We recorded magnetic brain activity from healthy human newborns when they heard frequency changes in an otherwise repetitive sound stream. We were able to record the magnetic counterpart of the mismatch negativity (MMN) previously described only with electric recordings in infants. The results show that these recordings are possible, although still challenging due to the small head size and head movements. The modeling of the neural sources underlying the recorded responses suggests cortical sources in the temporal lobes. NeuroReport 14:1871–1875 © 2003 Lippincott Williams & Wilkins.

Key words: Auditory; Infant; Magnetoencephalography; MEG; Mismatch negativity; MMN

INTRODUCTION

Human beings are already relatively skilled in sound processing at birth. During the last 3 months of intrauterine life, the auditory system of the fetus is operational [1] and in use [2]. The most important task of the central auditory system of a newborn is to recognize the voice of his/her mother. The brain correlates of these cognitive skills, although successfully demonstrated with behavioral methods [3], are still unknown.

The electromagnetic brain responses to sounds, auditory event-related potentials (ERPs) and magnetic fields (ERFs), allow us to follow the brain processes related to auditory information processing, including auditory short-term memory, with a temporal accuracy of milliseconds. Locating the neural sources of the observed responses is challenging with the ERPs: accurate estimates of the individual conductivities of the tissues and shapes of the fontanelles should be available for acceptable source localization. When the ERFs have been successfully recorded with magnetoencephalography (MEG), however, the spherical head model can be employed when estimating the locations of the sources without drastically compromising the spatial accuracy [4,5]. It should also be noted that a great advantage in using MEG in infant recordings is the possibility of comparing the data from fetuses and infants directly.

The auditory ERP to frequently repeated sounds (standards) in newborns is characterized by a single peak ~200–350 ms after stimulus onset, depending on the maturity of the neonate [6,7]. The only published report on the auditory ERF to repeated sounds in newborns confirms that this response is also detectable at about the same latency with the MEG [8], with field distributions suggesting sources within the auditory cortex.

When the standard sounds are replaced with occasional deviant sounds, differing from the standards in a feature such as pitch or duration, several evoked responses are elicited by the deviant sound. The mismatch negativity (MMN) [9] and its magnetic counterpart (MMNm) [10] are elicited as a response to the observed difference between the detected features or feature-combinations of the deviant sound and the representation of the standard sound in the auditory sensory memory [11]. It is noteworthy that the elicitation of the MMN and MMNm is automatic: no task or effort is required from the subject. The MMN has also been found in newborns [12–14] and even in infants born prematurely before the predicted date of birth [15]. In newborns, the MMN is also elicited in sleep [16], which allows MEG recordings, requiring immobility of the head, to be performed on sleeping infants.

The P3a response [17] is found in a passive oddball condition in response to deviant sounds differing relatively strongly from the standard sounds and it seems to be related to the involuntary switching of attention towards sound change. In adults, the P3a and its magnetic counterpart, the P3am, have generators in the auditory cortex area [18,19], but it seems that other sources contribute strongly to the electrically recorded P3a.

The late discriminative negativity (LDN) [20], and the negative component (Ne) [21], are quite common responses to deviant sounds occurring in infants and children. Their function is not yet clearly understood, and their magnetic counterparts have not been demonstrated.
The aim of this study was to investigate the auditory ERF response pattern to deviant sounds in newborns. Further, we aimed at recording the MMNm of the newborn infant and studying the location of its generators in the newborn brain.

MATERIALS AND METHODS

We recorded auditory event-related magnetic fields from 12 newborn infants aged 2–12 days (born at gestational ages between 38 weeks 2 days and 41 weeks, with birth weights between 2880 and 3930 g). All infants were considered healthy by a neonatologist and they passed a hearing screening by otoacoustic emissions. One or both parents of each infant signed a written informed consent prior to the study. The Ethical Committee of the Hospital District of Helsinki and Uusimaa approved the study plan.

The stimuli were presented in the oddball condition. The standard sounds of 500 Hz with two upper harmonics (1000 and 1500 Hz) were presented with a sound onset asynchrony (SOA) of 800 ms. These sounds were randomly replaced by deviant sounds of 750 Hz with two upper harmonics (1500 and 2250 Hz) in 12% of the cases. All sounds had a duration of 100 ms including 10 ms rise and fall times. The stimuli were binaurally presented, using the EAR loudspeaker and tube system compatible with MEG recordings, with a loudness of ~60 dB SPL.

