Event-Related Potentials in Pediatric Cochlear Implant Patients

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Objective: **The main objective of this study was to assess the correlation of auditory event related potential (ERP) measures with behavioral assessment data to identify if ERPs including mismatch negativity (MMN) can be used to categorize cochlear implant patients into good and poor performers.**

Design: **We investigated auditory event–related potentials to standard and deviant speech stimuli presented in a pseudorandom sequence in 35 cochlear implant patients between the ages of 7 and 17 yr. We compared the occurrence, latencies, and amplitudes of P1, N2, and MMN with overall behavioral outcome in these children. Behavioral measures included category of auditory performance scores and speech intelligibility rating scores.**

Results: **Auditory ERPs in response to standard stimuli were identifiable in 30 of 35 patients, demonstrating a major positive component (P1) followed by a negativity (N2) with absence of N1 in all patients. The P1 component in prelingually deaf patients showed a statistically significant reduction in its latency with increasing duration of implant use. MMN was recorded in 80–85% of star performers but in only 15–20% of poor performers. Patients with higher SIR scores demonstrated statistically significant longer duration of MMN compared with those with a lower SIR score.**

Conclusions: **These results indicate that MMN can be used to assess the functional status of the auditory cortex in terms of auditory memory and discrimination in young children with cochlear implants and may provide an objective mechanism for differentiating good from poor performers.**

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Auditory neurophysiologic investigations are presently used successfully in cochlear implant patients to confirm the diagnosis of profound hearing loss before cochlear implantation. They are also used to evaluate the integrity of the implant device and facilitate its programming after implantation.

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Short latency potentials such as auditory brain stem responses and middle latency responses have proved most valuable in this regard (Kileny & Kemink, 1987; Kileny, Zwolan, Zimmerman-Phillips, & Telian, 1994; Shallop, Beiter, Goin, & Mischke, 1990). Although very effective in evaluating the peripheral nerves and device, these potentials are incapable of assessing the status of the central nervous system, primarily the auditory cortex (Kileny, Boerst, & Zwolan, 1997).

Long latency potentials, also termed as event-related potentials (ERPs) or cognitive endogenous responses, have the potential to shed light in this area of auditory processing since their generators lie in the auditory cortex and they require mental activity on the part of the participant for their generation although this may be pre attentive. These long latency potentials typically have increased onset latency and can extend up to 800 msec after stimulus onset (Kileny et al., 1997; Naatanen, Paavilainen, Alho, Reinikainen, & Sams, 1989). The main components of auditory ERPs are N1, P2, P3, and mismatch negativity (MMN). However, in children below the age of 10 yr, adult-like N1/P2 complex is rarely obtained. Instead, the consistent ERP components recorded are the P1 (P85–120) and N2 (N200–240) (Korpilahti & Lang, 1994).

The most studied ERP components, which are associated with discrimination processes, are P3 and MMN. These are evoked by using an oddball paradigm, where deviant stimuli are embedded in a series of standard stimuli. The MMN, although it can be modulated by attention, is a task-independent ERP component and can be elicited when the subject's attention is directed to other auditory or visual stimuli (Naatanen, Gaillard, & Mantysalo, 1978; Naatanen, Jiang, Lavikainen, Reinikainen, & Paavilainen, 1993; Woldorff, Hackley, & Hillyard, 1991). The MMN typically peaks at 100–300 msec after the occurrence of sound change. It overlaps with other ERP components and is best seen as a difference wave obtained by subtracting the ERP to standard sounds from the ERP to deviant sounds. It is recorded with largest amplitudes over the fronto-central scalp areas. Source modeling of the ERP components and of the magneto-encephalographic counterpart of MMN suggests bilateral generators in the auditory cortices, resulting in summation of

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activity over the fronto-central scalp (Levanen, Ahonen, Hari, McEvoy, & Sams, 1996; Scherg & Von Cramon, 1986). Intracranial ERP recordings provide support to these models by recording MMN directly from the cortex (Liasis, Towell, & Boyd, 1999; Liasis, Towell, & Boyd, 2000).

It has been proposed that the MMN activity is generated by a mismatch between a deviant auditory input and auditory sensory memory representing the features of a repeating standard sound. A frontal cortex contribution to the MMN is generated by prefrontal mechanisms initiating an involuntary switch of attention to changes in our auditory environment (Giard, Perrin, Pernier, & Bouchet, 1990). Studies have shown that MMN is not just a response generated by new nonrefractory afferent elements activated by an occasional infrequent stimulus but instead is an outcome of a comparison process between a new deviant stimulus and a memory trace formed by the standard stimulus in the auditory system (Cheour, Leppanen, & Kraus, 2000; Cowan, Winkler, Teder, & Naatanen, 1993; Naatanen et al., 1989; Naatanen, Paavilainen, & Reinikainen, 1989; Yabe, Tervaniemi, Reinikainen, & Naatanen, 1997). It therefore reflects the operation of auditory sensory memory, which in itself is a major pre requisite for normal central auditory processing in the cerebral cortex.

MMN has been used in several studies to investigate neurophysiologic plasticity following learning. These studies have concluded that experience in a certain language environment can change MMN amplitude, latency, or duration. Importantly, the results of behavioral studies can be related to the results of MMN studies. Krause and coworkers, in 1995, demonstrated increase in duration, amplitude, and area of MMN in adult subjects after 1 wk of training to discriminate between two similar sounding variants of the phoneme /da/ and /ga/ (Kraus et al., 1995). Winkler and coworkers in 1999 showed that changes in MMN amplitude reflected neuronal plasticity in foreign language learning (Winkler et al., 1999). Several researchers have studied MMN in young children and infants using tonal and speech stimuli (Alho, Sainio, Sajaniemi, Reinikainen, & Naatanen, 1990; Ceponiene, Cheour, & Naatanen, 1998; Kurtzberg, Vaughan, Jr., Kreuzer, & Fliegler, 1995; Lyytinen, Blomberg, & Naatanen, 1992; Nyman et al., 1990). MMN can be obtained from the majority of school-age children by using a subtle, just-perceptible difference in stimuli, which suggests that MMN can be used as a clinical tool to investigate even subtle impairments of auditory perception in children (Kraus et al., 1993b).

A number of studies have investigated MMN in cochlear implant patients. Kraus and coworkers were one of the first to evaluate MMN in 9 postlingual, adult, cochlear implant patients using speech stimuli /da/ and /ta/. Eight of these subjects who were good users demonstrated an MMN, whereas 1 of these subjects who was a poor user did not. They concluded than MMN was a promising measure for the objective evaluation of cochlear implant function (Kraus et al., 1993c).

