Published in final edited form as:

Brain Dev. 2006 May ; 28(4): 207–214.

Auditory event-related responses in children with semi-lobar holoprosencephaly

Hongkui Jing^{a,b,*}, Judy Flax^a, Cynthia P. Roesler^a, Naseem Choudhury^a, and April A. Benasich^a

^a Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ 07102, USA

^b Department of Neurology, Arkansas Children's Nutrition Center, University of Arkansas for Medical Science, Slot #512-20B, 1120 Marshall Street, Little Rock, AR 72202, USA

Abstract

The purpose of this study was to evaluate auditory sensory and discrimination responses in children with semi-lobar holoprosencephaly (HPE). Event-related potential (ERP) signals were recorded to tone pair stimuli at 62 electrode sites from the scalp using an oddball paradigm (a two-block design, inter-stimulus interval=70 or 300 ms; frequency of tone pair=100 vs. 100 Hz for the frequent and 100 vs. 300 Hz for the infrequent). Latencies and amplitudes of P₁₅₀, N₂₅₀, and mismatch negativity (MMN)-like components were compared between children with HPE and controls. Our results revealed less organized ERP waveforms to both stimuli in children with HPE, with diminished P₁₅₀ and N₂₅₀ components across brain area. Robust and delayed MMN-like responses were elicited from the children with HPE, with decreased MMN amplitudes in the central, parietal, occipital, and posterior temporal areas. Our results suggest that while brain sensory responses to auditory tones may be impaired in children with semi-lobar HPE, subcomponents of auditory discrimination processes remain functional.

Keywords

Brain; EEG; Child; Holoprosencephaly; Mismatch negativity

1. Introduction

Holoprosencephaly (HPE) is a neural tube defect that results in a developmental anomaly of the embryonic forebrain [1]. It presents as a continuum of malformations of incomplete cleavage of the forebrain into distinct cerebral hemispheres, and is traditionally classified into three types: alobar (the most severe form), semi-lobar, and lobar (the mildest form). Language development in children with HPE tends to be severely limited. It is particularly difficult to accurately assess levels of cognitive functioning using standardized behavioral and language assessments.

In the auditory pathway, sounds are perceived by auditory receptors (hair cells) and transmitted to cochlear nuclei and then to the inferior colliculus from where neurons project to the primary auditory cortex via the laminated medial geniculate nucleus or project to the higher order auditory cortex (Wernicke's area) via the non-laminated portions of the medial geniculate nucleus [2]. In adults, early auditory responses, such as P₁ and N₁ components, are thought to

* Corresponding author. Address: Department of Neurology, Arkansas Children's Nutrition Center, University of Arkansas for Medical Science, Slot (512-20B, 1120 Marshall Street, Little Rock, AR 72202, USA. Tel.: + 1 501 364 6629; fax: + 1 501 364 3947. E-mail address: jinghongkui@uams.edu (H. Jing).

be exogenous and associated with neural activity involved in the lateral lemniscus nuclei, the inferior colliculus and the thalamic nuclei, whereas activations underlying adult P₂ component may involve nonspecific projections to auditory cortex. Dipole sources localized in the temporal lobe are thought to be generators of the P₁ and N₁ waves [3,4].

One useful method of assessing auditory discrimination abilities is to induce a mismatch negativity (MMN) component. MMN is elicited when the brain discriminates an infrequent sound from preceding frequently presented sounds [5]. Multiple MMN sources have been localized in the temporal lobe [6], the frontal lobe [7], and subcortical regions such as the thalamus, hippocampus [8], and the inferior colliculus [9].