The auditory evoked magnetic fields were recorded using a whole-head helmet-shaped VectorView magnetometer (Neuromag Ltd., Helsinki) with 306 channels. The channels are located at 102 positions uniformly over the adult head with two orthogonal planar gradiometers and one magnetometer at each location. The infants were tightly swaddled and the instrument was used in the supine position so that they were able to sleep throughout the recording. One hemisphere (left in seven and right in five infants) was placed close to the sensors, thus increasing the distance to the other hemisphere. Typically, the distance from the head surface to the sensors was 2.5 cm in the closer hemisphere closer to the helmet, while that from the more distant hemisphere was 10 cm. Data from active and quiet sleep stages were averaged together. The infants used a non-magnetic pacifier when necessary.

Four marker coils were attached to the head of the subjects in order to determine the position of the head with respect to the magnetometer [4]. The position of the coils in the head coordinate system was determined with an Isotrak 3D digitizer. The coils were activated before each block for determining the head position to ensure that it remained stable throughout the recording. The maximal movement at the location of the auditory cortex was 5.6 mm, with a mean of 4.3 mm.

The data were digitally filtered with a band pass of 0.01–90 Hz and sampled at 600 Hz. Epochs starting 150 ms before and ending 700 ms after sound onset underwent a rejection operation where all epochs > 1500 fT/cm on any of the planar gradiometer channels were discarded. Thereafter, the epochs were averaged according to the stimulus type. The number of accepted epochs was > 350 for the standard sounds and > 95 for the deviant sounds. The responses were filtered with a bandpass of 1–20 Hz. The window for determining the baseline correction started ~150 ms before and ended at stimulus onset.

The signal space projection method (SSP) [22] was used to project out the artefacts caused by external and cardiac magnetic fields. The projection operators contained 4–8 dimensions, typically consisting of 3–4 dimensions for the external fields and 0–2 dimensions for the cardiac fields. The SSP is particularly powerful in removing the cardiac artefacts, which would contaminate every epoch and thus prevent the use of simple artefact rejection schemes (see Fig. 1 for the data of one infant and Fig. 2 for the responses of all infants after SSP). Difference signals were formed by subtracting the response to the standard sounds from that to the deviant sounds.

Equivalent current dipole (ECD) modelling [4] was performed for the peaks observed in the response to the standard sounds and in the difference signals by using a spherical head model. The location of the sphere origin was (0, 0, 25) mm, obtained by downsampling by the head size the best-fitting sphere to an average adult intracranial volume. The position of the head with respect to the magnetometer was determined using the four marker coils. In three infants, the head location estimate was also partly based on the magnetic field patterns of the recorded brain responses. The ECDs were modelled by selecting 20–44 gradiometer channels above the strongest response separately for each hemisphere (see Fig. 3 for the result of ECD modelling in one infant).

RESULTS

The visual investigation of the responses to the standard sounds revealed that the MEG equivalent of the electric 250-ms response was clearly elicited in all infants in the hemisphere close to the sensors. In addition, evidence for the presence of a 250-ms response in the other hemisphere located further away from the instrument was obtained in most infants. The ECD modelling of the 250-ms response was successful in all infants in the closer hemisphere with a mean (± s.d.) latency of 208 ± 52 ms and a mean strength of 6 nAm. In addition, a vertex-negative late response to the standard sounds was found and successfully modelled with ECDs in six of 12 infants with a mean latency of 290 ± 50 ms and a mean strength of 8 nAm.

The locations of the ECDs for the 250-ms response were consistent with sources in or near the auditory cortices of the temporal lobes. The mean coordinates of the ECD locations were −22, −6, 38 and 24, −5, 29 mm in the left and right hemispheres, respectively. Similarly, the mean locations for the late response to the standard sounds were −21, −15, 33 and 19, −10, 30. The differences in the locations of these two responses were not statistically tested due to the small number of successful ECD fits (only three in each hemisphere).