Initial studies by Ponton and Don in 1995 reported that a robust MMN could be evoked by both duration and pitch differences in electrical stimuli in adult cochlear implant subjects (Ponton & Don, 1995). These studies also demonstrated that MMN waveforms for implanted and normal-hearing adults were very similar. Further studies comparing MMN between cochlear implant subjects varying in their spoken language performance showed large differences in MMN thresholds for duration discrimination (Ponton et al., 2000). The MMN threshold (Ponton, Don, Eggermont, & Kwong, 1997) was much better for the implanted adult with good spoken language perception skills. Although this study on two individuals did not demonstrate any correlation between spoken language perception skills and MMN, it highlighted the need to probe any such possible relationship.

Groenen et al. used speech stimuli (/ba/ and /da/) to record MMN in 3 "good" cochlear implant users and 4 "poor" cochlear implant users, categorized on the basis of their performance in monosyllable, spondee, and short vowel identification tests (Groenen, Snik, & van den, 1996). All the subjects were postlingually deaf adults. Group average analysis of the good performers revealed an MMN, whereas that of the poor performers did not. Individual analysis revealed absent MMN in one of the three "good" performers and all the "poor" performers. Based on these results, they proposed that electrophysiologic studies can be used to monitor the neurophysiologic function of cochlear implant subjects.

Kileny and coworkers in 1997 investigated MMN and P3 in 14 cochlear-implanted children between the ages of 4 and 12 yr, using differences in intensity and tone of stimuli and also using differences in speech stimuli (Kileny et al., 1997). They studied the relationship between amplitude and latency of the cognitive responses, namely N1, P2, N2, and P3 and MMN and speech recognition abilities. One of the main findings of their study was that all evoked potential components including P3 and MMN were identifiable in most subjects, although the N1 component was identified least often. The latencies of most components were affected by stimulus type. They tended to be shorter for the frequency contrast than for the loudness contrast, which, in turn, tended to be shorter than for the speech contrast although these differences were not statistically significant. They suggested that this may be a reflection of the increased processing time required for the speech stimuli because of its higher complexity. In frequency discrimination tasks, they showed shorter and stronger P3 and MMN that were associated with high sentence recognition scores. Based on this relationship between MMN and speech recognition scores, they concluded that MMN and P3 hold promise as clinically useful techniques for evaluating young children with cochlear implants.

Recently, Wable and coworkers in 2000 investigated MMN by using electrical stimuli in 8 adult cochlear implant subjects, aged 40–71 yr, having been postlingually deaf from 1 to 13 yr and implanted for 3–36 mo and compared it with their speech performance. Classical P1 N1 P2 wave was identified in 6 out of these 8 subjects. No relationship between MMN and speech performance was found. They suggested that this might be due to the small number of patients (Wable, van den, Gallego, & Frachet, 2000).

In normal-hearing 6- to 8-yr-old children, MMN recorded over the hemisphere contralateral to the side of stimulated ear appears to be adult-like (Ponton et al., 2000). In comparison, MMN recorded over the hemisphere ipsilateral to the stimulated ear is not evident until the age of 7 yr. After the age of 8 yr, the MMN begins to emerge in the ipsilateral hemisphere, gradually increasing in amplitude with age. As a result, the ratio of ipsilateral/contralateral magnitude of MMN shows an age-related increase from approximately 0.2 in the 5- to 6-yr-olds to 0.6 in the 18- to 20-yr-olds. It has been proposed that the later emergence and amplitude growth of MMN over the ipsilateral hemisphere may reflect the late maturation of cortical mechanisms and interhemispheric connections in superficial cortical layers where the MMN is presumed to be generated (Ponton, Moore, & Eggermont, 1999; Ponton et al., 2000). The cochlear implant patients are different in this respect. In most studies reported, all the implanted children demonstrate MMNs in both contralateral and ipsilateral sides.

In the field of cochlear implants, behavioral methods are the primary tools used at present to assess and predict outcome of implantation in adults and children. These are difficult to use effectively in young children due to poor communication and cognitive skills in the child. The recent decline in the age of implantation with a strong trend toward early implantation has created the need for a more objective tool to predict future outcome after cochlear implantation.

Current evidence regarding MMN suggests that it provides very useful information regarding processing of auditory stimuli at the level of cerebral cortex and may therefore prove to be a promising diagnostic or prognostic tool in clinical practice. The main advantages of MMN in this respect are: (a) The ability for it to be elicited without task vigilance renders it to be a strong candidate for objectively assessing auditory discrimination in young children who cannot participate in behavioral tests. It can even be obtained in sleep in infants, although not in older children or adults (Alho et al., 1990; Cheour-Luhtanen et al., 1995); (b) It can be recorded at a very early age, since it is developmentally quite stable in children (Cheour et al., 2000); and (c) It is noninvasive and assesses the functional aspects of the central auditory pathways such as central sensory processing and discrimination, which cannot be explored by standard radiologic investigations such as MRI (Kraus & Cheour, 2000).

In spite of two decades of intensive experiments with MMN, so far there has been limited documentation of its use in clinical practice. This may be due to great intersubject variability when assessed at an individual level compared with group average analysis but may also be due to inadequate number of subjects in trials assessing its role in clinical setups.

The objective of this study was to assess the relationship of auditory ERP measures with behavioral assessment data in school-age children using cochlear implants, validating its use in young cochlear implant patients as a measure of central auditory processing.

METHODS

Participants

Thirty-five patients who had undergone surgical implantation of a Nucleus multichannel cochlear implant device (Nucleus 22/Nucleus 24M/Nucleus 24 Contour; Cochlear UK, Ltd., London, UK) were investigated. The patients' age ranged from 7 to 17 yr (mean age, 12 yr). Prior to surgery, all patients had bilateral profound sensorineural hearing loss. After surgery, all subjects' peripheral hearing investigations revealed pure tone thresholds to warbled tone stimuli in the 30–40 dB range. All 22 electrodes were active in all patients except one, who had 20 active electrodes. All the patients used Nucleus behind-the-ear speech processor with SPEAK speech coding strategy. Twenty-seven subjects were implanted on the right side and 8 were implanted on the left side. Two subjects were postlingually deaf and 33 were prelingually deaf. Of the 33 prelingually deaf, the hearing loss was congenital in 26 and acquired in 7. Length of implant use ranged from 1 to 10 yr. Additional subject information is provided in Table 1.

