution technique is quite insensitive to MMN, even when a less conservative p value of 0.10 is employed. With a much less strict p value of 0.40, 81% of MMN identified by the observers would be classified as present. The number of MMN identified using integral-distribution versus area techniques is illustrated in Figure 2 for the different stimuli. Figure 3 shows an example of MMN identified visually that was classified as absent by the integral-distribution technique (p = 0.30).

The area criterion was chosen based on the data so, by definition, this technique has a high hit rate and low false alarm rate. It was not possible to find a criterion with an acceptable false alarm rate (close to 5%) that would classify all MMN as present that were

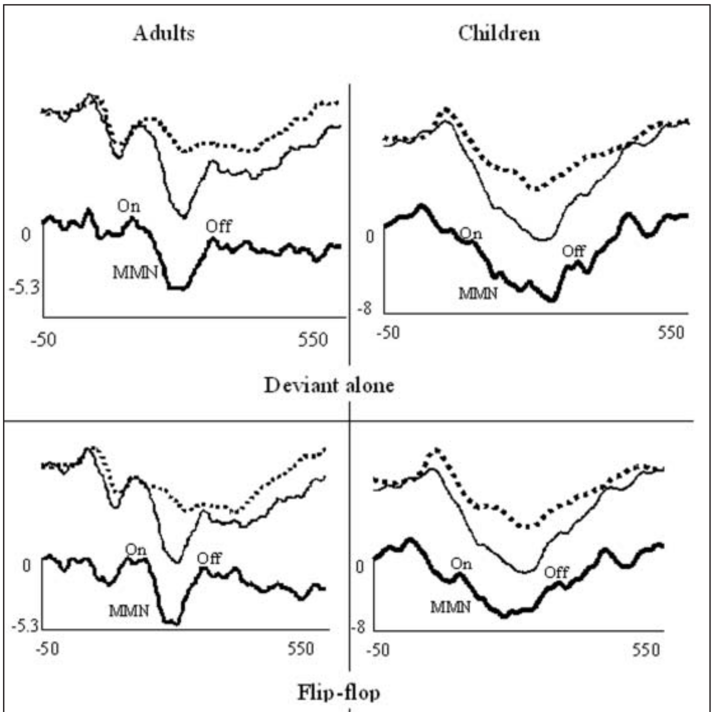

Figure 5. Grand average waveforms recorded at Fz for adults and children for the deviant-alone and flip-flop MMN extraction methods. Responses to standard stimuli are shown by dotted lines, deviants by thin lines, and difference waveforms at the bottom of each panel have thick lines. For the deviant-alone method, the difference waveform = /da/ deviant in oddball - /da/ deviant alone. For the flip-flop method, the difference waveform = /da/ deviant in oddball - /da/ standard in oddball. The amplitude scale on the x-axis differs between adults and children (5.3 μV per division for adults and 8 μV per division for children). "On" refers to the MMN onset, and "off" refers to MMN offset in the difference waveform.

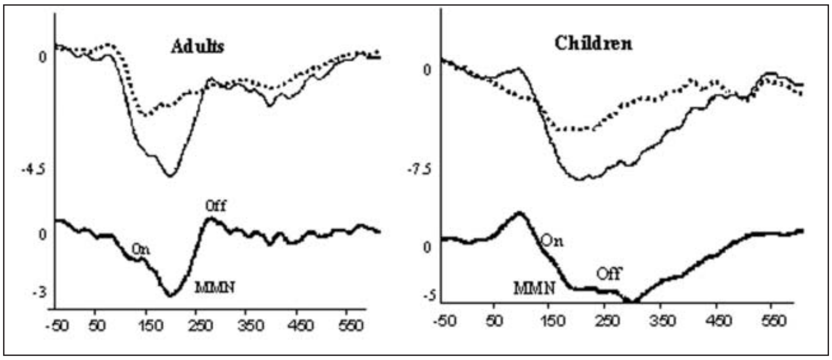

Figure 6. Grand average responses recorded at Fz for the standard chord stimulus (1, 1.1, 1.5 kHz) and the first deviant chord C1 (1, 1.1 kHz) in adults and children. The dotted lines show the response to the standard, and the thin solid lines show responses to the deviant. The difference waveforms at the bottom were obtained by subtracting the standard from the deviant waveforms. X- and y-axes show amplitude in microvolts and time in milliseconds respectively.

identified visually by the observers. Figure 4 shows an example of MMN identified visually that was classified as absent using the area criterion.