Brain evoked responses have only been examined in a few HPE cases [10]. How individuals with HPE perceive and discriminate auditory stimuli remains unclear. Considering the generation of evoked components and brain anatomical characteristics seen in HPE, we hypothesized that children with semi-lobar HPE would show attenuated auditory sensory responses with prolonged latencies. Given the fact that the scalp MMN may be generated by multiple cortical and subcortical sources, brain auditory discrimination responses were expected to be recorded in these subjects. In addition, we thought that subjects with HPE had more difficulties than normal controls in discriminating rapidly changing stimuli than in differentiating slowly changing stimuli. For these purposes, tone pair stimuli were used in the examinations of event-related potentials (ERPs). The frequencies of these stimuli were within the range of fundamental frequencies of speech sounds.

2. Methods

2.1. Participants

Seven children diagnosed as semi-lobar HPE were separated into three groups: 16-month (1 male, M), 36-month (1 female, F), and 60-month (2M, 3F, mean age=65 months). Examinations of magnetic resonance imaging (MRI) were completed for each of the subjects prior to study initiation. Incomplete cleavage was seen in the frontal lobes, with varying degrees of malformations in the basal ganglia and the thalamus for all the subjects. Enlarged ventricular systems were also found in these subjects, with absence of the anterior horns of the lateral ventricles (Fig. 1A). ERPs of normal subjects were also collected in three age-matched groups: 16 months (9M, 6F), 36 months (2M, 4F), and 60 months (5M, 3F).

No hearing problems (such as otitis media) were present and no histories of hearing or other neurological or developmental disorders were reported for each of these subjects. Prior to participation, informed consent was obtained. The protocol of this study was approved by the Institutional Review Board of Rutgers University.

2.2. Stimuli and event-related potential recording

Sound stimuli were presented using an oddball paradigm. Each frequent stimuli (or standard, 85%) contained two complex tones with the same fundamental frequency of 100 Hz. The infrequent stimuli (or deviant, 15%) contained a 100-Hz complex tone and a 300-Hz complex tone (Fig. 1B). The stimuli were presented in two experimental blocks, with a 70 ms inter-stimulus interval (ISI, offset-to-onset) or a 300 ms ISI between the two tones. There was a 705 ms inter-trial interval (ITI, offset-to-onset) between each two consecutive stimuli (the ITI of the 70-ms-ISI block was 5 ms short due to hardware limitations). A total of 833 stimuli were presented in each block. About 3–11 standard stimuli were played before each deviant stimulus. The stimuli were played binaurally (75 dB sound pressure level) through a pair of speakers on either side of the subject. Note that the only difference between the standard stimuli and deviant stimuli was the frequency of the second tones.

ERP signals were recorded in a dimly lighted, electrically shielded and sound attenuated room. During each session, the child was awake and seated comfortably in front of a computer monitor. Silent movies were played to engage the child's attention. An entertainer was also present to engage the child with books or quiet toys as needed. All the EEGs were recorded by the same group of assistants using the same machine. Both recording system and sound system were calibrated prior to each session.

Geodesic sensor nets (Electric Geodesic Inc., Eugene, OR, USA) were used for recording ERPs (62 channels; reference: vertex; bandpass filter: 0.1–100 Hz; sampling rate: 250 Hz). Electrodes placed above both eyes were used for monitoring eye movements. Offline, the EEG signals were re-referenced to both mastoids, digitally filtered (bandpass filter: 0.1–40 Hz), and segmented (including a 50 ms pre-stimulus segment and a 650 ms post-stimulus segment). At least 60 artifact-free EEG segments were used in the average of ERPs to each stimulus.

2.3. Measures and statistical analyses

For the 16- and 36-month groups, ERPs of the child with HPE were visually compared with grand averaged ERPs of corresponding controls. Peak latencies and amplitudes were measured in the 60-month groups for the positive component (60–200 ms after each stimulus onset) and negative component (130–320 ms). Peak amplitudes were measured as the largest positive or negative amplitudes relative to the pre-stimulus baseline. Peak latencies corresponded to the time points of the peak amplitudes. Latencies and amplitudes were not measured in the 70-ms-ISI block due to the overlapping of ERPs. Latencies and amplitudes of the MMN-like components were calculated in both ISI blocks at 100–390 ms after the onset of the second tones from the difference waves that were obtained by subtracting ERPs to the standard stimuli from those to the deviants.

