Evaluation of Auditory Cortical Development in the Early Stages of Post Cochlear Implantation using Mismatch Negativity Measurement

Maojin Liang[1, 2*],M.D., Xueyuan Zhang[1,2 *], M.D., Tao Chen[1,2],M.D, Yiqing Zheng[1,2],B.M., Fei Zhao[3],PhD, Haidi Yang[1,2], M.D. , Zhiru Zhong [4], B.M., Zhigang Zhang[1,2],M.D., Suijun Chen[1,2],Ph.D., Lin Chen[1,2],B.M.

1. Department of Otolaryngology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China,
2. Institute of Hearing and Speech-Language Science, Sun Yat-sen University, Guangzhou, China,
3. Centre for Hearing and Balance Studies, University of Bristol, England,
4. Guangdong rehabilitation center for persons with disabilities, Guangzhou, China

Address for Correspondence :	Professor Yiqing Zheng Department of Otolaryngology SunYat-sen Memorial Hospital, Sun Yat-sen University, No. 107, West Yan Jiang Road, Guangzhou 510120, China
Phone number:	+86 2081332655
Fax number:	+86 2081332155
Email:	yiqingzheng@hotmail.com

* These authors contributed equally to this work.

Conflicts of Interest and Source of Funding: This work was supported by the

National Natural Science Foundation of China (awarded to Yiqing Zheng, Grant No.81170921), British Council PMI2 funding (awarded to Fei Zhao), and the Natural Science Foundation of Guangdong Province (awarded to Yiqing Zheng, Grant No.S2011010004576).

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Evaluation of Auditory Cortical Development in the Early Stages of Post Cochlear Implantation using Mismatch Negativity Measurement

Abstract

Objective: The aim of this study was to investigate auditory cortical development using mismatch negativity (MMN) in pre-lingual severe to profound hearing-impaired children from switching on the cochlear implantation (CI) and 6 months post-CIs

Method: 18 children were recruited and examined at the stage of initial switch on of the CIs (M0), as well as several follow-up periods, i.e., one month post CI (M1), three months post CI (M3) and six months post CI (M6). The MMN responses were measured using 128-Channel Dense Array EEG System. The group average and individual MMN analysis were used to investigate the longitudinal changes of the MMN characteristics. The relationship between MMN characteristics and scores of Categories of Auditory Performance (CAP) was also investigated.

Results: Although the MMN incidence was much lower at the periods of M0 and M1, significantly higher MMN incidence was found in M3 and M6. The MMN latencies decreased significantly from M3 to M6, but no significant difference in the amplitudes was found between these periods. There was a negative correlation between the increment of CAP scores and decrement of MMN latency from M3 to M6.

Conclusions: MMN incidence increases and latency decreases are likely to be the objective and noninvasive indicators for evaluating auditory central development at an

early stage in children post cochlear implantation. Moreover, the latency decreases from M3 to M6 correlated significantly with the increases of the CAP scores, indicating a fast maturation period, which might be a key period for auditory rehabilitation.

Keywords: Cochlear implantation; Mismatch negativity; Profound hearing loss; Auditory cortical development

Introduction

Cochlear implant (CI) is a surgically implanted electronic device that provides a sense of sound to a person who is profoundly deaf or severely hard of hearing. The main principle of the CI is to convert sound into an electric stimulus that sends impulses to the auditory nerves, and consequently nerve impulses are directly transmitted to the brain through the auditory nerve system (1). Cochlear implantation has been a widely accepted surgical intervention for both children and adults to habilitate/rehabilitate severe to profound sensory hearing loss all around the world (2). The effectiveness of cochlear implantation has been evaluated in numerous studies (3). These studies have demonstrated that cochlear implants provide not only audiological benefits in terms of sound awareness and improved speech perception (e.g., using the telephone, enjoyment of music, watching the TV), but also reduce activity limitation and participation restriction (e.g., improvement in general communication and self-confidence), and consequently improve the quality of life (QoL) (4).

For children with profound hearing impairment, one of the most important outcomes derived from CI in the context of their early habilitation is speech and language development associated with auditory cortical maturation and development (5). Various studies have revealed that CI delivers electrical stimulation and thus facilitates neuroplasticity of the central auditory system (6). This is mainly due to the formation of important connections after the introduction of stimulation to the auditory pathway via a CI, while there are synaptic deficits of cortical neurons and

auditory deprivation as a consequence of the lack of significant extrinsic auditory stimulation to auditory cortical development.

Recent studies have also indicated that the effect of CIs on neuroplasticity of the central auditory system occurs only when adequate stimulation is delivered during a sensitive period in early childhood (7-10). For example, evidence obtained from evoked cortical potential studies demonstrated that the sensitive period of human central auditory pathway plasticity ended around three and a half years old (9,10). In these studies, Sharma et al. (9) examined P1 latency in 245 congenital deaf children with CIs, and found that children had normal P1 latencies if they received CIs before three and a half years old, whereas children had abnormal or highly variable cortical response latencies if they received CIs later than three and a half years old.