TABLE 1. Patient demographics

Patient	AI (yr)	DU (yr)	AT (yr)	Side	Sex	Etiology	CAP score	SIR score
1	8.01	8.82	16.83	R	M	A (unknown)	7	5
2	15.37	1.08	16.44	L	F	P (meningitis)	7	6
3	12.97	3.11	16.08	R	M	P (meningitis)	7	6
4	4.89	10.17	15.06	L	M	C	7	3
5	11.31	6.43	17.75	R	M	A (meningitis)	7	5
6	2.38	9.14	11.51	R	M	C	7	6
7	3.05	8.12	11.18	R	F	C	7	6
8	6.73	10.19	16.92	L	F	A (unknown)	6	4
9	4.05	7.33	11.39	L	M	C	6	3
10	4.47	9.33	13.8	L	M	A (meningitis)	6	4
11	6.9	7.07	13.97	R	F	C	6	3
12	5.72	6.37	12.09	R	F	C	6	3
13	2.81	8.39	11.2	R	M	C	6	4
14	2.37	5.36	7.73	R	F	C	6	5
15	4.48	5.72	10.2	R	F	C	5	2
16	9.23	6.47	15.7	R	M	C	5	3
17	4.86	6.3	11.16	R	F	C	5	3
18	4.41	10.32	14.73	L	F	A (hypoxia)	5	4
19	5.46	6.04	11.5	R	M	C	5	3
20	3.2	7.38	10.58	R	M	C	5	2
21	5.94	8.09	14.04	L	M	C	5	3
22	7.02	9.45	16.47	R	M	C	5	3
23	12.07	1.66	13.73	R	M	C	5	6
24	5.61	5.42	11.03	R	F	C	5	2
25	4.72	7.26	11.98	R	M	A (hypoxia)	5	3
26	4.85	7.02	11.87	R	M	C	5	4
27	6.34	4.22	10.56	R	F	C	4	2
28	3.15	5.05	8.2	R	M	C	4	3
29	4.26	3.09	7.35	R	F	C	4	3
30	4.68	5.08	9.76	L	M	A (meningitis)	4	3
31	6.16	1.07	7.23	R	F	C	4	4
32	6.66	1.31	7.97	R	F	C	4	4
33	13.21	1.18	14.39	R	F	C	4	4
34	6.78	3.08	9.86	R	F	C	4	1
35	2.21	5.45	7.65	R	M	C	3	3

AI = age at implantation; DU = duration of implant use; AT = age at test; side of implant, sex of patient, Category of Auditory Performance (CAP) and Speech Intelligibility Rating (SIR) scores (obtained within 3 months of event-related potential recording). A = acquired prelingual; P = postlingual; C = congenital.

Experiment

Procedure • All patients undertook passive oddball auditory tasks involving consonant-vowel syllables. During all recordings, a pseudorandom sequence of stimuli was presented with a deviant probability equal to 0.12. Throughout the recording, the patients watched a silent movie of their own choice on a computer monitor place 1 meter in front of them to minimize head and eye movements. The entire recording was obtained during passive listening.

The Inter Stimulus Interval was set at 1000 msec. The stimuli were presented in 4 blocks of 500 stimuli containing 60 deviants /da/ and 440 standards /ba/ for each subject, with breaks of 2 minutes between each block. As a control, 1 block of 200 presentations of /da/ was presented alone (/da/ alone condition), also at 1 per sec.

Stimuli • Computer-generated speech stimuli /ba/ and /da/ were used to elicit the ERPs. These syllables were selected from a synthesized-voice, place-of-articulation continuum, varying in the starting frequencies of their second and third formant (we wish to thank Prof. Janet Werker for the speech stimuli that we used) (Werker & Lalonde, 1988) (Fig. 1). Both stimuli were 275 msec in duration. The fundamental frequency was steady at 100 Hz for the first 100 msec, and then gradually rose to 120 Hz during the remaining 175 msec. The first formant (F1) rose from 250–500 Hz in a 50 msec transition, whereas the fourth and fifth formants were constant at 3500 and 4000 Hz, respectively. The steady state for the second and third formants (F2 and F3) was 1090 and 2240 Hz, respectively. The standard stimulus /ba/ had F2 and F3 frequencies of 900 Hz and 2240 Hz, whereas the deviant stimulus /da/ had F2 and F3 frequencies of 1600 and 2912 Hz varying over 50 msec to 1090 and 2440 Hz, respectively. These particular /ba/ and /da/ stimuli have been reported to be reliably identified as /ba/ and /da/ and discriminated from one another behaviorally and

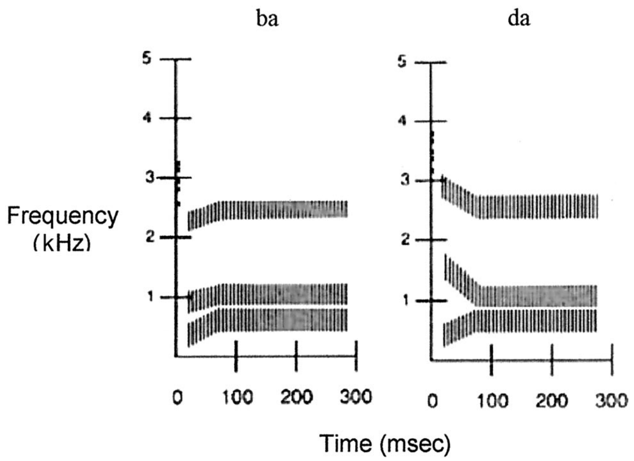

Fig. 1. Spectral array of syllables /ba/ and /da/ used in our recordings. Note major difference between the two stimuli is the first 50 msec of the second formant (Werker et al., 1988).

electrophysiologically by British native English speakers (Rivera-Gaxiola, Johnson, Csibra, & Karmiloff-Smith, 2000). The stimuli were delivered by a computer (Neuroscan-STIM Version 3; Compumedics USA, Ltd., El Paso, TX), using free-field stimulation with loudspeakers placed 1 meter to either side of the patient (75 dB SPL).

Data Acquisition • Twenty-one silver–silver chloride electrodes were used to record the electroencephalographic activity [Fz, F3, F4, Cz, C3, C4, T3, T4, Pz, P3, P4, Oz, O1, O2, T5, T6], using a modified 10:10 montage (Le, Lu, Pellouchoud, & Gevins, 1998). The reference electrode was placed at the mastoid contralateral to the side of cochlear implant; the ground electrode was placed on the subject's forehead. An electrode placed above the contralateral eye to the side of implant was used for artifact rejection of eye blinks online. Cochlear implant artefacts were dealt with as previously reported (Singh, Liasis, Rajput, & Luxon, 2004). Because of a large artifact in the electrode sites adjacent to the cochlear implant, these were excluded from the $\pm 100\ \mu V$ artifact rejection algorithm, applied to all other electrodes. The cochlear implant and speech processor device were kept at the individual patients' standard comfortable settings. The continuous electroencephalogram was collected at a sampling rate of 1000 Hz, with a band pass of 0.1–100 Hz and stored on a personal computer for further processing.