Instead of comparing latencies or amplitudes between electrodes, we were more interested in the comparisons among brain areas. We thought that mean latencies or amplitudes averaged within one brain area could reflect overall neurophysiological processes of that brain lobe. For this purpose, latencies and amplitudes were calculated in the prefrontal, frontal, central, parietal, occipital, anterior temporal, mid-temporal, and posterior temporal areas of each hemisphere. About 3–5 electrodes were included in each brain area. ERP waveforms were not averaged for those electrodes. They were inspected channel by channel. A repeated-measure analysis of variance (ANOVA) was employed to determine the effects of group, stimulus type, brain area, and hemisphere. Effect of ISI (70 and 300 ms) was also examined for the MMN responses. Greenhouse–Geisser adjustments were performed when applicable. Planned comparisons were used as post hoc tests for examining individual values. The significant level was set at $P < 0.05$.

3. Results

3.1. Visual comparisons for all age groups

3.1.1. Control groups—ERP waveforms prominently consisting of a positive and a negative component were elicited by each tone of the standard stimuli from each brain area in all control subjects, irrespective of age. In the 70-ms-ISI block, the overlapped ERPs resulted in a prolonged waveform with a prominent positive component peaking around 140 ms at all ages. An additional small positive component was elicited by the deviant stimuli, peaking at 250 ms after the onset of the first tone. In the 300-ms-ISI block, distinct responses were induced by each of the tones, with a positive component around 150 ms followed by a negative component around 250 ms after each tone onset, regardless of age. Accordingly, they were referred to P₁₅₀ and N₂₅₀, respectively (Fig. 2). MMN-like components were observed at about 170 ms, followed by a positive response at about 270 ms in all three age groups.

3.1.2. HPE groups—Several ERP alterations were observed in the HPE groups for both ISI blocks. First, poorly developed waveforms were observed to the standard stimuli across the scalp, reflected by less identifiable ERP components. Second, the P₁₅₀ and N₂₅₀ components were remarkably attenuated across the scalp and were not discernible in the parietal and posterior temporal areas (Fig. 2). However, mismatch responses were robustly elicited from these subjects, with similar amplitudes relative to controls in the frontal and anterior temporal areas. Low amplitudes were found in the central, parietal, and posterior temporal areas. These differences were seen in all children with HPE, regardless of age (Fig. 3).

3.2. Statistical comparisons for the 60-month groups

3.2.1. The P₁₅₀ component—Significant differences in the P₁₅₀ latencies were detected among the brain areas ($F_{7,77}=2.25$, $P<0.05$). In both groups, the P₁₅₀ component appeared earlier in the frontal and central areas than other brain areas. The interaction between stimulus type and hemisphere was also significant ($F_{1,11}=9.72$, $P<0.01$), showing that the overall latency to the standard stimuli was relatively shorter in the left hemisphere, whereas the measures to the deviants were relatively shorter in the right hemisphere. There was a marginal interaction effect between group and stimulus type ($F_{1,11}=3.18$, $P=0.10$). In the control group, the P₁₅₀ latency induced by the deviant stimuli was slightly shorter than that to the standards; however, in the HPE group, the ERPs induced by the deviants had longer latencies than those to the standards, suggesting that children with HPE need more time to process different sounds.

Differences were also detected for the amplitudes among brain areas ($F_{7,77}=7.28$, $P<0.01$) and between groups ($F_{1,11}=22.6$, $P<0.01$). The highest amplitudes were seen in the frontal and central areas, particularly in the control group. The P₁₅₀ amplitudes were relatively lower in the subjects with HPE in all brain areas (Fig. 4, see P₁₅₀ for 60 months). An interaction effect of group by stimulus type by brain area was detected ($F_{7,77}=2.23$, $P<0.05$), revealing that the decrease of amplitudes to the standard stimuli in the HPE group was greater in the anterior brain areas (frontal and central areas) than in the posterior brain areas (posterior temporal and occipital areas, see Table 1).