Furthermore, modern imaging techniques such as Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) have also been used as objective tools to evaluate the neuroplasticity in terms of the activity changes in the central auditory cortex after CIs (7,8). For example, a fMRI case study reported by Lazeyras et al.(7) found bilateral activations of the auditory cortex after stimulation provided from a right-sided CI, showing that the activities on the ipsilateral side of the auditory cortex increased close to normal level, while even greater activation was seen on the contralateral side. Further study demonstrated that the increment of auditory cortex activation areas found in cochlear implant users correlated significantly with their performance improvement (7).

Although neuroimaging methods offer good spatial resolution, which can demonstrate the integrity of the central auditory pathway and thus provide a useful insight into the auditory cortex in terms of its functionality, their poor temporal resolution only reflects the activation areas of the auditory cortex in response to auditory stimuli. It is unable to distinguish between the activation patterns associated with the auditory discrimination process. Moreover, these neuroimaging methods are not suitable for assessing CI patients or repeatedly used mainly due to either the strong magnetic field (fMRI) or harmful radioactivity (PET). Therefore, the neuroimaging methods might be not ideal tools in assessing auditory cortex activity in post-CI patients, particularly in children (11,12).

Mismatch negativity (MMN) is one kind of event-related potential (ERP), which is in response to any distinguishable change (e.g. deviant stimulus vs. standard stimulus) in the auditory stimulus stream, and its largest amplitude is generally recorded over the fronto-central scalp areas at around 200ms post stimulus (13,14). It represents neurophysiologic changes in the brain's electrical activity in response to auditory discrimination (15), and therefore, it is considered to be an objective measurement to assess the auditory cortical function as well as central auditory processing function (16,17). Cheour et al. (17) reported that the MMN presented in 8 of 12 full-term neonates (66.7%) and all of six 3-month-old infants (100%). Consequently they suggested that the presence of the MMN is likely to be used as an index for auditory cortical maturation (17).

Furthermore, various studies have also shown that MMN is likely to provide essential information on central auditory cortex development (18-20). Trainor et al. (18) investigated the presence of MMN in 43 infants aged between 2 and 6 months. They reported that the standard stimuli evoked only a positive slow wave at the age of 2 months, whereas the deviant stimuli evoked increased negative waveforms at approximately 200 ms by 6 months, which was similar to adulthood MMN response. For assessing patients with CIs using the MMN, Singh et al. (21) showed that there was a MMN response in 80–85% of good CI performers, but only in 15–20% of poor CI performers. Reassessing after two years, 50% of the poor CI performers with MMN became good CI performers, while only 25% poor CI performers with no MMN became good CI performers. They concluded that MMN presence could be a good indicator for evaluating cortical status post cochlear implant.

Although several cross section studies on the correlation between MMN measurement and speech perception in CI users have been conducted(22,23), to the best of our knowledge, there is no longitudinal MMN study on maturation and development of auditory cortex in children post CIs. The longitudinal study will provide important information for a better understanding of auditory central development in children with CIs, and consequently a clinical rehabilitation strategy for CI children can be further developed. Moreover, the high-density electrode recording system used in the present study provides several advantages in terms of avoiding artifacts and minimizing topographic errors (24), and thus makes the

determination of the MMN responses in individuals more robust (25).

The present study aimed to conduct a longitudinal investigation of the auditory cortical development using mismatch negativity (MMN) in pre-lingual severe to profound hearing-impaired children from switching on the CI to 6 months post-CIs. The MMN characteristics (e.g. incidence, latency and amplitude) were analysed. The relationship between MMN latency and auditory performance, evaluated using Auditory Performance (CAP), was also compared in this group of children.

Materials and Methods

Participants

Forty-two pre-lingually severe to profound hearing-impaired children who had been fitted with cochlear implants between March, 2010 and December 2000 at Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University and Guangzhou Children Hospital were initially approached. Of these, eighteen children accepted to participate in the present study. Table 1 shows detailed information of the children, including their demographic data as well as other essential information, such as age at identification of deafness, age at CI, socio-economic status, communication mode and education. All children were in good general health. For the purpose of the present study, children with auditory neuropathy, mental retardation or other severe somatic disease were excluded.

Insert Table 1 near here

Ethical approval was obtained from the Institutional Review Board at Sun Yat-sen Memorial Hospital of Sun Yat-sen University, prior to the start of the study. The parents or guardians were informed regarding the nature of this study and their children's involvement. After fully understanding the terms of the consent, they signed the written consent form voluntarily before the test.

