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Fetal magnetoencephalography

Curtis L. Lowery [a], Hari Eswaran [a], Pamela Murphy [a], Hubert Preissl [a,b,*]

[a] *University of Arkansas for Medical Sciences, Department of Obstetrics and Gynecology, 4301 W Markham St. Slot 518, Little Rock, AR 72205, USA*
[b] *University of Tübingen, MEG-Center, Tübingen, Germany*

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Summary The assessment of the neurological integrity of the human fetus in utero is a technically challenging problem. New brain imaging devices can substantially improve our capabilities to describe functional brain activity in the fetus. It has been well established by fetal behavioral studies and investigations in preterm and term newborns that the brain is functional in utero. The major effort required to perform effective neurological functional investigations is designation of an integrated approach to neurological assessment and the generation of normative data. Currently, it is possible to record evoked brain activity elicited by auditory and visual stimulation from the fetus. In addition, there is growing evidence that spontaneous brain activity can be recorded in the fetus. This paper explores the current status of the brain-imaging field for fetal investigations and currently available data.

Introduction

The prevalence of chronic congenital neurological disorders is remarkably high. Newacheck and Taylor[1] derived the following figures from the 1988 National Health Interview Survey: cerebral palsy: full-term 2/1000, preterm ~16/1000; epilepsy: 2/1000; deafness/hearing loss: 15/1000; and blindness: 12/1000. One review focusing on mental retardation reported a range of 6.7—30+ per 1000.[2] In 1985, approximately 850,000 children were mentally retarded, while 750,000 suffered from cerebral palsy. In all, neurological and communicative disorders cost society over $100 billion dollars per year.

Congenital neurological disorders can result from a wide range of underlying causes, making their early diagnosis particularly difficult. This difficulty is compounded by the problems associated with direct measurements of fetal neurophysiological status. Current fetal imaging techniques, such as ultrasound (US) and magnetic resonance imaging (MRI), can detect gross anatomical anomalies and severe neurological damage, but are insensitive in detecting numerous conditions that result in poor long-term neurological outcome. Fetal heart-rate monitoring can detect severe fetal distress; however, the interpretation of fetal heart rate varies widely, and correlation with outcome is weak.

While genetic factors play a significant role, many congenital neurological disorders are associated with prenatal[3] and occasionally perinatal[4] infection, toxic insult, hypoxia, ischemia, hemorrhage and low birth weight. Susser et al.[5] endeavored to derive quantitative estimates of the causal relevance of these factors to cerebral palsy,

* Corresponding author. University of Arkansas for Medical Sciences, Department of Obstetrics and Gynecology, 4301 W Markham St. Slot 518, Little Rock, AR 72205, USA. Tel.: +1 501 686 5847; fax: +1 501 603 1544.
E-mail address: preissl@uams.edu (H. Preissl).

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mental retardation, and epilepsy in order to estimate which factors could potentially be eliminated or ameliorated through timely intervention. In the case of cerebral palsy, they found low birth weight to be the single greatest risk factor, with perinatal asphyxia a close second. In spite of the greatly increased risks associated with low birth weight and perinatal asphyxia, neither are good predictors of cerebral palsy, as many neonates suffer these risk factors without developing cerebral palsy. Epilepsy is strongly associated with both cerebral palsy and mental retardation, presumably reflecting severe prenatal neurological damage.

Because developmental brain processes in the human fetus are difficult to assess directly, indirect measures such as observation of fetal behavioral changes have frequently been utilized. Behavioral changes related to external stimuli were observed by monitoring variations in fetal heart rate and by recording eye and body movements using ultrasound.[6] Functional magnetic resonance imaging (fMRI)[7] and fetal magnetoencephalography (fMEG),[8] two techniques based on technology developed for the investigation of adult brain processes, are beginning to emerge as viable applications in the study of fetal brain function. Each technique has both advantages and limitations. fMRI has inherent drawbacks based on difficult access to the measuring space, high sound levels, and safety issues, but delivers both functional and anatomical information. However, there is concern that the high magnetic fields used for fMRI may potentially cause fetal damage, particularly in regard to the lens of the fetal eye. In contrast, fMEG is a completely passive and non-invasive method with superior temporal resolution, but it does not directly provide anatomical information which could be obtained only by complementary imaging techniques such as ultrasonography. The signal acquired by fMRI and fMEG are of very different natures. fMRI records a vascular response called the blood-oxygenation-level-dependent (BOLD) response which is changed by neuronal activity.[9] However, time resolution is in the range of seconds. In contrast, fMEG,[10] which measures the magnetic field generated by electrical currents in biological tissue, can record the magnetic field generated by electrical activation of neuronal populations in the developing brain with a temporal resolution down to milliseconds, the inherent timescale of neuronal activity.