3.2.2. The N₂₅₀ component—Significant differences in the N₂₅₀ latencies were detected among brain areas ($F_{7,77}=3.09$, $P<0.01$). The N₂₅₀ component was present earlier in the central and temporal areas than in other brain areas for both hemispheres, particularly in the control group. Although the difference was not statistically significant, the latencies to the deviant stimuli were shorter than those to the standard stimuli in the controls. An opposite trend was found in the HPE group. For example, compared with the results to the standard stimuli, the latency to the deviants was increased by 43 ms in the left frontal area and 33 ms in the right frontal area ($P<0.01$). Similar changes were observed in all other brain areas.

The amplitudes significantly differed between the groups ($F_{1,11}=6.72$, $P<0.05$) and among the brain areas ($F_{7,77}=119$, $P<0.01$). The absolute values of amplitudes were decreased in the subjects with HPE relative to the controls (e.g. decreased by 2.55 μ V in the right parietal area, $P<0.05$), and the decrease was greater in the anterior brain areas (i.e. frontal, central and anterior temporal areas) than in the posterior brain areas (i.e. occipital, mid-temporal and posterior temporal areas). Further, significant interactions were found among group, stimulus type and brain area ($F_{7,77}=3.84$, $P<0.01$), and among group, brain area and hemisphere ($F_{7,77}=2.37$, $P<0.05$), showing that the decrease in amplitudes in the HPE group was more pronounced in the right frontal and anterior temporal areas than that of homologous left brain areas. The maximal negative amplitudes were recorded in the frontal and central areas in the control group, but this scalp distribution pattern moved laterally and posteriorly in the HPE group (Fig. 4, see N₂₅₀ for 60 months).

3.2.3. MMN-like response—An interaction effect of group by brain area by hemisphere was detected ($F_{7,154}=2.13$, $P < 0.05$). The HPE group had longer MMN latencies than the controls for all brain areas (e.g. differing for 49 ms in the right frontal, $P < 0.05$). Similar results were found in all brain areas. Between-hemispheric differences were significant in the HPE group only, e.g. compared with the results of the left brain areas, the latencies were 17 ms (frontal) and 19 ms (anterior temporal) longer on the right side ($P < 0.05$). The controls had longer MMN latencies in the 70-ms-ISI block than in the 300-ms-ISI block for all brain areas. In the HPE group, the overall MMN latency in the 300-ms-ISI block was only slightly shorter. These results suggest that brain discrimination responses to rapid sequential auditory stimuli are slow in children with HPE (Fig. 5).

With respect to the amplitudes, the MMN responses significantly varied among brain areas ($F_{7,154}=3.71$, $P < 0.01$). A significant interaction of group by block by brain area was indicated ($F_{7,154}=2.44$, $P < 0.05$), showing that the highest amplitudes were measured in the fronto-central areas in the control group in contrast to the frontal and anterior temporal areas in the HPE group.

4. Discussion

4.1. Auditory sensory responses

As expected, compared with controls, longer latencies of P₁₅₀ and N₂₅₀ components were observed in children with HPE, suggesting a slow response to rapid sequential auditory stimuli. Amplitudes of the P₁₅₀ and N₂₅₀ components were also attenuated in all brain regions of the children with HPE. These results are comparable with previous findings of low-amplitude auditory brainstem evoked potentials and impaired sensory-evoked potentials recorded in subjects with HPE [10]. Amplitude topographic distributions of the P₁₅₀ and N₂₅₀ components were displaced laterally and posteriorly in children with HPE.

Given the MRI results, it is not surprising that the P₁₅₀ and N₂₅₀ responses were diminished in the subjects with HPE. Neural generators of the P₁₅₀ and N₂₅₀ components are linked to brain regions including the inferior colliculus, the medial geniculate nucleus, the primary auditory cortex, and the higher order auditory cortex [2]. Malformations that occur anywhere in this pathway can result in changes of brain signals recorded from the scalp. There are several possible explanations for our data.