Procedures

MMN measurement

For each participant with a CI, MMN assessments were performed at initial switch on of the CIs (M0), and at several follow-up periods, i.e., one month post CI (M1), three months post CI (M3) and six months post CI (M6).

In the present study, the MMN responses were measured using 128-Channel Dense Array EEG System with HydroCel Geodesic Sensor Nets (EGI, USA). Each participant was sedated to sleep with 10% chloralic hydras (0.5ml/kg) in a comfortable chair in a soundproofed and electrically shielded room. All the electrode impedances were maintained at less than 40 kΩ during the test (26) .

Pure tones were used as the auditory stimuli, which was similar to our previous study (14). A standard stimulus of 1000Hz was presented at a proportion of 85%, together with a deviant stimulus of 1500Hz at a proportion of 15% in a pseudorandom sequence. 60 standard stimuli preceded the first deviant stimulus and at least two standard stimuli before each deviant stimulus. The duration of each stimulus was

50ms with 10ms on-set and off-set time, and the interstimulus interval (ISI) was 900ms, with the task consisting of a total of 1000 trials, divided into 2 blocks of 500 identical trials, with a 10 minute break between the 2 blocks. Stimuli were delivered through two loudspeakers at a distance of 100 cm from the subjects, with around 75 dBA at both ears (via Eprime 2.0, Psychology Software Tools, Inc.).

The ERP responses were recorded continuously using Net Station 4.3 (EGI, USA) and were then analyzed off-line. The ERP signals obtained were digitally filtered with a band-pass of 0.1Hz～30Hz, and signals with a segment of 700 ms including 100ms for pre-stimulus baseline were collected. Any signals with amplitudes of electro-oculography (EOG) exceeding 75μV were excluded as artifacts which were likely to be caused by eye movement and eye blinks. Subsequently the amplitude of any electrode site exceeding 75μV was defined as a poor channel. If the poor channels were equal to or more than six in a segment, this segment was excluded. By contrast, when the poor channels were less than six in a segment, the segment was valid, and the poor channels were replaced using the average value obtained from surrounding channels. The response waveforms evoked by standard and deviant stimuli were obtained by averaging all valid segments. All responses at individual electrodes were referred to the average reference (27). The baseline was corrected according to the mean amplitude over the 100ms pre-stimulus. The difference in waveform between deviant and standard stimuli was calculated to determine the mismatch negativity (MMN). In the present study, the configuration, peak latency and amplitude were

recorded and analyzed.

MMN determination and analysis

Two methodologies were used to determine the presence of MMN waveforms and analyse the parameters if MMN was present.

[1] Group average analysis.

The method of group average analysis has been used in previous studies for assessing MMN data in CI users (23,28) as this approach can reduce variability and improve reliability. In the present study, the group average of the different response (i.e., target response minus standard response) was performed using the data obtained from all CI children at the M0, M1, M3, M6 stages respectively.

In order to avoid false positive responses, a relatively robust criterion for identifying and determining valid MMN responses was used, i.e., the presence of MMN was determined when the first and/or the largest negativity wave was found during 100-300ms, in combination with identifying a corresponding brain topographic mapping distributed at the frontal lobe (13,14). If two or more negativity waves with similar amplitudes were found, the first wave was always defined as the MMN response. In addition, once the group average MMN was obtained, individual MMN latencies were extracted for further statistical analysis on the basis of the minimal points between -50ms and +50ms to peak MMN latency of the group average using the Statistic Extraction function affiliated in the Net Station 4.3

[2] Individual MMN response

Individual MMN response was also determined using the criterion mentioned above. Once the MMN response was identified by visual inspection, its latency and amplitude were measured manually (13,14,29).

Categories of Auditory Performance (CAP)

In the present study, the CAP assessment tool was used to evaluate the outcomes from pediatric cochlear implantation in everyday communication skills as a mark for auditory development. The CAP was first developed by Archbold (30) in 1995. It has a scale for assessing auditory ability development in children, which is rated in eight categories in an order of increasing complexity, i.e.,

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

A teacher of the deaf in the cochlear implant center categorized the CAP score when she assessed the children at the initial stimulus time after cochlear implantation (CI), and at follow up assessments at 1 month, 3 months and 6 months post-CI.

Statistical analysis

SPSS 16.0 was used for the statistical analysis. The group comparisons among

different sites of the scalp were examined using One-way-ANOVA. Chi-square test was performed for the ratio comparison and paired or independent-sample *t*-test in the follow up study of MMN latency and amplitude. Significance was set at the conventional 5% level for all statistical tests.