Figure 5 shows the overlaid adult grand average /da/ standard, /da/ deviant, and difference waveforms at Fz for deviant-alone and flip-flop methods. MMN parameters (area, duration, peak latency, peak amplitude) were compared to see whether extraction method had a significant effect on speech-evoked MMN. MMN area for /ga/ was significantly affected by extraction method ($F_{1, 9}$ = 8.91, p = 0.015), with the deviant-alone method producing greater area values (515 ± 353 µV x msec) than the flip-flop method (473 ± 366 µV x msec) across montage. Similarly, MMN duration for both /da/ and /ga/ were affected by extraction method ($F_{1, 6}$ = 6.99, p = 0.039), with duration being greater for the deviant-alone method (178 ± 55 msec versus 171 ± 48 msec for flip-flop).

MMN in Children *versus* Adults

Figure 6 shows averaged responses to the chord standard (1, 1.1, 1.5 kHz), the chord 1 (1, 1.1 kHz) deviant, and the difference waveform for adults and children. Adult and child data (group effects) were studied for each stimulus for all MMN parameters. Since MMN area and duration for /da/ and /ga/ were affected by extraction method, group effects on speech-evoked MMM were investigated separately for each method.

Figure 7 shows mean MMN areas and standard deviations for the six deviant stimuli for the two groups, averaged across electrode montage. In general, MMN area was larger in children than in adults; however, there were no significant group differences for

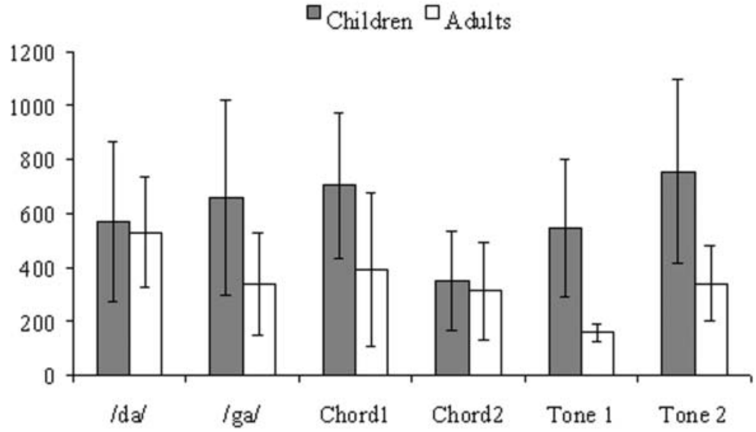

Figure 7. Mean area (µV x msec) for the two groups at all electrode montages for each stimulus. The dark bars represent the mean areas for children while white are for adults. The error bars show the standard deviations.

MMN area except for tone 1 ($F_{1, 8}$ = 7.9, p = 0.023). Across stimuli, MMN duration was consistently longer in children than adults. MMN duration averaged across stimuli and montages was 205.89 msec (± 72.93) and 161.70 msec (± 47.13) for children and adults, respectively. There were significant duration differences between groups for tone 1 ($F_{1, 6}$ = 13.5, p = 0.011). MMN latencies and amplitudes showed no significant group, stimulus, or electrode montage effects. MMN peak latencies averaged across stimuli and montages were 219 msec (±36.4) and 216 msec (±37.3) for children and adults, respectively. Average MMN peak amplitudes were -5.2 μV (±2) and -3.3 μV (±1.5) in children and adults, respectively.

DISCUSSION

Obligatory Cortical Responses

N1 was approximately 30 msec earlier for simple tonal stimuli than for complex stimuli (chord and speech stimuli). Similar N1 latency differences were reported by Pang and Taylor (2000) when comparing a 2 kHz tone and the speech stimulus /da/ presented binaurally via a loudspeaker. A similar range of N1 latency variation (20–30 msec) has been seen with change in pure-tone frequency in the 500 Hz to 5 kHz frequency range for monaurally presented tones (Roberts and Poeppel, 1996). The auditory cortex is tonotopically organized, and thus it is likely that simple tones, speech stimuli, and chords activate different cortical regions, contributing to the differences in latency (Verkindt et al, 1995). In the current study, N1 was earlier for /da/ than for /ga/. This is in contrast to Bellis et al (2000), who found no differences in P1-N1 latencies and amplitudes for /da/ and /ga/ presented to the right ear via an insert earphone (the same mode of stimulus presentation as the current study). The current study used natural speech tokens rich in formants with preserved vocal tract variations, possibly resulting in /da/ and /ga/ being more distinct than Bellis et al's synthetic speech stimuli.

P1 and N1 were bigger and later in children than adults, consistent with previous studies (Kraus et al, 1993; Gomes et al, 2000; Pang and Taylor, 2000; Ponton et al, 2000). In children the response was dominated by a robust P1 with a very small P2, as seen previously (Csepe et al, 1992; Ceponiene et al, 1998). Hyde (1997) described N1-P2 waveform variations across children (9–12 years), with P2 ranging from very small to a robust response. In the current study, P2 was very small in the children.