Data Processing • The data were digitally filtered off-line with a low pass of 30 Hz and a 12 dB/octave roll-off and analyzed as epochs of -100 to $+ 900$ msec after stimulus presentation. The zero baseline was defined as the average voltage of the prestimulus baseline (-50 to 0 msec). Artifact rejection of epochs containing transients greater than $\pm 100\ \mu V$ was carried out off-line.

Latencies and amplitudes of the following components were investigated: P1, N1, P2, N2, and MMN from electrodes Fz, F3, F4, C3 and C4. Deviant, standard (excluding the postdeviant standards) and deviant alone ERPs were constructed. All ERPs were constructed from a minimum of 100 epochs. Peak latency and amplitude of P1 and N2 was measured from the "standard" ERP (/ba/ standard). The MMN was analyzed as a difference wave obtained by subtracting the "deviant alone ERP" (/da/ standard) from that of the "deviant" ERP (/ba/ standard, /da/ deviant).

The MMN was defined as a visually identified negativity above baseline in the subtraction waveform peaking between 100 and 350 msec after stimulus presentation by the first two authors, who were blinded to the behavioral outcome scores. If there was no negative peak in this time interval, it was regarded as a case of absent MMN. For each difference waveform the onset, peak and offset latency was measured. The onset and offset latency were defined as the time at which the negativity crossed baseline before and after the peak, respectively. MMN duration was calculated as offset minus onset latency. MMN area was calculated as a product of duration and amplitude (Groenen, Snik & van den, 1996).

The reproducibility of MMN was assessed by comparing averages constructed from equal numbers of random epochs, and odd and even averages were extracted from the complete data sets. If the MMN identified in the subtraction waveform was not reproducibly present in the subaverages in any of the above-described averages, then it was not regarded as a true MMN.

Behavioral Assessment • Overall behavioral measures of these patients was obtained from their Category of Auditory Performance (CAP) score and Speech Intelligibility Rating (SIR) scores, based on overall assessment by their respective teachers of the deaf and speech and language therapists at the time of their last evaluation. Behavioral assessment was carried out within 3 mo of the ERP recording and was done with the cochlear implant settings at the individual patient's standard comfortable level, the same as when doing the ERP recordings.

The CAP score is a standard scale used to rate outcomes from pediatric cochlear implantation in everyday life (Table 2). It is an 8-point hierarchical scale of auditory performance, ranging from no awareness of environmental sounds (score 0) to use of the telephone with a known speaker (score 7) (Nikolopoulos, O'Donoghue, & Archbold, 1999). The SIR score is an outcome measure of speech produc-

TABLE 2. Category of Auditory Performance score

	Category of Auditory Performance score
0	No awareness of environmental sounds
1	Awareness of environmental sounds
2	Response to speech sounds (e.g., go)
3	Identification of environmental sounds
4	Discrimination of speech sounds
5	Understand common phrases, no lipreading
6	Understands conversation, no lipreading
7	Use of telephone—known speaker

tion in real-life situations and has been used reliably in cochlear implant patients. It ranges from 1 (prerecognizable words in spoken language) to 5 (connected speech intelligible to all listeners, child understood easily in everyday contexts) (Allen, Nikolopoulos, & O'Donoghue, 1998), although in the present investigation score 2 was expanded into a further two categories, resulting in a 6-category scale (Table 3). In this study, patients with a CAP score of 7 or SIR score of 6 were categorized as "star" performers. Those with a CAP score of ≤5 or SIR score ≤3 were categorized as "poor" performers.

Statistical Analysis

Parameters from the Fz electrode site were used for all statistical analysis. The alpha level for statistical significance was set at 95%.

The amplitude and latency parameters of ERP components were compared with measures of behavioral outcome (CAP and SIR scores), using independent *t*-tests and bivariate correlations.

The relationship between occurrences of MMN and CAP/SIR score was assessed by using Pearson Chi-square and Fisher exact probabilities.

The symmetry of the responses evoked by the subjects was investigated by comparison of component amplitudes, latencies, and duration over the frontal (F3, F4) and central (C3, C4) sites, using analyses of variance.

TABLE 3. Speech Intelligibility Rating score

	Speech Intelligibility Rating score
1	Prerecognizable words in spoken language
2	The primary mode of communication is manual. The speech or vocalization patterns that accompany the use of sign/gesture may give some additional information at the lipreading level.
3	Speech is unintelligible. All experienced listeners can follow a known topic via lipreading and context clues. It is not possible to follow an audiotape sample.
4	Connected speech is intelligible to a listener who concentrates and lipreads.
5	Connected speech is intelligible to a listener who has a little experience of a deaf person's speech.
6	Connected speech is intelligible to all listeners. Child is understood easily in everyday contexts.

Maturational profile of ERP components in prelingually deaf patients was investigated by studying bivariate correlations between amplitude and latency parameters of the ERP components with age of the patient/duration of implant use (time in sound). The two postlingual patients were excluded from this analysis because maturation of the ERP components in these two patients would be similar to that of a normal-hearing patient of the same age, and in this respect not fit in the same model describing maturational trends in prelingually deaf cochlear implant subjects.

Results

Obligatory Components

Auditory ERPs in response to standard stimuli were identifiable in 30 of 35 patients. Of these patients, 24 cases had congenital deafness, 4 cases had acquired prelingual deafness, and 2 cases were postlingually deaf.

Grand averages of all patient data revealed responses consisting of a major positivity (labeled P1) followed by a negativity (labeled N2) (Fig. 2A). The mean latency of P1 and N2 was 109.27 ± 24.78 msec and 241.03 ± 35.78 msec, respectively. The mean amplitude of P1-N2 was 6.83 ± 3.54 μV.