Results

The MMN incidence and its changes at different post CI stages

Based on criteria for identifying and determining the MMN responses mentioned in the methodology session, the MMN incidence was calculated. **Figures 1a, 1b, 1c and 1d** show examples of the MMN recordings at different post CI stages. The results showed that none of 18 children had MMN at the time of switch on (i.e., M0). The MMN incidence increased significantly from M1 to M3 and M6 (P_{1m} vs. P_{3m}: x^2=25.1, p<0.001; P_{1m} vs. P_{6m}, x^2=28.14, p<0.001). However, there was no significant difference in the percentage of MMN incidence between 3-month and 6-month post CI (P_{3m} vs. P_{6m}, x^2= 0.36, p=0.55) (**Figure 2**).

Insert Figures 1a, 1b, 1c and 1d near here

Insert Figure 2 near here

Latencies and amplitudes of MMN in children at different period of post-CI

As indicated, only one case had the MMN response at the M1 stage. Its latency and amplitude were 219.0ms and 5.9 μV, respectively. As shown in **Table 2**, the latencies and amplitudes obtained from the stages of M3 and M6 were compared.

Paired *t*-test analysis results showed that the latencies decreased significantly from M3 to M6 (t=6.43, p<0.001). However, there was no significant difference in the amplitudes between M3 and M6 (t=1.24, p=0.20).

Insert Table 2 near here

The analysis of MMN characteristics using group average method

The MMN characteristics at the electrodes of Fz, F3, F4 were analysed using group average method when the MMN responses were obtained at the periods of M3 and M6. **Figures 3a, 3b, 3c and 3d** show clear and robust group average MMN responses at Fz at the periods of M3 and M6 respectively, in comparison with no clear responses at M0 and M1 stages.

As shown in **Table 3**, paired *t* test showed that the MMN latencies decreased significantly from M3 to M6 at all individual electrodes (Fz, F3 and F4) (Fz: t=6.77, p<0.001; F3: t=6.39, p<0.001; F4: t=7.35, p<0.001). However, there was no difference in amplitude changes from M3 to M6 at any of these three electrodes. Further analysis showed that no statistical differences were found in either the MMN latency, or in the MMN amplitude among these three electrodes at the periods of M3 and M6 respectively (ANOVA, L_{3m}:F=0.13, p=0.72; A_{3m}:F=0.05, p=0.83; L_{6m}:F=0.01, p=0.91; A_{6m}:F=0.63, p=0.43).

Insert Figure 3 and Table 3 near here

Comparing the MMN latency at Fz using the group average analysis with the data obtained from individual analysis, no statistical difference was found at the stage of

M3 (one sample *t*-test, t=1.14, p=0.27). However, the MMN latency using the group average analysis at the stage of M6 was significantly shorter than that using an individual method (one sample *t*-test, t=2.16, p=0.04).

Changes of the CAP scores in children at different post-CI stages

At early stages of post-CI (i.e., M0 and M1), low CAP scores were obtained from the majority of children (maximum score: 3, 11.1% and 33.3% at M0 and M1, respectively) **(Figure 4)**. By contrast, the median CAP scores obtained from children at the period of M3 was 3, together with two of them having CAP scores of 4 and 5. In addition, nine children had CAP scores equal to or above 4 (one child scored 6) at M6.

Compared with the CAP scores at M1, 13 (72.2%) and 16 (88.9%) out of total 18 children had scores above 2 at the periods of M3 and M6, respectively. Chi-square analysis shows a significant difference (3m vs. 1m: x^2=5.46; df=1, p<0.05; 6m vs. 1m: x^2=11.7; df=1, p<0.001). In addition, a significantly higher proportion of children having a CAP score of 4 or above was found at the period of M6 than that at the period of M3 (2/18 vs. 9/18; x^2 =6.42; df=1, p<0.005).

Insert Figure 4 near here

Furthermore, in the present study, the correlation between CAP scores and MMN incidence at M3 or M6 were analyzed. Spearman correlation analysis showed no significant correlation between CAP Scores and the MMN incidence at either M3 or M6 (r3m=0.20, p>0.05; r6m=0.12, p>0.05). Further analysis showed a significant

negative correlation between CAP Scores and MMN latency at M6 (rh6m=-0.80, $p<0.05$), but no correlation was found at M3 (rh3m=-0.25, $p>0.05$). In addition, the changes in CAP scores from M3 to M6 correlated significantly with the changes in MMN latency during this period (r=-0.52, $p=0.04$).

There was no significant correlation between CAP sores and MMN amplitude at either M3 or M6 (rh3m=-0.30, $p>0.05$; rh6m=-0.22, $p>0.05$). The changes in CAP scores from M3 to M6 did not correlate significantly with the changes in MMN amplitude during this period (r=-0.18, $p=0.50$).

Discussion

The present longitudinal follow-up study was conducted using mismatch negativity (MMN) measurement to evaluate the auditory cortex development and maturation in young children post CI. Although the MMN incidence was much lower at the periods of M0 and M1, significantly higher MMN incidence was found in M3 and M6, which are very similar to the findings obtained from 3-month-old normal hearing infants reported by Cheour et al. (17). These results imply the importance of auditory stimulation delivered by CIs for the process of auditory cortex development post CI from the premature period to quickly catching up with normal auditory development when having the cochlear implantation at early age.