N1-P2 amplitudes increase with ISI. Walker et al (2001) and Czigler et al (1992) reported small P2 amplitudes for short ISIs of 500–800 msec. In the current study ISI was 540 and 620 msec for speech and tonal stimuli respectively. Ceponiene et al (1998) reported overlapping of N160 and N250 (following P2) with fast ISIs of 350 and 700 msec in children. Thus, the short ISI could explain small P2 amplitudes seen in both children and adults in the current study.

For /da/, /ga/, and the simple tone, P2 was bigger at Cz than at frontal electrodes. This is consistent with Czigler et al (1992) and Bertoli et al (2002), who reported bigger P2 amplitudes at Cz than at Fz. There were no montage effects for P1 and N1, consistent with previous studies showing similar N1 amplitudes across hemispheres in children and adults (Pang and Taylor, 2000; Ponton et al, 2000; Gomes et al, 2001).

To determine the effect of extraction method on responses to the speech stimuli, obligatory cortical responses obtained using the flip-flop and deviant-alone methods were compared. Latencies and amplitudes of the cortical responses to the standard stimuli did not differ between these two methods, consistent with Walker et al (2001).

MMN Identification

Simple visual recognition is most commonly used for MMN identification (e.g., Sharma and Dorman, 1998, 1999; Escera et al, 2000; Gomes et al, 2000; Uwer and von Suchodoletz, 2000; Walker et al, 2001). Visual identification is problematic, however, because MMN can be very small and difficult to identify if traces are noisy, and the technique is subjective and hence subject to bias and observer error.

The integral-distribution technique is appealing because it uses a statistical criterion to identify MMN in individual responses. The integral-distribution technique was quite conservative in identifying MMN relative to the expert observers. There were many cases where

MMN was identified visually by two independent observers, and the integral p value was greater than 0.1. Unfortunately there is no gold standard for MMN identification. Inclusion of a control condition with identical standard and deviant stimuli (and therefore no possibility of MMN) would help to clarify whether the integral distribution or the visual identification technique provides the true answer about MMN detectability. Area criteria (expressed as μV x msec) differ across the studies that have used this technique for MMN identification, ranging from 110 (in this study and in Dalebout and Fox, 2001) to 180 (Dalebout and Stack, 1999) to 225 (McGee et al, 1997). If an area criterion is used for MMN identification, more extensive normative data collection for the specific target population and stimuli is recommended.

MMN Extraction Method

The deviant-alone and flip-flop extraction methods differ in the context in which the standard stimuli occur and the timing of the standard stimuli. Both methods have been widely used in MMN studies using speech stimuli. A simple subtraction method that compares the responses to different stimuli in an oddball paradigm (e.g., /da/ versus /ga/) is not recommended for speech stimuli since the subtracted waveform could reflect differences in the obligatory cortical response to the standard versus deviant, as well as MMN. In the current study, N1 latency (Table 2) did differ significantly for /da/ versus /ga/, supporting the use of the flip-flop or deviant-alone methods for speech stimuli so that the same stimulus is compared when extracting MMN (e.g., /da/ as standard subtracted from /da/ as deviant).

Both adults and children showed differences in speech-evoked MMN due to extraction method. The flip-flop method resulted in smaller MMN area for /ga/ and shorter MMN duration for /da/ and /ga/ than the deviant-alone method. The ISI varies for the standard stimulus in the flip-flop method, due to the presence of the deviants. On average the ISI is slightly longer, and the presence of a deviant after every 3.5 sec would also cause a release from the refractory cycle for the standard stimulus in the flip-flop method. Thus, the differences in MMN obtained using deviant-alone and flip-flop methods could result from stimulus timing and context effects. The finding of a significant difference in MMN area and duration between deviant-alone and flip-flop methods contrasts with Walker et al's (2001) study that showed no differences in MMN between extraction methods for adults using tonal stimuli. Our results indicate that extraction method should be considered when establishing normative data and comparing MMN results from different studies using speech stimuli and/or children.

MMN in Adults *versus* Children

Kraus et al (1993) reported that MMN is mature in school-aged children, but children had bigger MMN than adults. Our findings are consistent with this. Overall, MMN was more robust, with greater area, bigger amplitudes, and longer duration in children than in adults. Although MMN amplitudes were generally greater in children, no statistical significance was achieved. The standard deviations for MMN area (Figure 7) are as high as the average area values, indicating very high variability, especially for children. Adults showed less variability. As MMN is a neurophysiologic reflection of just-perceptible acoustic differences and is modifiable with learning and experience (Kraus and Cheour, 2000), it is possible that variations are more prominent in children because they have greater variability in their auditory experiences than adults.

Stimulus Effects on MMN Detectability in Adults

Wunderlich and Cone-Wesson (2001) found considerable MMN variability in adults depending on the stimulus contrast. This is consistent with our finding that chords 1 and 2 evoked MMN more often (88%) than both speech stimuli [/ga/ (75%), /da/ (56%)] in adults. Relatively poor MMN for speech stimuli in adults is consistent with Dalebout and Fox (2001).