1. The ERP changes may have been caused by cortical malformation and impairment of the auditory radiation in brains with HPE. In our study, non-separated frontal cortex was seen in MR images for all patients. Enlarged frontal horns of the cerebral lateral ventricles were also evident in these subjects, suggesting impaired temporal lobe functions. Furthermore, previous studies have reported histological abnormalities of cerebral cortices in brains with HPE [11], with rudimentary cortical structures [12] and delayed myelination [13].
2. Amplitude changes of the P₁₅₀ and N₂₅₀ components might be associated with the presence of disorders of the thalamic nuclei. As shown on the MR scans, our subjects had varying degrees of thalamic malformations. Non-separation of the deep gray nuclei including the thalamic nuclei is a frequent feature in HPE [14,15]. As stated above, the thalamocortical ascending pathways are important mediators of acoustic stimuli. It has been demonstrated that auditory evoked potentials could be directly recorded from the medial geniculate body [16]. Stimulation of the ventral and dorsal divisions of the medial geniculate body can also activate the thalamocortical projections [17]. All these results indicate that the thalamus plays a critical role in modulation of auditory responses. Taken together, it seems that auditory stimuli are not well functionally processed at the cortical level in the brains with HPE. In other

words, with information only processed at lower levels of the auditory pathway, subjects with HPE may not fully cognitively understand the meanings of stimuli. These findings may explain why patients with HPE have extreme difficulties in acquiring and comprehending language.

3. Because of the enlargement of ventricular systems, alterations of brain cortical topology need to be considered when signal amplitude distributions are interpreted for the HPE groups, i.e. the cerebral region under the same electrode may not be the same between normally developing brains and brains with HPE. This topological change may cause shift of amplitude topographical distribution in subjects with HPE.

As we mentioned before, numerous subcortical physiological responses were involved in the fundamental auditory sensory processing. Whether functions of those brain structures were impaired needs to be determined. One approach is to record auditory brainstem responses (ABR). However, due to the limitations of our EEG machine (such as sampling rate), we were unable to obtain ABR from these subjects at this time. We expect more investigations in the future.

4.2. Auditory discrimination responses

Despite cortical and subcortical malformations, robust mismatch responses were elicited in the HPE groups, suggesting that difference in the stimuli was discriminated in these subjects despite the fact that the stimuli might not be efficiently processed at the cortical level. These findings strongly support previous observations that the elicitation of MMN does not require attention of subjects [18].

With no obvious changes in the frontal and anterior temporal areas between the HPE and control groups, the MMN amplitudes were remarkably attenuated in the central, parietal, mid-temporal and posterior temporal areas in the HPE groups. The dissociation of MMN amplitudes between the anterior and posterior brain areas suggests a neural mechanism consisting of multiple MMN sources [7]. The reduced MMN responses in the posterior brain areas may be caused by several reasons. First, it has been demonstrated that the location of MMN dipole source is close to that of N_1 component in the temporal lobe [19]. Thus, it is quite likely that the MMN and the N_1 sources are compromised simultaneously in the brain of HPE. Second, as stated above, the changes in cortical topology may contribute to the differences in the topographical distribution of MMN amplitude. According to the MR images, the MMN responses recorded from our subjects with HPE suggest that some subcortical neural sources might still be functional, such as those located in the inferior colliculus [9]. Therefore, the possibility that the MMN-like responses were contributed from subcomponents of MMN sources from those brain regions cannot be ruled out in our subjects.