The results of MMN latencies are in keeping with the findings of auditory cortex maturation found in normal hearing children (17,20), i.e., the MMN latency becomes shorter in association with normal auditory cortex development and

maturation(17,20,28). Moreover, such latency decreases from M3 to M6 correlated significantly with the increases in the CAP scores. These results indicate that a fast maturation period at the stage between M3 and M6 post CI might be a key period for auditory rehabilitation. In the meantime, the MMN latency is likely to be used as a useful parameter in the evaluation of auditory cortex development post CI.

However, the present study found that the MMN amplitude was not a good indicator for auditory cortical development evaluation because the MMN amplitude did not differ significantly at the periods of M3 to M6. Previous studies have shown that the MMN amplitude did not differ significantly among the different age groups of children with normal hearing. For example, studies by Shafer et al. [19] and Morr et al. [33] reported no significant differences in the MMN amplitudes in a group of 4-10 years old children and 2-47 months infants, respectively. In addition, similar results were also found among the groups of premature infants, full-term newborns and 3-month-old infants (17). This is likely due to the large intersubject variability and/or factors associated with the synchronization of neural discharge, electrode impedance and attention state (14). Although the MMN incidence increased significantly from M1 to M3, there was no significant difference in MMN amplitude between M1 and M3. These results imply no inherent relationship between amplitude growth and incidence increase during auditory cortical development.

It is noteworthy that the individual MMN analysis adopted in the present study is crucial for the purposes of clinical application and longitudinal follow up comparison

in children with CIs, even though it is likely to increase the possibility of false positive or negative rates (29). Previous studies have suggested that MMN group average method would improve the signal-to-noise and consequently provide clear MMN responses(17,23,28). Due to the nature of the present study, a combination of both individual MMN analysis and group average method provides a better approach to identify and determine a reliable individual MMN response for analyzing its characteristics.

Several limitations exist in this study. Due to great difficulties in recruiting healthy children, a limitation here was in not carrying out case control comparisons. Although the difference in the MMN changes during auditory cortex development and maturation between normal hearing children and children with CIs still remains unclear, a six month longitudinal follow up provides insight into changes in the MMN characteristics, which have great value for clinical application for CI children as an objective in the early stage of auditory cortex development. The other limitation is that CAP is not a tool for measuring speech perception or discrimination. It might be one of the reasons to explain no significant correlation between CAP and MMN latency. However, since the CAP was firstly developed by Archbold(30) in 1995, it has been widely used for measuring the auditory ability development in children with and without hearing impairment, particularly for those with severe hearing impairment, who are unlikely to perform speech perception tests. Evidence has also shown that the CAP is an appropriate measure to evaluate speech and language

development in children with CIs (31,32).

Conclusions

MMN incidence increases and latency decreases are likely to be the objective and noninvasive indicators for evaluating auditory central development at the early stage in children post cochlear implantation. Moreover, the latency decreases from M3 to M6 correlated significantly with the increases in the CAP scores, indicating a fast maturation period, which might be a key period for auditory rehabilitation.

Acknowledgments

We would like to thank the editor and two anonymous reviewers for their helpful suggestions. We would also like to acknowledge Mrs. Norma Meechem for her proofreading. This work was supported by the National Natural Science Foundation of China (awarded to YQZ, Grant No.81170921), British Council PMI2 funding (awarded to FZ), and the Natural Science Foundation of Guangdong Province awarded ((awarded to YQZ, Grant No.S2011010004576) .