The difference signals revealed the MEG equivalent of the MMN response, the MMNm, in 11 of 12 infants in the closer hemisphere, with evidence of the presence of the MMNm in the opposite hemisphere in some infants. The ECD modelling of the MMNm response was successful in 10 of 12 infants, with a mean latency of 247 ± 25 ms and a mean strength of 10 nAm. In two of 12 infants, the MEG equivalent of the LDN response, the LDNm, was elicited and successfully modelled with ECDs with a mean latency...
of 262 ms and a mean strength of 9 nAm. None of the 12 infants showed the MEG equivalent of the P3/P3a response to the deviant sounds.

The locations of the ECDs for the MMNm were also consistent with sources in or near the auditory cortices of the temporal lobes. The mean locations of the MMNm were $-27, -11, 31$ and $26, -9, 31$ in the left and right hemispheres, respectively. The locations of the MMNm were compared with those of the 250-ms response, and no significant differences were found.

The mean coordinates for the LDNm were $35, -6, 27$ (both in the right hemisphere). No statistical testing of the differences in the locations of the LDNm responses with respect to the other responses was performed due to the small number of successful ECD fits (only two in the right hemisphere).
Fig. 2. Evoked magnetic fields of all subjects to standard (thin line) and deviant (thick line) sounds are shown from one gradiometer channel. The polarity of the curves depends on the direction of the gradiometer, the position of the head, and on which hemisphere was closer to the instrument. The channels on the left show the largest response to the standard sounds while the channels on the right show, from the same hemisphere, the largest discriminative or MMN response (standard with thin line, deviant with thick line, difference area shaded with grey). The arrows show the time moment of the dipole fitting for the 250-ms and MMNm dipoles. The time scale is from −150 to 700 ms.

Fig. 3. (a) Equivalent current dipole (ECD) modelling of the 250-ms response and the MMNm of one infant. The magnetic field maps are drawn on the measurement helmet from the back left view showing a clearly dipolar field pattern for the 250-ms response (upper) and a dipolar but more noisy field pattern for the MMNm (lower helmet). The location of the dipole is presented with a circle. The contour step of the lines is 5 fT. (b) A schematic illustration of the coordinate system and the locations of the head model and the dipolar sources. The x-axis passes through the preauricular points to the right, the y-axis passes through the nasion, and the z-axis points approximately to the vertex. The origin of the spherical head model (dashed line) was at (0, 0, 25) mm. The mean locations of the dipolar sources are presented with squares for the 250-ms and the late response for the standard tones and with diamonds for the MMNm and LDNm responses for the deviant tones, estimated from the subtraction curves. The open and filled marks correspond to the left and right hemispheres, respectively.
DISCUSSION
It was possible to model the 250-ms response to the standard sounds in all infants and the MMNm to the deviant sounds in most infants. The 250-ms and MMNm response patterns found in the present infants correspond to the ERP findings of Kushnerenko et al. [7] obtained with similar stimuli and paradigm. However, no evidence of a magnetic P3/P3a was observed in the present data and, further, the LDN was obtained in only a few infants. This suggests that these responses are either not located cortically, or in other than clearly tangential directions, or both, whereas the sources of the 250-ms response and MMNm are mainly located within the auditory cortex with a tangential orientation.

This is the first study to demonstrate magnetic fields elicited by auditory stimulation in healthy newborns in the oddball condition. As already shown by Lengle et al. [8], auditory responses of newborns can be recorded with the MEG, even though the task is made somewhat challenging by the small head size and head movements. Here, we present results from the oddball paradigm, which gives more information on the cognitive functions of a newborn than the mere recording of frequently presented sounds. Since memory-related processing of the standard stimulus and the comparison process, followed by later processes, are detected in the oddball paradigm [11], one can assume that the responses to the deviant sounds, especially the MMNm response, will provide very interesting information on the developmental status of the newborn. Currently, there is growing interest in understanding the neural processes (and their behavioural correlates) underlying the recorded event-related responses in terms of human development [23,24] in their behavioural correlates) underlying the recorded event-related responses in terms of human development [23,24] in order to determine the developmental milestones corresponding to the obvious and dramatic changes of the peak latencies and amplitudes of the auditory evoked responses during development. This task remains challenging, but the use of the MEG may be helpful in determining the innate and learned features of memory functions, control of attention, and the role of these cognitive functions in speech processing [25].

REFERENCES

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