Magnetoencephalography is feasible for infant assessment of auditory discrimination

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Abstract

Magnetoencephalography (MEG) detects the brain’s magnetic fields as generated by neuronal electric currents arising from synaptic ion flow. It is noninvasive, has excellent temporal resolution, and it can localize neuronal activity with good precision. For these reasons, many scientists interested in the localization of brain functions have turned to MEG. The technique, however, is not without its drawbacks. Those reluctant to employ it cite its relative awkwardness among pediatric populations because MEG requires subjects to be fairly still during experiments. Due to these methodological challenges, infant MEG studies are not commonly pursued. In the present study, MEG was employed to study auditory discrimination in infants. We had two goals: first, to determine whether reliable results could be obtained from infants despite their movements; and second, to improve MEG data analysis methods. To get more reliable results from infants we employed novel hardware (real-time head-position tracking system) and software (signal space separation method, SSS) solutions to better deal with noise and movement. With these solutions, the location and orientation of the head can be tracked in real time and we were able to reduce noise and artifacts originating outside the helmet significantly. In the present study, these new methods were used to study the biomagnetic equivalents of event-related potentials (ERPs) in response to duration changes in harmonic tones in sleeping, healthy, full-term newborns. Our findings indicate that with the use of these new analysis routines, MEG will prove to be a very useful and more accessible experimental technique among pediatric populations.

Keywords: Auditory discrimination; Event-related potentials (ERPs); Infants; Magnetoencephalography (MEG)

Introduction

The investigation of auditory discrimination in infants has largely been done via behavioral methods (for a review, see Kuhl, 2000; Stockard-Pope, 2001; Werker and Rubel, 1992). More recently, however, direct brain measurements such as functional magnetic resonance imaging (fMRI) (Dehaene-Lambertz and Pena, 2001), optical topography (Pena et al., 2003), and especially electroencephalography (EEG) (Cheour et al., 1997; Dehaene-Lambertz et al., 2002; for a review see Cheour et al., 2001) have been employed in pediatric populations. Unfortunately, each of these methods has its limitations, due to, for instance, spatial (EEG) or temporal resolution (fMRI, optical topography). Moreover, many other factors besides brain functions affect results obtained by EEG. Extracellular flow, for example, is affected significantly by the differing electrical conductivity...
properties of the scalp, skull, cerebrospinal fluid, and the brain itself (Lounasmaa et al., 1996).

Although it has been available for more than 35 years, having been invented in 1968 (Cohen, 1968), MEG has only rarely been employed among pediatric populations. MEG is noninvasive and offers excellent temporal and spatial resolution, especially when multiple active sources are compared within a single experimental session. It works by detecting magnetic fields generated by the brain’s cellular currents during synchronized neural activity. Among the few infant MEG experiments is a study by Paetau et al. (1994) in which data from a single 3-month-old infant and from a group of older children and adults are reported. In this study, tones, tone pairs, and pseudowords were presented to the subjects. The authors reported that all stimulus types elicited substantially similar responses in all age groups. However, in the infant, the authors did not see any N1m response but a large positivity P1m peaking at 190 ms and dominating the response up to 500 ms. Another example of the rare infant MEG experiments is a study by Lengle et al. (2001) on twenty 2- to 6-week-old infants. Authors report that in all neonates tones presented to them elicited a dominant component that was negative toward the face and positive toward the occiput. Huotilainen et al. (2003) also published recently the infant MEG responses recorded from the infant’s left hemisphere, where they showed mismatch activity in response to a frequency-deviated sound.

Recently, a few MEG fetus studies have also been published. Blum et al. (1985) were the first to demonstrate that MEG can be used to obtain fetal auditory evoked responses. Since then, some other researchers have applied this technique to study fetuses. These studies have reported that auditory evoked potentials can be detected in 28–80% of the subjects, depending on, for example, how many times MEG recordings were performed for each subject (Eswaran et al., 2002a,b; Lengle et al., 2001; Schneider et al., 2001; Wakai et al., 1996; Zappasodi et al., 2001).