Reference

1. Sharma A, Campbell J. A sensitive period for cochlear implantation in deaf children. *J Matern Fetal Neonatal Med* 2011;24 Suppl 1:151-3.
2. Fallon JB, Irvine DR, Shepherd RK. Cochlear implants and brain plasticity. *Hear Res* 2008;238:110-7.
3. Bond M, Mealing S, Anderson R, et al. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technol Assess* 2009;13:1-330.
4. Govaerts PJ, De Beukelaer C, Daemers K, et al. Outcome of cochlear implantation at different ages from 0 to 6 years. *Otol Neurotol* 2002;23:885-90.
5. Kral A, O'Donoghue GM. Profound deafness in childhood. *N Engl J Med* 2010;363:1438-50.
6. Kral A, Sharma A. Developmental neuroplasticity after cochlear implantation. *Trends Neurosci* 2012;35:111-22.
7. Lazeyras F, Boex C, Sigrist A, et al. Functional MRI of auditory cortex activated by multisite electrical stimulation of the cochlea. *Neuroimage* 2002;17:1010-7.
8. Green KM, Julyan PJ, Hastings DL, et al. Auditory cortical activation and speech perception in cochlear implant users: effects of implant experience and duration of deafness. *Hear Res* 2005;205:184-92.
9. Sharma A, Dorman MF. Central auditory development in children with cochlear implants: clinical implications. *Adv Otorhinolaryngol* 2006;64:66-88.
10. Sharma A, Nash AA, Dorman M. Cortical development, plasticity and re-organization in children with cochlear implants. *J Commun Disord* 2009;42:272-9.
11. Kim LS, Jeong SW, Lee YM, et al. Cochlear implantation in children. *Auris Nasus Larynx* 2010;37:6-17.
12. Sonnenburg RE, Wackym PA, Yoganandan N, et al. Biophysics of cochlear implant/MRI interactions emphasizing bone biomechanical properties. *Laryngoscope* 2002;112:1720-5.
13. Duncan CC, Barry RJ, Connolly JF, et al. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clin Neurophysiol* 2009;120:1883-908.
14. Zheng YQ, Zhao F, Liang MJ, et al. Toward an Understanding of Auditory Evoked Cortical Event-Related Potentials:Characteristics and Classification. *Audiological Medicine* 2011;9:16-25.
15. Näätänen R, Paavilainen P, Rinne T, et al. The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clin Neurophysiol* 2007;118:2544-90.
16. Bauer P, Burger M, Kummer P, et al. Correlation between psychometric tests and mismatch negativity in preschool children. *Folia Phoniatr Logop* 2009;61:206-16.
17. Cheour M, Alho K, Ceponiene R, et al. Maturation of mismatch negativity in infants. *Int J Psychophysiol* 1998;29:217-26.
18. Trainor L, McFadden M, Hodgson L, et al. Changes in auditory cortex and the development of mismatch negativity between 2 and 6 months of age. *Int J Psychophysiol* 2003;51:5-15.

19. Shafer VL, Yu YH, Datta H. Maturation of speech discrimination in 4- to 7-yr-old children as indexed by event-related potential mismatch responses. *Ear Hear* 2010;31:735-45.
20. Lonka E, Kujala T, Lehtokoski A, et al. Mismatch negativity brain response as an index of speech perception recovery in cochlear-implant recipients. *Audiol Neurootol* 2004;9:160-2.
21. Singh S, Liasis A, Rajput K, et al. Event-related potentials in pediatric cochlear implant patients. *Ear Hear* 2004;25:598-610.
22. Näätänen R. The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). *Psychophysiology* 2001;38:1-21.
23. Zhang F, Hammer T, Banks HL, et al. Mismatch negativity and adaptation measures of the late auditory evoked potential in cochlear implant users. *Hear Res* 2011;275:17-29.
24. Junghofer M, Elbert T, Tucker DM, et al. Statistical control of artifacts in dense array EEG/MEG studies. *Psychophysiology* 2000;37:523-32.
25. Nelson CA, 3rd, McCleery JP. Use of event-related potentials in the study of typical and atypical development. *J Am Acad Child Adolesc Psychiatry* 2008;47:1252-61.
26. Guideline 6: A proposal for standard montages to be used in clinical EEG. *J Clin Neurophysiol* 2006;23:111-7.
27. Jung J, Morlet D, Mercier B, et al. Mismatch negativity (MMN) in multiple sclerosis: an event-related potentials study in 46 patients. *Clin Neurophysiol* 2006;117:85-93.
28. Roman S, Canevet G, Marquis P, et al. Relationship between auditory perception skills and mismatch negativity recorded in free field in cochlear-implant users. *Hear Res* 2005;201:10-20.
29. McGee T, Kraus N, Nicol T. Is it really a mismatch negativity? An assessment of methods for determining response validity in individual subjects. *Electroencephalogr Clin Neurophysiol* 1997;104:359-68.
30. Archbold S, Lutman ME, Marshall DH. Categories of Auditory Performance. *Ann Otol Rhinol Laryngol Suppl* 1995;166:312-4.
31. Schauwers K, Gillis S, Daemers K, et al. Normal hearing and language development in a deaf-born child. *Otol Neurotol* 2004;25:924-9.
32. Schauwers K, Gillis S, Daemers K, et al. Cochlear implantation between 5 and 20 months of age: the onset of babbling and the audiologic outcome. *Otol Neurotol* 2004;25:263-70.

Captions of Figures

Figure 1. Examples of the MMN recordings at different post CI stages obtained from Case LL

Figure 2. MMN incidence recordings at different post CI stages

Figure 3. Group average MMN responses at Fz and corresponding brain topographic mappings at different post CI stages

Figure Legend:

a, At M0, there was no negative response in 100-300 ms;

b, At M1, there was an negative response, but no clear corresponding topomapping distribution;

c and d, At M3 and M6, respectively, there were clear MMN responses and corresponding topomapping distributions at left front lobe.