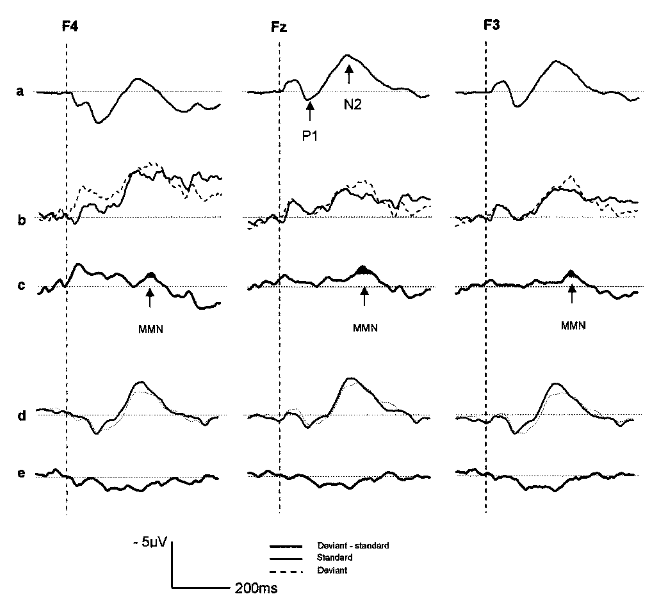

Fig. 2. Grand average event-related potentials of cochlear implant patients recorded at F4, Fz, and F3. (a) Obligatory components, P1 and N2 in all patients (*N* = 30), (b) standards and deviants in star performers (*N* = 7), (c) mismatch negativity (*MMN*) revealed by the subtraction wave form in star performers shaded area, (d) standards and deviants in poor performers (*N* = 21), (e) subtraction wave revealing no MMN in poor performers.

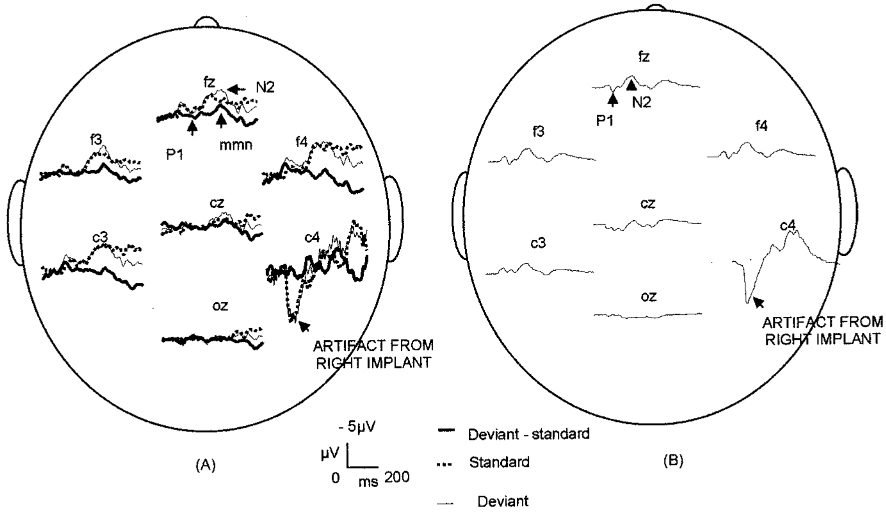

Fig. 3. Event-related potentials in star performers showing distribution of mismatch negativity (*MMN*) (A) and P1, N2 (B). Note the presence of artifact at C4 due to cochlear implant package on the right side.

An assessment of the symmetry of responses over the frontal and central electrodes revealed no significant differences in the peak latency or amplitude of P1 and N2 components between the right and left electrode sites [maximum F ratio, $F(1,16) = 1.87$, $p = 0.019$] (Fig. 3).

Independent t-tests comparing P1, N2 latency and P1-N2 amplitude in star performers [CAP 7 ($N = 7$) or SIR 6 ($N = 5$)) and in poor performers [CAP ≤ 5 ($N = 17$) or SIR ≤ 3 ($N = 15$)] categories did not reveal any statistically significant difference. Bivariate correlation analysis assessing the relationship of obligatory components (latency and amplitude of P1 and N2) with behavioral score (CAP and SIR score) also did not reveal any significant relationship. Latency and amplitude measures of these components across all behavioral groups are detailed in Table 4.

In prelingually deaf children, bivariate correlation analysis assessing the relationship between latency of P1 and age of the patient did not reveal any relationship. A similar analysis assessing the relationship of P1 latency with duration of implant use (time in sound) revealed a statistically significant negative correlation (Pearson correlation = -0.45, $p = 0.01$). Patients who had used cochlear implants for longer durations irrespective of outcome demonstrated statistically significant shorter latency of P1 (Fig. 4). Similar analysis carried out for N2 latency and P1-N2 amplitude did not reveal any significant relationship.

Mismatch Negativity

MMN was identified in 10 of the 35 patients recorded in our study (Figs. 2 and 5). The MMN had a mean peak latency of 267 ± 62 msec, mean onset latency of 168 ± 61 msec, and amplitude (peak to peak) of 4.7 ± 1.4 μV (Table 5).

Pearson Chi-square analysis revealed a trend of CAP score (7, 6, 5, ≤ 4) and presence of MMN (Pearson Chi-square = 15.2, $p = 0.002$) with those patients with a higher CAP score revealing an MMN in comparison to those with a lower CAP score who did not. Further analysis investigating the presence or absence of MMN and SIR (6, 5, 4, ≤ 3) score also revealed a similar trend (Pearson Chi-square = 11.14, $p = 0.01$). These trends were supported by using the Fisher exact probability test (CAP: 7 versus ≤ 6, $p = 0.001$; SIR: 6 versus ≤ 5, $p = 0.017$).

TABLE 4. Latency and amplitude (mean ± SD) of obligatory components in different behavioral groups based on CAP and SIR scores

	P1 Latency ± SD (msec)	N2 Latency ± SD (msec)	P1 N2 Amplitude ± SD (μV)
All patients	109.28 ± 24.78	241.04 ± 35.79	6.84 ± 3.55
CAP 7 (n = 7)	103 ± 32.17	238.5 ± 35.88	5.98 ± 3.8
CAP 6 (n = 6)	112.17 ± 21.79	241 ± 16.45	6.52 ± 2.98
CAP 5 (n = 10)	105.78 ± 31.18	232.67 ± 41.36	7.61 ± 4.4
CAP ≤ 4 (n = 7)	115.75 ± 12.71	254 ± 41.33	6.69 ± 3.09
SIR 6 (n = 5)	113.8 ± 39.86	241.8 ± 28.03	6.21 ± 3.7
SIR 5 (n = 3)	99.33 ± 4.73	205.5 ± 16.26	3.99 ± 0.3
SIR 4 (n = 7)	113.86 ± 14.9	253.4 ± 37.94	8.43 ± 3.19
SIR ≤ 3 (n = 15)	107.5 ± 26.12	241.4 ± 38.58	6.9 ± 3.81

CAP = Category of Auditory Performance score; SIR = Speech Intelligibility Rating score.