Four factors help to explain why infant MEG studies are still rare. Naturally, the higher price of MEG as compared to EEG might be one of the reasons why MEG infant studies are so rare. Second, to obtain reliable results in MEG experiments, it is important that the subject remains relatively still. Obviously, this is difficult to achieve in infants. Third, MEG requires that the infant’s head is close to the MEG helmet wall to obtain reliable results. This presents a challenge because existing helmets are designed for adults, making them too large to offer uncompromised accuracy in infant studies. Fourth, factors such as the proximity between the heart and the MEG helmet can greatly influence the MEG signal. The infant heart is closer to the head than it is in adults and infant heart beats, approximately 10 times larger than their brain magnetic fields at MEG sensor location, largely disturbs MEG recordings.

In the present study, as the first report of a series of experiments on neonates, 6-month-olds, and 12-month-olds using simple tones, complex harmonic tones, and syllables, we report preliminary results indicating the feasibility of using MEG to study auditory discrimination in neonates. Our findings rely on the invention of MEG techniques that helped us to overcome some of the aforementioned problems with infants. First, we localized the head position and orientation during each epoch, making it possible to average the epochs by selecting those in which the head position was close enough to a predefined reference position. Secondly, we employed an algorithm, called the signal space separation (SSS) method, that greatly reduces magnetic disturbances that originate outside the multi-channel sensor helmet by separating the signal space that produces brain signals (those inside the sensor helmet) from the disturbance space outside the sensor helmet (Taulu et al., in press). The magnetic field distributions over the sensor volume that are induced by currents from the inside are fundamentally different from those induced by currents on the outside, allowing us to effectively reduce magnetic noise originating from outside the helmet. The combination of these features made it possible to use the magnetic responses of infants to examine their abilities to discriminate auditory signals.

Materials and methods

Subjects

Eight full-term newborns (five females, gestational age [GA]: 37–42 weeks) participated in this study. Parents provided written informed consent for their infants to participate in the experiments. Infants were tested 1–5 days after birth. During the recordings infants were asleep.

Stimuli

An oddball sequence was employed, including a single standard (P = 85%) and a single deviant stimulus (P = 15%) that differed in duration; the standard sounds were 100 ms in duration and the deviant sounds were 40 ms. All the sounds were composed of three sinusoidal partials of three 500-Hz harmonic sounds, that is, 500, 1000, and 1500 Hz. The constant stimulus-onset asynchrony was 800 ms. Stimulus sequences were pseudo-random and each deviant tone was preceded by at least two standard tones. The stimuli were delivered via nonmagnetic headphones to the right ear of each subject. The duration of the experiment was about half an hour.

Recording

All experiments were conducted in a magnetically shielded room of the BioMag Laboratory of the Helsinki
University Central Hospital. Although the helmet geometry of whole-head 306-channel MEG system (Elekta Neuromag®, Elekta Neuromag Oy, Helsinki, Finland) is designed for adult measurements, this system was employed to record the infant’s auditory magnetic responses from their left hemisphere. In the Elekta Neuromag® system, the magnetic field is sampled with 510 superconducting sensor loops at distinct locations. One hundred two loops are used as magnetometers and the remaining 408 are hardwired to form 204 planar gradiometers. The bases of the gradiometers are orthogonal and their midpoints coincide. First, the planar gradiometers measure two orthogonal spatial derivatives of $B_x$ ($\partial B_y/\partial x$ and $\partial B_y/\partial y$); $B_x$ is the radial component of the brain’s magnetic field $B$. For idealized dipolar sources, this planar-type gradiometer shows the maximum amplitude right above a local current source in the brain. The baseline length of each planar gradiometer is 16.5 mm and the size of this pickup coil is $2 \times 10 \times 28$ mm. Second, a single magnetometer records $B_z$. As a result, the spatial distributions of $B_x$, $\partial B_y/\partial x$, and $\partial B_y/\partial y$ are recorded. Average physical center-to-center distance between sensors is $35.7 \pm 1.1$ mm, which corresponds to an effective channel separation at 20 mm (see Ahonen et al., 1993). The origin of the device coordinate system is at the center of the sensor helmet with the $x$-axis directing from left to right channel and the $y$-axis from posterior to anterior channel. The left side of each infant’s head was positioned over a part of the 306-channel sensor array that would correspond to the adult occipital region.