The human fetus shows an elaborate behavioral repertoire which is the basis for the investigation of fetal functional brain development. The progress of the developing brain is reflected by the changes in fetal behavior pattern that can be observed through gestation. As referenced above, studies in this field have primarily investigated behavioral changes of the fetus through the observation of body movements and heart-rate parameters in response to external stimuli. Most of these investigations are related to the processing of auditory stimuli. The auditory environment of the fetus in utero is characterized by a low-frequency noise up to 70 dB, especially in the very-low-frequency range (<10 Hz), produced by the mother's intestinal tract. External stimulation of the fetus is only possible if an effective transmission of sound through the maternal abdomen is guaranteed. Animal and modeling studies have shown that frequencies above 1000 Hz are strongly attenuated by the abdomen, and frequencies below this cut-off are transmitted with an attenuation of around 30 dB.[6] Hepper and Shahidullah[11] reported that fetuses are able to perceive single-frequency tones starting at 19 weeks of gestation. Other studies indicate that fetuses are able to discern musical notes, syllables, and voices. It has also been established that the fetus has a basic capacity for learning and memory. van Heteren et al.[12] used fetal habituation to repeated vibroacoustic stimulation to assess fetal memory and reported that fetuses exhibited short-term memory of at least 10 min, and a long-term memory of at least 24 h. The human capacity to learn and understand language is dependent on the cognitive function of sound discrimination, which seems to be functional in the fetus. It is known that newborns can demonstrate this cognitive ability in the first hours after birth. However, the question of when the process of sound discrimination actually begins in the human fetus remains unclear. This kind of learning and auditory perception is further substantiated by the investigation of newborns, which show shortly after birth a preference for their mother's voice.[13]

In addition to fetal responses elicited by auditory stimulation, it has also been reported that visual stimulation delivered by light flashes to the maternal abdomen leads to specific fetal brain responses. Woods and Plessinger[14] recorded visual evoked responses (VER) in fetal lambs using implanted electrodes on the scalp and demonstrated that the visual system develops progressively during the fetal life and is functional prior to birth.

A third approach for the characterization of fetal brain development is the investigation of developmental changes in spontaneous brain activity. It is well established that preterm and term newborns show specific patterns in spontaneous electroencephalography. Recordings of spontaneous brain activity in the fetus could be used to assess functionality as well as the state of the fetus.

This review describes the systems used for the recording of fetal MEG, explores the data analysis approach, and reports results for auditory and visual stimulation studies and approaches to using spontaneous MEG recordings for fetal and newborn assessment.

Systems for recording fMEG

The basic devices for the recording of magnetic fields generated in the brain are superconducting quantum interference devices (SQUIDs). Based on the low amplitude of the measured magnetic fields, which are in the range of 10^{-12}–10^{-15} Tesla, only low-temperature SQUIDs can be used (for comparison the earth magnetic field has a strength of 10^{-4} Tesla). The SQUIDs must be cooled to liquid helium temperature (around 4 K) in a special cryogenic device called a dewar. In 1985, Blum et al.[15] published the first recording of auditory evoked magnetic fields from human fetuses. This study used a single sensor device positioned over the fetal head. Following this pioneering study, several groups used devices designed for adult brain or cardiac investigations. The systems used in these studies include up to 34 channels and are arranged in a flat panel positioned over the fetal head. In 2000, the first MEG dedicated for fetal investigation was installed at the University of Arkansas