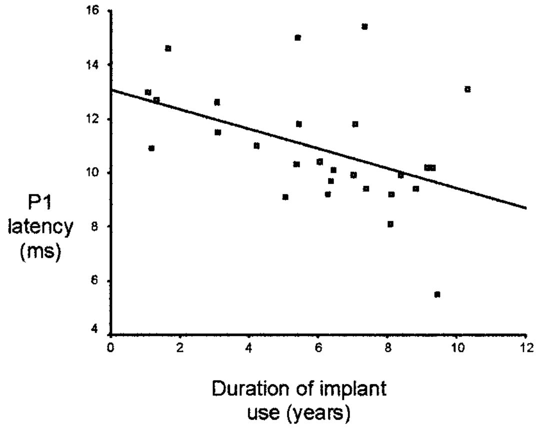

Fig. 4. P1 latency versus duration of implant use in prelingually deaf patients (Pearson correlation = −0.45, p = .01).

In the grand averages of patients with a CAP score of 7 (star performers, N = 6) an MMN was clearly evident in the frontal and central electrode positions, with a peak latency of 267 msec (Fig. 2B and C, and Fig. 3). The onset time was 127 msec and offset time was 375 msec. Grand averages of patients with a CAP score of ≤5 (poor performers, N = 21) revealed no MMN (Fig. 2D and E).

Investigation of the symmetry of responses over frontal and central electrodes revealed no significant differences in the peak latency, duration, and amplitude measures of MMN between the right and left electrode sites [maximum F ratio, $F(1,7) = 1.84$, $p = 0.218$].

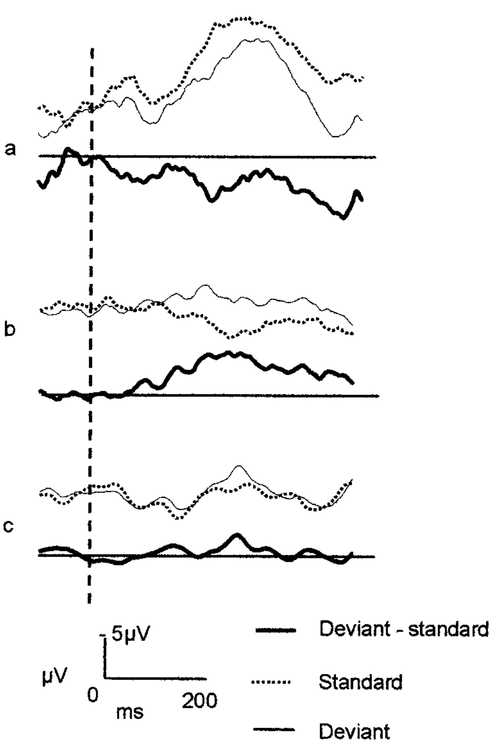

Fig. 5. Individual recordings of three patients from Fz. (a) mismatch negativity absent, (b) and (c) mismatch negativity present.

The outcome of bivariate correlation analysis carried out to assess the relationship of MMN (peak and onset latency, amplitude, area, and duration measures) with behavioral assessment measures (CAP and SIR scores) revealed no significant correlation between latency, amplitude, and area measures and behavioral scores. However, the duration of MMN demonstrated a significant positive correlation with the SIR score (Pearson correlation = 0.73, p = 0.01) (Fig. 6).

In prelingually deaf children, bivariate correlation analysis assessing the relationship between MMN (amplitude, duration, area, and latency) and age of the patient/duration of implant use did not reveal any significant relationship.

DISCUSSION

Obligatory Components

The majority of our patients (30 of 35) demonstrated the obligatory components P1 and N2. A convincing N1 was not observed in any of our patients. The presence of P1 and N2 components and the absence of N1 is not surprising in the light of the known maturational profile of these components in normal-hearing children.

The ERPs of normal-hearing young children are dominated by a large positivity (P1) with a peak latency slightly earlier than that of the adult N1, followed by a negative trough at about 180 msec, which corresponds to the adult N2, although with a slightly shorter latency. It is not known, however, if these components are analogous to the adult P50-NIOO-P200 in terms of polarity or latency (Korpilahti & Lang, 1994). The N1 peak is not consistently present until the age of 9–10 yr. By 12–13 yr, the ERP waveforms assume an adult-like morphology, with the N1 becoming increasingly negative with P1 decreasing in amplitude indicating that most of the reduction in P1 latency and amplitude could reflect phase cancellation of a mature P1 peak by amplitude increases in the maturing N1 peak (Ponton et al., 2000). Based on the above, one would expect that P1 and N2 components dominate the picture in cochlear implant patients until about 10–12 yr of implant use (analogous to a normal-hearing child of 10–12 yr) and that N1 would begin to emerge at about 12–13 yr of implant use. Since the maximum duration of implant use in our study was 10 yr, we did not expect to see any N1 component in our study, which fit in very well with our findings.

TABLE 5. Mismatch negativity parameters and behavioral scores (CAP and SIR) in 10 cochlear implant patients demonstrating mismatch negativity

Patient	CAP score	Etiology	SIR score	Peak latency (msec)	Onset latency (msec)	Amplitude (μV)	Duration (msec)
1	7	Acquired	5	226	189	1.98	128
2	7	Postlingual	6	261	76	6.04	384
3	7	Postlingual	6	279	101	3.45	377
4	7	Congenital	3	162	113	5.88	144
5	7	Acquired	5	396	212	7.26	219
7	7	Congenital	6	271	216	4.19	187
23	5	Congenital	6	214	117	4.91	342
24	5	Congenital	2	255	184	5.12	139
26	5	Congenital	4	286	229	3.97	200
30	4	Acquired	3	320	250	4.54	111
			Mean	267	168.7	4.73	223.1
			SD	62.95	61.42	1.48	105.67

CAP = Category of Auditory Performance; SIR = Speech Intelligibility.

Analysis of the waveforms of the two postlingual patients in our study also did not demonstrate any convincing N1. The age of deafness in the two postlingual patients included in our study was 12 and 15 yr. This suggests that these two patients were at the borderline with respect to emergence of the N1 component. It is possible that meningitis leading to deafness arrested the maturation of ERPs, resulting in persistence of the P1 and N2 components. The latency of P1 in one of these patients (12 yr old at the time of deafness) was 66 msec, similar to the expected value for a prelingually deaf child using a cochlear implant for 10–12 yr. The other patient (15 yr at deafness) demonstrated a P1 latency of 163 msec, which does not fit in with the above model. It is possible, however, that in this particular patient a partially emerging N1 may have distorted the morphology of P1, giving the false impression that its latency was 163 msec.