Figure 4. Correlation between CAP score change and MMN incidence at different post CI stages

Note:

+: presence of MMN response;

-: Absence of MMN response.

Table 1 Demographical data and other information in children with cochlear implants

Case (initials)	Gender	Age at hearing loss being identified (Years)	Age at CI (Years)	CI Side	Cochlear Implant + Sound Processor	Education setting	Communication mode	Socio-economic status
LZQ	M	$2\frac{11}{12}$	$6\frac{1}{12}$	R	C40^{+}+OPUS2	Special school	Sign language	Middle-class
LGF	M	$3\frac{4}{12}$	$5\frac{2}{12}$	L	Pulsa+OPUS2	Special school	Simple speech	Middle-class
CHH	M	$2\frac{1}{12}$	$3\frac{3}{12}$	L	C40^{+}+OPUS2	Home education	Simple speech + Sign language	Low-class
WQY	M	$2\frac{4}{12}$	$3\frac{5}{12}$	R	Pulsa+OPUS2	Home education	Sign language	Middle-class
CXM	F	$\frac{10}{12}$	$1\frac{3}{12}$	R	C40^{+}+OPUS2	Home education	Simple speech + Sign language	Low-class
HSM	M	$2\frac{4}{12}$	$2\frac{9}{12}$	R	C40^{+}+OPUS2	Special school	Simple speech + Sign language	Middle-class
LL	F	$\frac{4}{12}$	$\frac{10}{12}$	R	Pulsa+OPUS2	Home education	Sign language	Low-class
ZS	M	$3\frac{1}{12}$	$3\frac{5}{12}$	R	Sonata+OPUS2	Special school	Simple speech	High-class
CWQ	M	$3\frac{8}{12}$	$3\frac{11}{12}$	L	Pulsa+OPUS2	Special school	Sign language	Middle-class
GYC	M	$\frac{11}{12}$	$1\frac{2}{12}$	R	C40^{+}+OPUS2	Home education	Simple speech	Low-class
YJH	M	$2\frac{6}{12}$	$2\frac{12}{12}$	R	Sonata+OPUS2	Home education	Sign language	High-class
HXS	F	$4\frac{1}{12}$	$4\frac{5}{12}$	R	C40^{+}+OPUS2	Special school	Speech sound	Middle-class
HJX	M	$1\frac{3}{12}$	$2\frac{3}{12}$	R	C40^{+}+OPUS2	Home education	Simple speech	Low-class
CWX	F	$2\frac{1}{12}$	$3\frac{1}{12}$	R	Pulsa+OPUS2	Special school	Simple speech + Sign language	Middle-class
LZH	M	$1\frac{4}{12}$	$2\frac{5}{12}$	R	C40^{+}+OPUS2	Home education	Speech sound	Low-class
LHY	F	$1\frac{8}{12}$	$2\frac{2}{12}$	R	Pulsa+OPUS2	Home education	Simple speech	Middle-class
YJH	F	$\frac{10}{12}$	$2\frac{1}{12}$	R	C40^{+}+OPUS2	Home education	Simple speech + Sign language	Middle-class
HHW	M	$2\frac{7}{12}$	$3\frac{1}{12}$	R	Sonata	Home education	Sign language	High-class

Table 2 Averaged MMN latency and amplitude at Fz measured using individual response analysis at stages of M3 and M6 in children with cochlear implants

	M3(n=16)	M6(n=17)	*p* value
Latency (ms)△	211.3±35.3	149±32.3	<0.001
Amplitude (μV) △	-3.4±3.3	-4.2±1.8	＝0.665

△**:Mean±1SD**

Table 3 Averaged MMN latencies and amplitudes at Fz, F3 and F4 at stages of M3 and M6 using group average analysis

		M3	M6	*p* value
Fz	**Latency (ms)**[△]	211.3±35.3	149±32.3	<0.001
	Amplitude (μV)	-3.4±3.3	-4.2±1.8	＝0.665
F3	**Latency (ms)**	207.1±35.0	140.6±36.1	<0.001
	Amplitude (μV)	-4.7 ±6.9	-7.3±9.6	＝0.428
F4	**Latency (ms)**	208.6±36.8	137.2±23.5	<0.001
	Amplitude (μV)	-5.0±7.5	-5.9±9.8	=0.790