Epochs of 800-ms duration (including a 100-ms prestimulus baseline) were digitized at 600 Hz (analog filter pass band 0.1–172 Hz). During the recording, each subject’s head location and orientation with respect to the device’s coordinate system was recorded (every 167 ms; carrier frequencies: 154, 158, 162, and 166 Hz) by the continuous head monitoring system.

Analysis

Because we recorded the head position and orientation every 167 ms, first we calculated the head position and orientation of every epoch. Epochs that had the head location closer than 5 mm to the median head location of all recorded epochs were accepted to be averaged. Therefore, epochs that had the head position more than 5-mm far away from the median location were rejected. Subsequently, artifacts arising from outside the sensor array, such as those stemming from infant heart beat, limb movement, or other ambient magnetic disturbances, were greatly reduced by the signal space separation method (SSS) (Taulu et al., in press). This method efficiently separates brain signals from external disturbances based on fundamental properties of the magnetic fields.

The SSS method is based on the fact that a modern MEG device, comprised of more than 300 signal channels, provides generous spatial oversampling of both biomagnetic and external disturbance magnetic fields. This is true for all sources located more than a couple of centimeters from the nearest sensor in the array, an assumption valid for the possible magnetic sources in the current MEG devices. As the spatial complexity of the field decreases as a function of distance, the number of channels exceeds the essential number of degrees of freedom of the measured field even for the nearest sources. Consequently, a relatively low-dimensional magnetic subspace spanning all measurable magnetic fields can be determined.

Because the sensor array is located in a source-free volume between the volume of interest and the volume containing all sources of external interference, it turns out that the magnetic subspace can be split into two separate, linearly independent subspaces: one containing signals of interest to us coming from the volume surrounded by the sensors and another containing signals from sources outside the array. As the former volume contains the biomagnetic signal sources and the latter volume contains the external disturbance sources, any measured signal can be uniquely decomposed into the magnetic subspace with separate coefficients corresponding to the subspace spanning the biomagnetic signals and to the subspace spanning the external disturbance signals.

The basic assumption of having a source-free sensor volume means that the magnetic field $b$ can be expressed as a gradient of a harmonic scalar potential $V$ in that volume. The harmonicity of the potential allows one to express $V$ as an expansion of harmonic basis functions, for example, spherical harmonic functions. Furthermore, this expansion can be separated into two different expansions; one for the sources closer to the center of the expansion than any of the sensors and another for sources more distant to the center of the expansion than any of the sensors. Consequently, different basis signal vectors can be determined for signals produced by internal and external sources. In this way, the linearly independent SSS basis is formed for modern multichannel measurement devices with a sufficiently high number of channels allowing one to elegantly reduce the external interference signals.

After completing the SSS process, the averaged data were digitally lowpass filtered (cutoff, 20 Hz; decay, 48 dB/oct), and then the linear trend was eliminated by removing the DC components of the 100-ms prestimulus and the 100-ms tail baselines; the 100-ms tail baseline is equivalent to the 100-ms prestimulus baseline of the next epoch.

Because the head location and orientation determined by the median location during each subject’s measurement were not equivalent across subjects, each subject’s original head coordinate system was translated and rotated to correspond to a reference or standard head location; the head coordinate system has its $x$-axis directing from the left to right pre-auricular point and its $y$-axis from the origin to the nasion. To convert into the standard head location, each subject’s head was virtually moved as follows. First, the center of a sphere approximated to each subject’s brain was
moved to the point \((0.0 \ -30.0 \ 10.0) [\text{mm}]\) of the device coordinate system. Second, each subject’s head was rotated so that all three axes of its head coordinate system ran parallel to the axes of the device coordinate system (see Fig. 1). We assumed that the center of the approximated sphere of the newborn infant’s brain was at \((0.0 \ 4.7 \ 36.6) [\text{mm}]\) with respect to the head coordinate system and its radius was 50.0 [mm]; these specific values were obtained by reducing the adults’ average brain size and approximated sphere. The magnetic data at each channel were converted using minimum norm estimates (Uutela et al., 2001) as if the infant’s head position had been at the standard head position and orientation.

The difference waveforms were obtained by subtracting the averaged response to repetitively presented standard stimuli from the response to occasionally presented deviant stimuli. After the head position standardization, the following two analyses were performed.