One methodological issue is that a relatively shorter inter-stimulus interval was used in our study. Therefore, latencies and amplitudes to the second tones might be affected by the ERP responses induced by the first tones. We noted this influence and accordingly, latencies and amplitudes were not measured from the 70-ms-IS1 block. Since the standard and deviant stimuli only differed for the second tones, we thought that physiological processes induced by the first tones of both types of stimuli should be similar. Further, this influence was reduced by subtracting ERP waves to deviant stimuli from those to standards—a procedure used for obtaining MMN responses. It is worth mentioning that to extend the present results to other sound stimuli needs to be manipulated circumspectly.

In summary, in the present study, longer MMN latencies were seen in children with HPE as compared with those obtained from the control groups, suggesting that children with HPE had more difficulty in processing rapidly changing auditory input than normally developing children. With respect to the changes of MMN, our data suggest that the non-separation of

brain structures possibly interfere with the organization of neural networks that support auditory discrimination processing in HPE.

References

1. Cohen MM Jr. Perspectives on holoprosencephaly: part 1. Epidemiology, genetics, and syndromology. *Teratology* 1989;40:211–35. [PubMed: 2688166]
2. Martin, JH. The auditory and vestibular systems. In: Martin, HJ., editor. *Neuroanatomy*. New York: Elsevier; 1989. p. 165–205.
3. Pang EW, Gaetz W, Otsubo H, Chuang S, Cheyne D. Localization of auditory N1 in children using MEG: source modeling issues. *Int J Psychophysiol* 2003;51:27–35. [PubMed: 14629920]
4. Ponton C, Eggermont JJ, Khosla D, Kwong B, Don M. Maturation of human central auditory system activity: separating auditory evoked potentials by dipole source modeling. *Clin Neurophysiol* 2002;113:407–20. [PubMed: 11897541]
5. Naatanen R, Gaillard AWK, Mantysalo S. Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol* 1978;42:313–29.
6. Scherg M, Vajsar J, Picton TW. A source analysis of the late human auditory evoked potentials. *J Cogn Neurosci* 1989;1:336–55.
7. Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Naatanen R. Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage* 2000;12:14–19. [PubMed: 10875898]
8. Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear Hear* 1995;16:38–51. [PubMed: 7774768]
9. Al'tman YA, Bekhterev NN, Vaitulevich SF, Nikitin NI. The role of phase changes in sound signals in localization of sound sources. *Neurosci Behav Physiol* 2004;34:765–71. [PubMed: 15587804]
10. Saito Y, Adachi K, Nezu A, Deguchi K, Kimura S. Topographical features of the sensory-evoked responses in malformed brains. *Pediatr Neurol* 2000;23:243–9. [PubMed: 11033288]
11. Wong HS, Tang MH, Yan KW, Cheung LW. Histological findings in a case of alobar holoprosencephaly diagnosed at 10 weeks of pregnancy. *Prenat Diagn* 1999;19:859–62. [PubMed: 10521846]
12. Seki V, Kumagai K, Goto N. Holoprosencephaly. *J Kanazawa Med Univ* 1978;3:117–25.
13. Barkovich AJ, Simon EM, Glenn OA, Clegg NJ, Kinsman SL, Delgado M, et al. MRI shows abnormal white matter maturation in classical holoprosencephaly. *Neurology* 2002;59:1968–71. [PubMed: 12499493]
14. Plawner LL, Delgado MR, Miller VS, Levey EB, Kinsman SL, Barkovich AJ, et al. Neuroanatomy of holoprosencephaly as predictor of function: beyond the face predicting the brain. *Neurology* 2002;59:1058–66. [PubMed: 12370462]
15. Simon EM, Hevner R, Pinter JD, Clegg NJ, Miller VS, Kinsman SL, et al. Assessment of the deep gray nuclei in holoprosencephaly. *AJNR Am J Neuroradiol* 2000;21:1955–61. [PubMed: 11110554]
16. Yvert B, Fischer C, Guenot M, Krolak-Salmon P, Isnard J, Pernier J. Simultaneous intracerebral EEG recordings of early auditory thalamic and cortical activity in human. *Eur J Neurosci* 2002;16:1146–50. [PubMed: 12383244]
17. Di S, Barth DS. The functional anatomy of middle-latency auditory evoked potentials: thalamocortical connections. *J Neurophysiol* 1992;68:425–31. [PubMed: 1382119]
18. Fischer C, Morlet D, Bouchet P, Luaute J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin Neurophysiol* 1999;110:1601–10. [PubMed: 10479027]
19. Huotilainen M, Winkler I, Alho K, Escera C, Virtanen J, Ilmoniemi RJ, et al. Combined mapping of human auditory EEG and MEG responses. *Electroencephalogr Clin Neurophysiol* 1998;108:370–9. [PubMed: 9714379]