[△]**Mean±1SD**

Figure 1

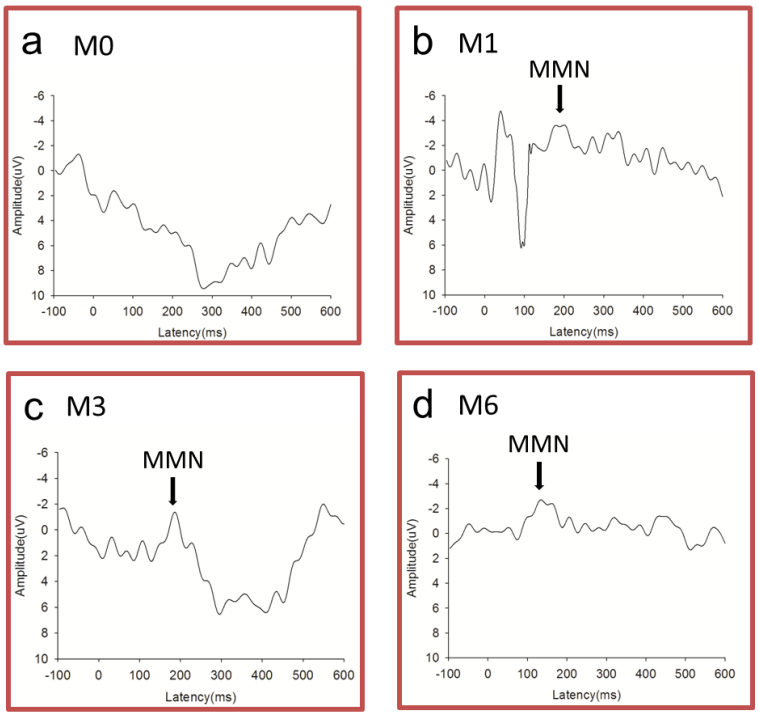

Figure 2

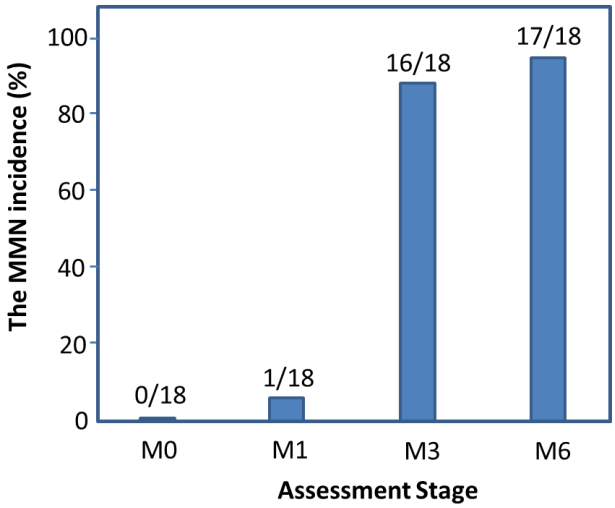

Figure 3

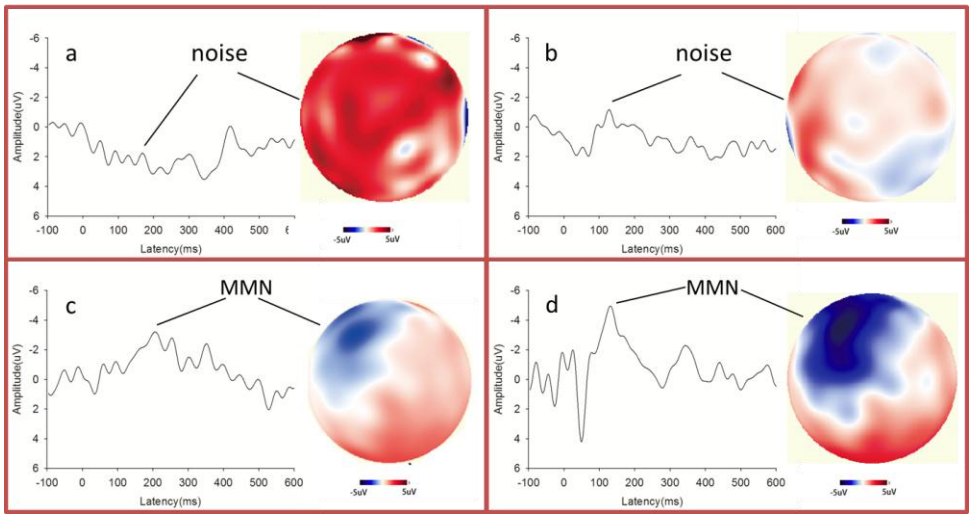

Figure 4

		M0		M1		M3		M6	
		+	-	+	-	+	-	+	-
Score	Category of Auditory Performance score								
7	Use of telephone—known speaker								
6	Understands conversation, no lipreading							•	
5	Understand common phrases, no lipreading					•		•	
4	Discrimination of speech sounds					•		•••••	
3	Identification of environmental sounds		••		•••••	••••••		•••••	
2	Response to speech sounds (e.g., go)		•••••		•••••	•••	••	•	•
1	Awareness of environmental sounds		•••••	•	••				
0	No awareness of environmental sounds								