The magnetic amplitude of the gradiometer was calculated at 10 channel locations that have distances less than 65 mm to the leftmost point of approximated sphere, which was \((-50.0 \ 4.7 \ 36.6) [\text{mm}]\) with respect to the head coordinates (see Fig. 2). Because we do not have each subject’s magnetic resonance images, this leftmost point is supposed, based on adult brain structure, to be located at the leftmost point of the left temporal region along or close to the Sylvian fissure, which is the auditory region. To obtain a good S/N ratio comparable to the adult measurement, the reference distance 65 mm was determined in such a way that 95% of the Elekta Neuromag\textsuperscript{R} channels are closer than this distance to the approximated sphere when the adult sits in the average position (calculated from 206 experiments). If the distance is longer, the signal from the brain is very small, resulting in worse S/N ratio. The waveforms from the gradiometers are analyzed because they show a maximum peak right above the neuronal current (good spatial correspondence) and also show an approximate direction of the neuronal current beneath that channel. We mainly analyzed the difference waveforms. To find the peak amplitudes and latencies of the difference waveforms, we

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**Fig. 1.** Effect of SSS algorithm. In the left panel, responses of subject SH to the deviant stimulus are shown for 18 channel locations covering the left hemisphere after lowpass filter (cutoff: 40 Hz) processing and a baseline (−100 to 0 ms) correction. The location of brain relative to the channel locations is described in the inset. Waveforms in triple sensor 25 are enlarged on the right panel, where thin red curves are original waveforms and thick blue curves are waveforms after applying the SSS algorithm. In the right panel, the left upper frame shows the waveforms recorded by a \(y\)-axis-oriented gradiometer, the left lower frame shows the waveforms recorded by an \(x\)-axis-oriented gradiometer, and the right frame shows the waveforms recorded by a magnetometer. The directions of \(x\)-axis and \(y\)-axis, shown in the inset, are based on the channel coordinate system, and therefore the absolute directions are different depending on the channel location and direction on the sensor helmet. A filled green circle indicates the channel closest to a point \((-50.0 \ 4.7 \ 36.6) [\text{mm}]\), which is the leftmost point of the approximated sphere, in the original measurement location. An open green circle shows the location closest to the above point after the head position standardization; in Figs. 2 and 3, waveforms, contour maps, and arrow maps are always illustrated after head position standardization. See Materials and methods section.
divided the latency range into three sections based on visual inspection of the data and previous studies (compare Cheour et al., 1998); the first range from 40 to 100 ms corresponding to event-related potential’s (ERP’s) early component (EC), the second one from 200 to 300 ms corresponding to ERP’s mismatch negativity (MMN), and the third one from 350 to 550 ms corresponding to ERP’s late discriminative negativity (LDN). We identified the peaks separately depending on the current orientation in terms of ERP measurement, namely positive and negative current, where the negative current flows through the auditory region from the superior to inferior direction, resulting in a vertex negativity in an EEG recording. For further analysis, we employed the peak whose amplitude has the S/N of more than 2. The noise level was the standard deviation of the first baseline ([C0]100 to 0 ms). The amplitude refers to the vector sum of a pair of orthogonal gradiometer outputs.

**Results**

Using the real-time head-position tracking system, we could effectively reject the epochs in which the head position was farther than 5 mm from the reference head position. The SSS algorithm reduces noise components from sources originating outside the sensor helmet (Taulu et al., in press). Fig. 1 illustrates the effects on gradio- and magnetometer channels in a representative infant. The inset of Fig. 1 shows a sketch of the brain to show its approximate location relative to the sensor channels after head position standardization.

After the SSS process, large artifacts still remained in four out of eight subjects. We regarded that the data were contaminated by the large artifact when the maximum waveform peak, calculated from the waveforms digitally filtered at 20 Hz and with removal of the DC component during the two baselines, resides outside the latency range from 60 to 700 ms. These data were eliminated from further analysis, resulting in a final analysis of MEG data from four females (age: 2–5 days, GA: 38–42 weeks). Fig. 2 shows the difference waveforms obtained from four subjects at 10 triple sensor locations (20 gradiometers and 10 magnetometers), covering most of the left hemisphere. Large deflections are seen mainly in the channels close to the left auditory region.