Absent N1 in cochlear implant patients has been reported by other researchers as well. Ponton and coworkers reported an absent N1 to be a notable feature in ERPs recorded in cochlear implant patients (Ponton & Eggermont, 2001). Groenen et al. recorded event-related potentials in 7 cochlear implant patients. Their group average analysis revealed N1 in both good and poor performers. However, all subjects in their study were postlingually deaf adults (Groenen, Makhdoum, van den Brink, Stollman, Snik & van den, 1996).

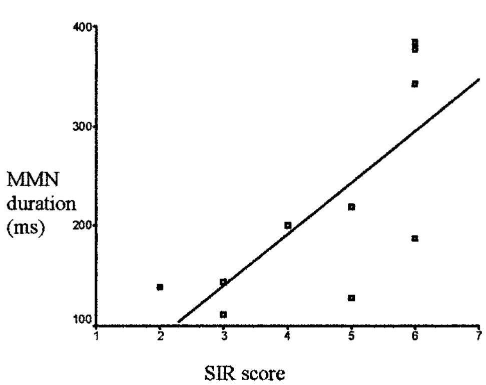

Fig. 6. Mismatch negativity (*MMN*) duration versus speech intelligibility rating (*SIR*) score in cochlear implant patients (Pearson correlation = 0.737, *p* = .01).

Assessment of the maturational profile of these obligatory components in 24 patients who were prelingually deaf with congenital etiology revealed considerable individual variation in amplitude and latency but a significant trend toward decreasing P1 latency with increasing duration of implant use (time in sound period for this group). No such pattern of maturation was observed when the P1 latency was compared with the age of the patient at the time of testing.

Assessment of N2 latency with duration of implant use or age of the patient did not reveal any pattern of age-related latency decrease. This was in agreement with the findings of Ponton and coworkers in 1996 (Ponton, Don, Eggermont, Waring, & Masuda, 1996; Ponton et al., 1996). A symmetrical distribution of the obligatory components in our study, as suggested by no differences in the latency and amplitude measures of P1 and N2 between the two hemispheres in cochlear implant patients, further supports previous work (Ponton et al., 2000).

ERP studies looking at maturation rate of obligatory components in normal-hearing children have previously been carried out. A series of studies carried out by Ponton and coworkers between 1996 and 2001 in cochlear-implanted children and normal-hearing children initially indicated that the rate of maturation in cochlear implant and normal-hearing groups was the same, but that the cochlear implant group lagged behind the normal-hearing group by the duration of deafness prior to implantation (Ponton et al., 1996; Ponton et al., 1999; Ponton et al., 2000; Ponton, Eggermont, Kwong, & Don, 2000). Similar results were reported by Eggermont and coworkers in cochlear implant children, implanted after an average period of deafness of 4.5 yr (Eggermont, Ponton, Don, Waring, & Kwong, 1997). Later studies by Ponton et al. (Ponton et al., 2001), however, concluded that cochlear implant patients actually had a faster rate of maturation than the normal-hearing group, although this is contradictory to the concept of delayed maturation due to sensory deprivation in the cochlear implant group. Sharma and coworkers in 2002 demonstrated that the P1 latency in normal-hearing and cochlear implant subjects was the same in those children who had deafness for less than 3.5 yr prior to cochlear implantation (Sharma, Dorman, & Spahr, 2002).

The pattern of maturation of P1 with the use of an implant, as noted in our study, suggests that during the period of deafness, some aspects of the central auditory nervous system activity do not mature completely, as indicated by prolonged latencies in those who had used the implant for shorter durations. Once stimulation of the auditory pathways is restored by the use of a cochlear implant, maturation of the neural sources contributing to P1 is resumed. As a result, those who had used their implant for longer duration demonstrated a reduction of their P1 latency. The absence of N1 in all children included in our study and its presence in postlingually deaf adults as demonstrated by other studies (Groenen, Snik & van den, 1996) further suggests that this pattern of maturation is not complete in spite of prolonged use of a cochlear implant. This may indicate that a cochlear implant cannot substitute normal hearing from the point of maturation of auditory pathways even in those children who were implanted after 15 yr of age, the oldest in our series.

These findings further emphasize that maturation of the part of auditory cortex associated with the generation of P1 does not follow an autonomous course in the absence of auditory input, as suggested by a longitudinal study of two cochlear implant patients (Ponton, Moore, & Eggermont, 1999). Also, maturation of the cortical pathways giving rise to P1 does not appear to be strongly related to proficiency in receptive and expressive language, since no maturational pattern was observed when comparing the latency of P1 with behavioral scores (CAP and SIR).

When applied to a clinical setting, serial recordings of ERPs demonstrating abnormal maturation of obligatory components can be a possible indicator of abnormal functioning of the cochlear implant or speech processor, since a malfunctioning implant package would not provide adequate auditory input required for normal maturation of obligatory components, thus leading to absent/delayed maturation of P1.

Mismatch Negativity

MMN studies carried out in healthy subjects and clinical groups clearly demonstrate that a prominent, well-developed, stable MMN can be obtained from all normal-hearing adults and children, although in the latter, the amplitude and latency of MMN exhibits much wider variation and has been shown to be absent in 25–30% of infants (Cheour et al., 1998; Kurtzberg et al., 1995) and 50% of newborns in some studies (Leppanen, Eklund, & Lyytinen, 1997). MMN has a fast maturational profile and is developmentally quite stable from early childhood (Kraus, McGee, Sharma, Carrell, & Nicol, 1992; Kraus et al., 1993a; Kraus et al., 1993b). Based on current evidence, it is reasonable to conclude that MMN is an indicator of normal central auditory processing at the level of cerebral cortex. These attributes have projected MMN as a promising tool to investigate language perception, memory, and auditory discrimination in groups of children.

Based on the above, we hypothesized that cochlear implant patients who are doing very well in terms of good receptive and expressive language development may be able to demonstrate an MMN to speech stimuli. Those who are not doing well either because of inherent neurologic limitations such as poor cortical plasticity or other developmental deficits or because of inadequate rehabilitation are less likely to demonstrate an MMN. Further, although MMN attributes in children have been shown to exhibit wide variability, we tried to analyze these parameters in our study to demonstrate any correlation with behavioral scores as this would help in quantifying any effect observed.

The Chi-square analysis and the Fisher exact test results indicate that MMN is much more likely to be present in those patients who have better behavioral performance scores, namely CAP and SIR. In comparison to 80–85% of star performers demonstrating the MMN, only 16–20% of poor performers demonstrated the wave. This is in agreement with our original hypothesis that star performers are more likely to demonstrate the MMN in comparison to the poor performers.