MMN detectability was poorest for simple tones in adults. Tone 1 (1.1 kHz) evoked MMN in only three adults (34%). More adults (53%) had MMN for the 1.5 kHz deviant. Previous MMN studies also show bigger and more consistent MMN with greater stimulus deviance (Sams et al, 1985; Tiitinen et al, 1994; Gomes et al, 2000; Tervaniemi et al, 2000; Ceponiene et al, 2002).

The finding of better MMN for speech stimuli than for tones is in contrast to Wunderlich and Cone-Wesson (2001), who found that tones elicited MMN more often than speech in adults. In the current study, natural speech tokens were used, whereas Wunderlich and Cone-Wesson used synthetic speech. Speech stimuli spoken with a local accent are likely to be more familiar, and will have greater spectral and temporal complexity than synthetic speech. Plasticity and training studies have shown that familiar stimuli yield better MMN (Näätänen et al, 1993; Kraus et al, 1995; Tremblay et al, 1997; Tremblay and Kraus, 2002).

Stimulus Effects on MMN Detectability in Children versus Adults

Chord 1, tone 1, and /ga/ all elicited MMN in most of the children (88%). These were followed by tone 2 (75%), and /da/ as deviant (75%), and lastly by chord 2 (50%). Thus, unlike adults, MMN presence in children did not correlate with stimulus complexity. Tone 1 yielded a much higher percentage of MMN in children than in adults (88% of children versus 34% of adults). This difference is not easily explained as N1 enhancement in the children, since N1 enhancement occurs with greater stimulus deviance (Näätänen, 1992; Picton et al, 2000), and tone 1 differed from the standard by just 10%.

P3a Elicited by Greater Stimulus Deviance

For tone 2, all adults showed a "P3a" positivity in the deviant response at about 264 msec as well as MMN, signifying that the stimulus change was large enough to pre-consciously switch attention toward the deviant (Näätänen, 1992). Näätänen (1992) described P3a as the involuntary attentional switch when the presented stimulus does not match the passively formed neural trace of another stimulus. The difference between deviant and standard stimuli is critical for eliciting passive P3a (Holdstock and Rugg, 1995). In the responses where P3a was more robust, MMN was small or absent, consistent with Wunderlich and Cone-Wesson (2001). In children, both tone 2 and chord 2 elicited a P3a along with MMN (two children) or only P3a (two children for both stimuli, one child for chord 2, two children at only one montage). Thus, P3a partly overlapping with MMN could account for relatively poor MMN for the tone 2 and chord 2 deviants in children.

Electrode Montage Effects on MMN

Brain lesion, fMRI, source-current distribution studies, and multiple channel recordings have shown that MMN activity across the hemispheres is dependent on the type of stimulus used to elicit MMN. Using fMRI, Opitz et al (2002) found bilateral superior temporal gyri activation and noted that temporal activity increased especially in the right hemisphere with increasing degree of deviancy. Schairer et al (2001) used 72 electrode sites and equivalent current dipoles to investigate MMN generators for different stimulus contrasts (intensity, frequency, and duration) and did not find any significant effect of stimulus. In the current study MMN duration for chord 2 was significantly longer over the right hemisphere (at F4). No other montage effects were seen. Bellis et al (2000) too found MMN to be similar across the temporal lobes (for the speech stimulus /da/). The general lack of montage effects suggests that one could use just one montage to record MMN. One advantage of multiple electrode recordings is that the reliability of the responses can be affirmed, especially in extremely noisy recordings, providing the signal-to-noise ratio is not identical at all electrode sites. Across hemisphere recordings may also be informative in clinical populations. Recent plasticity studies report different changes across hemispheres in obligatory cortical responses after training (Ponton et al, 2000; Tremblay and Kraus, 2002).

SUMMARY AND CONCLUSIONS

The P1-N1 obligatory cortical response was later and larger in children than in adults. P2 was absent or very small in the children. The integral-distribution technique was quite conservative in identifying MMN relative to the opinions of two expert observers. A simple area criterion is an alternative objective technique for MMN identification. The area criterion derived in the current study agrees with that used by

Dalebout and Fox (2001). MMN area differed across stimuli, and there was a trend for larger MMN areas in children, and thus normative area data should be collected for the specific population and stimulus if an area criterion is to be used clinically for MMN identification. There were differences in speech-evoked MMN area and duration between deviant-alone and flip-flop methods, and hence extraction method does need to be considered when establishing normative data and comparing MMN results from different studies. There were few significant group differences; however, for all stimuli, MMN had greater area and longer duration in children than adults. The speech stimuli and the 1/1.1 kHz chord elicited the most consistent MMN across children and adults. Tone 1 (1.1 kHz) elicited MMN in most children but in very few adults.

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