As indicated in the Materials and methods section, the difference waveforms at the 10 triple sensor locations shown in Fig. 2 were analyzed in two ways after head position standardization. Table 1 shows the significant negative and positive peak data for the three latency ranges. In the first latency range (40–100 ms), one subject showed a negative peak and two subjects showed a positive peak. In the second latency range (200–300 ms), one subject showed a negative peak and three subjects showed a positive peak. In the third
latency range (350–550 ms), two subjects showed a negative peak and two subjects showed a positive peak. Except for one case in the first latency range, all significant peaks have the S/N of more than 4.

Fig. 3 shows each individual’s contour maps and arrow maps at the maximum peak latencies (Table 1) in each of three latency ranges. The arrow maps show the approximate current flow (direction and relative magnitude) beneath each channel location.

Discussion

Our results demonstrate that MEG is a promising tool for recording auditory ERP in infants. The real-time head-position tracking system enabled us to average the epochs by rejecting the epochs in which head location deviated significantly from the reference head position. Moreover, the new algorithm reduced the magnetic interference from outside the sensor helmet in our newborn baby recording as well.

The waveform peak analysis showed that at the first latency range (40–100 ms) there was no clear consistent tendency across subjects but one subject showed a negative peak and two subjects showed a positive peak. The second latency range (200–300 ms) showed a trend of a positive peak although one subject showed a negative peak. The third latency range (350–550 ms) did not show a consistent tendency across subjects either because two subjects showed a negative peak and two subjects showed a positive peak.

Although we could not find a consistent magnetic counterpart of ERP’s early component, two subjects showed a magnetic peak corresponding to the positive current. In some previous EEG studies, early negativity has been reported instead of positivity. This has typically not been very large in amplitude and, according to some studies, seems to appear so quickly after the stimulus presentation that it may include some middle-latency components (Cheour et al., 1997; Ceponiene et al., 2002; Pihko et al., 1999). If this is the case, it is unlikely that MEG would detect these deep sources. One also needs to take into account that due to individual variation in ERP latencies in infants, it is likely that in the figures presenting group data this EC often seems to be overlapped by the next component, MMN (Ceponiene et al., 2002).

In the third latency range (350–550 ms), a significant peak was detected in all subjects; two out of four subjects showed a magnetic deflection corresponding to a positive current.
current and the others showed a magnetic deflection corresponding to a negative current. Most EEG studies have reported a large amplitude negative response called late discriminative negativity (LDN) at this latency range (Ceponiene et al., 2002; Korpilahti et al., 1995; Martynova et al., 2003).

Our results show that individual variations seem to be quite large in infant MEG data. This finding is consistent with infant EEG studies. Several explanations have been put forth. Some authors have suggested that infant hearing is quite immature and it is likely that not all infants are able to accurately discriminate sounds. This may very well be the case, especially if simple tones are used, because recent studies have shown that the infant auditory cortex is, indeed, quite immature (Moore, 2002).

It has been further proposed that some of the components may overlap. It has been debated whether large positive responses commonly reported at the latency of 200–350 ms reflect a drift in attention, and whether they obscure an underlying negative component (Ceponiene et al., 2002; Kushnerenko et al., 2002). Although it seems unlikely that this positive response solely reflects orientation toward the stimuli and therefore is an infant version of the P3a component, it seems nonetheless likely that there are two different components appearing in infant ERPs at the latency range of 200–300 ms. Unfortunately, this debate has thus far been futile because EEG offers only limited capacity to separate two different components. MEG has the potential to offer, for the first time, the genuine possibility of separating infant ERP components that have different scalp distributions.

The present study demonstrates a substantial methodological improvement in MEG data collection and data analysis. Disturbances due to the heart and limbs remain a problem in some infants. In addition, adult-sized helmets are too large for infants; to improve data quality, infant-sized helmets should be designed. In spite of these limitations, however, the present study demonstrates that MEG is a viable tool for research on infant auditory processing. As such, MEG will be a valuable asset for future investigations of infants’ perception of complex auditory stimuli such as speech.

Fig. 3. Contour maps and arrow maps from each individual. Contour maps and corresponding arrow maps at the peak latencies in each latency range. In the contour maps, the magnetic flux comes out of the head in the red line regions and goes into the head in the blue line regions. In the arrow maps, the arrow direction shows the current direction below each sensor and the arrow size relatively corresponds to the current magnitude. The arrow size is consistent only within a subject.
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