Fig 1.

Transverse T₁-weighted MRI scan through the thalamus to show the non-separated frontal lobes of a subject with semi-lobar holoprosencephaly (A) and visual representation of auditory stimuli for the 70- and 300-ms-ISI blocks (B).

Fig 2.

P₁₅₀ and N₂₅₀ components in grand averaged ERP waveforms induced by the standard stimuli (300-ms-ISI block, all subjects). Two prominent components (P₁₅₀ and N₂₅₀) were elicited by the tones in the control subjects. Waveforms recorded at four electrodes are displayed (positions are indicated as 8: left frontal, 3: right frontal, 16: left mid-temporal, 57: right mid-temporal).

Fig 3.

Grand averaged difference waveforms (deviant-standard) for the 300-ms-ISI block (all subjects). Mismatch negativity (MMN)-like responses were elicited in both control and HPE (indicated by hollow arrows) groups. Waveforms recorded at four electrodes are demonstrated (positions are indicated as 8: left frontal, 3: right frontal, 16: left mid-temporal, 57: right mid-temporal).

Fig 4. Comparisons of amplitude distributions of event-related potential components (P₁₅₀: left, N₂₅₀: right) for the 300-ms-ISI block. Higher amplitudes are shown in red, whereas lower amplitudes are in blue. The data were averaged from all subjects.

Fig 5.

Averaged latencies of mismatch negativity-like components in the left and right hemispheres (60 months, all subjects). The bars indicate one standard deviation. Marginal significance ($P < 0.07$) was also observed in the 300-ms-ISI block in the left parietal, mid-temporal and posterior temporal areas and right central and parietal areas. FP, prefrontal; F, frontal; C, central; P, parietal; O, occipital; AT, anterior temporal; MT, mid-temporal; PT, posterior temporal; ISI, inter-stimulus interval. * $P < 0.05$ (compared between control and HPE groups).

Table 1

Comparisons of mean P₁₅₀ amplitudes (μV) to standard stimuli between HPE group and control group (300-ms-
ISI bock)

Brain areas	Left hemisphere		Right hemisphere	
	Control (SD)	HPE (SD)	Control (SD)	HPE (SD)
Prefrontal	4.67 (1.37)	1.35 (1.58)**	5.11 (1.97)	1.53 (1.40)**
Frontal	5.70 (1.81)	0.88 (2.27)**	6.32 (2.11)	0.01 (2.62)**
Central	5.57 (2.05)	0.90 (0.76)**	5.75 (2.14)	0.58 (1.92)**
Parietal	3.59 (1.87)	1.06 (2.30)	3.02 (1.76)	0.27 (0.83)**
Occipital	1.23 (1.00)	0.01 (0.75)*	1.30 (0.60)	0.31 (0.52)*
Anterior temporal	4.07 (1.58)	0.44 (1.28)**	4.50 (1.52)	2.59 (3.62)
Mid- temporal	4.09 (0.86)	0.86 (1.02)**	4.23 (1.89)	0.30 (1.46)**
Posterior temporal	1.36 (0.84)	0.73 (1.23)	1.49 (0.98)	0.51 (0.68)

The data were obtained from the 60-month groups and were averaged from 3 to 5 electrodes in each brain area. SD, standard deviation.

* 0.01 < *P* < 0.05,

** *P* < 0.01.