The reason for the absence of MMN in 15% of star performers and its presence in about 15% poor performers can be explained as below. With regard to star performers, only 1 patient in this category on the basis of CAP or SIR score did not demonstrate an MMN. Detailed analysis of this individual's wave forms (Fig. 5A) in fact did reveal a negative-going component in the subtraction wave form. However, since this negative component did not rise above the baseline, it did not meet our criterion for a MMN. With regard to poor performers, 4 of 21 (based on CAP scores) and 3 of 19 (based on SIR scores) poor-performing patients demonstrated an MMN. Presence of MMN in those patients who were poor performers based on behavioral assessment scores is interesting. The reason for their poor behavioral score may lie in other factors such as duration of implant use, coexisting medical conditions, and nature of rehabilitation. In one of these children, who demonstrated a good MMN, the development of expressive and receptive language was significantly limited by the nature of his rehabilitation, which was based primarily on sign language, since the subject's teacher was a deaf signer herself. It may be that in a longitudinal study, presence of MMN is associated with good behavioral outcome in these children.

Given that MMN is an indicator of normal auditory sensory memory and auditory discrimination, which are prerequisites for normal central auditory processing, if used as a clinical test, the above figures would suggest a sensitivity and specificity of 80–85% in detecting good central processing skills objectively, using MMN in cochlear implant patients (Table 6). Given the fact that recording MMN is a completely safe, noninvasive procedure, the above figures are supportive of its use as a clinical tool in cochlear implant patients to shed more light on the central processing skills of some patients who are borderline in their behavioral performance or in those patients in whom behavioral tests cannot be carried out. Presence of MMN in these patients will indicate good auditory memory and discrimination skills, suggesting a positive prognosis.

In normal-hearing children, MMN may become similar to that observed in an adult at a very early age, about 2 yr (Ponton et al., 2000). Therefore, in congenitally deaf children who receive a cochlear implant, in the absence of any other pathology that may have affected the maturation or plasticity of the auditory cortex, it should be possible to record MMN 2 yr after implantation. This suggests that the majority of patients who demonstrate an MMN would have done so 2 yr after implantation if tested at that time. Although our study does not prove this evolution, since we did not perform any serial recordings of MMN, if true, as derived from the maturation pattern of MMN, carrying out the test 2 yr after implantation would have a predictive value in assessing future prognosis after implantation.

Investigation of the symmetry of distribution of MMN was carried out at group level. The analysis revealed MMN to be equally distributed over both hemispheres. This finding is very interesting, since normal-hearing children demonstrate significant asymmetry with a predilection for the contralateral side and emergence of MMN on the ipsilateral side only at the age of 8 yr (Ponton et al., 1999; Ponton et al., 2000). Although in normal-hearing children this phenomenon of asymmetry at earlier ages has been explained on the basis of maturation of the intercortical pathways with passing age, it is difficult to describe why cochlear implant children should demonstrate MMN on the ipsilateral side from the beginning. Interestingly, this finding in cochlear implant patients has been reported by other researchers as well, although no satisfactory explanation has been attributed to the phenomenon (Ponton et al., 2000). It is possible that in reality there does exist a pattern of maturation in cochlear implant children, as seen in normal-hearing children with a shift in the distribution of MMN from the contralateral side to both sides. However, combining the data in our study across all age groups may have smeared the results, creating this false impression of equal distribution of MMN over both hemispheres.

Bivariate correlation analysis assessing MMN parameters with behavioral outcome results revealed a positive correlation between MMN duration and SIR score but not CAP score. No such relationship was observed for MMN peak latency, area, and peak amplitude with either CAP or SIR score. This was not surprising, in light of the fact that MMN parameters are known to be quite variable at individual level (Cheour et al., 1998; Kurtzberg et al., 1995; Leppanen & Lyytinen, 1997) and the small

TABLE 6. Sensitivity and specificity of MMN (recorded at Fz) as a clinical test identifying good central auditory function based on CAP/SIR scores

	CAP score		SIR score	
	7	≤5	6	≤3
Total patients	7	21	5	19
MMN +	6	4	4	3
MMN −	1	17	1	16
Sensitivity	85.71%		80.00%	
Specificity		80.95%		84.21%

MMN = Mismatch negativity; CAP = Category of Auditory Performance; SIR = Speech Intelligibility.

number of patients demonstrating MMN in our study. Detailed analysis of the relationship between MMN duration and SIR score revealed a statistically significant relationship best described by a linear model (Fig. 6). These results are suggestive of the fact that MMN duration is indicative of the level of cortical maturation and thus behavioral outcome in cochlear implant patients. A longer duration of MMN is an objective indicator of better behavioral results. Although this fact may not seem very interesting, in our subjects in whom we have both electrophysiologic and behavioral results, it would be very valuable, when carrying out MMN studies in very young cochlear implant patients or those with complex problems, in whom behavioral analysis is difficult. Presence of MMN in these patients may serve as a valuable positive prognostic marker indicating favorable prognosis in the long run, since the likelihood of recording MMN is much higher in those patients who achieve good behavioral outcome, and at present there is no other reliable index to predict outcome of cochlear implantation in this group. However, keeping in mind that a large percentage of patients did not demonstrate an MMN, an absent MMN should be interpreted with caution, since a poor signal-to-noise ratio for reasons such as inadequate duration of recording may be the reason why MMN is not evident in some patients.

The positive correlation between duration of MMN and behavioral score suggests that MMN can indicate overall performance in cochlear-implanted children and can be used in clinical settings on an individual. Of interest was the finding that unlike obligatory components such as P1, MMN did not demonstrate any correlation with age of the patient or duration of implant use. This may, however, be due to the small number of patients demonstrating MMN compared with P1 in our study.

The clinical application of MMN so far has been limited to a great extent by the lack of an objective detection method that can be applied to a single subject. Our study indicates that duration of MMN, which is derived from the offset and onset latency of MMN, is a useful measure for assessing the magnitude of MMN. This is in partial agreement with the results of McGee and coworkers, who demonstrated that combination of area and latency criterion was best in objective identification and assessment of MMN and that statistical techniques such as point-to-point *t*-tests and integral analysis (Ponton et al., 1997) did not fare well in determining response validity, especially at the individual level (McGee, Kraus, & Nicol, 1997) We did not find area to correlate with behavioral results of our patients.

Future research is now being aimed at establishing the age at which MMN matures in cochlear implant children by recording MMNs in cochlear implant patients soon after implantation and following this up with serial recordings until MMN matures.

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