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Fetal Magnetoencephalography – Achievements and Challenges in the Study of Prenatal and Early Postnatal Brain Responses: A Review

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Abstract

Fetal magnetoencephalography (fMEG) is the only non-invasive method for investigating evoked brain responses and spontaneous brain activity generated by the fetus in utero. Fetal auditory as well as visual evoked fields have been successfully recorded in basic stimulus-response studies. Moreover, paradigms investigating precursors for cognitive development, such as habituation and mismatch response have been applied successfully with fMEG. These and other studies have shown that the prenatal stage of life could be an important indicator for later cognitive development. This review addresses the achievements of fMEG and constructively discusses its challenges. It concludes with proposals for future studies as well as with designated new applications. Fetal MEG is a promising, and to date it is the only non-invasive approach for the prenatal assessment of precursors for cognitive development. Future fMEG studies might even enable the diagnosis of developmental delays. Furthermore, fMEG could be critical for the implementation and evaluation of fetal intervention programs in at-risk populations.

Keywords

fetal magnetoencephalography; cognitive development in the fetus

Introduction to fetal magnetoencephalography

The natural activity of brain cells generates electrical currents, which also produce magnetic fields. Both, electrical and magnetic brain signals are detectable non-invasively through the scalp. The first successful recording of human electrical activity with electroencephalography (EEG) was conducted by Hans Berger in 1924, whereas magnetic fields in the brain were not detected until almost 25 years later (Cohen, 1968). Since then, so-called magnetoencephalography (MEG) has undergone multiple technological advancements. Modern multichannel whole-head systems function with highly sensitive SQUID sensors (Superconducting Quantum Interference Devices). They are now established in both basic research and clinical settings. These applications have contributed substantially to the current understanding of normal as well as abnormal cortical processes.

The investigation of functional brain processes during development by EEG or MEG recordings has been restricted to the postnatal stage of life. This is mainly due to the difficulties in assessing fetal brain signals. Protected by the maternal abdomen, the fetus is quite secluded from the external environment. Previous studies on early functional brain development have been conducted on infants using EEG (e.g., Benasich et al., 2002; Benasich et al., 2006). Some authors have investigated preterm infants in order to get better insight into even earlier developmental stages (e.g., Cheour-Luhtanen et al., 1996; Tokioka, Pearce, & Crowell, 1995). But such infants often experience dramatic alterations in their environment and the determinants of preterm delivery usually indicate a poor state of health. Therefore, the study of preterm infants may not be representative for undisturbed development in utero.

Other studies have assessed early brain development in non-human primates (e.g. Kuboshima-Amemori & Sawaguchi, 2007; Schneider, & Coe, 1993; Schneider et al., 1998). Even though the anatomical similarities of human and primate cortices suggest parallels in their functional development, conclusions drawn from primates to humans have to be regarded as hypothetical. Some researchers have carried out EEG measurements on fetal sheep by applying electrodes directly on the unborn sheep's head (e.g., Szeto et al., 1994). However, such procedures are highly invasive and therefore not applicable to humans.

Non-invasive recordings of fetal electrocortical activity in utero would be in principle obtainable from the surface of the maternal abdomen. Body tissue, however, such as the mother's skin, muscles and water constitutes electrical resistance and weakens the initially small signals produced by fetal cortical activity even further and disturbs its spatial and temporal characteristics. Fetal electrocortical signals are, thus, not reliably detectable on the surface of the maternal abdomen. Advanced brain-imaging methods that are based on the measurement of magnetic fields rather than electrocortical potentials have an advantage in prenatal studies. Magnetic fields permeate through body tissue and bones with no significant distortion, and are therefore detectable from the surface of the mother's skin. With devices such as fMEG (e.g., Eswaran et al., 2005), the assessment of early functional brain development was improved. In addition, the detection of functional brain activation is also possible by functional magnetic resonance imaging (fMRI) (e.g., Fulford et al., 2004; Fulford et al., 2003; Moore et al., 2001; Stiles et al., 2003). Fetal MEG technology, however, is the only method that allows completely non-invasive recordings during the fetal life.

In 1985, Blum, Saling and Bauer successfully recorded the first fetal evoked fields with an adult MEG system. The first device built exclusively for fetal and neonatal recordings was installed at the University of Arkansas for Medical Sciences in 2000 (Preissl, Lowery, & Eswaran, 2004), a multi-channel system referred to as SARA (Squid Array for Reproductive Assessment). Figure 1 shows a pregnant woman seated on the SARA system for a fetal study. The mother is leaning forward with her abdomen resting on the 151-channel sensor array. For follow-up recordings on newborns, the mother's seat is replaced by a cradle attachment. Figure 2 depicts the setup for a neonatal study.

Fetal MEG studies

After installation in 2000, several pre- and neonatal MEG studies have been conducted with the SARA system. The initial studies investigated prenatal evoked fields in response to basic stimuli. Eswaran et al. (2002a) showed that auditory responses to pure tone stimuli were detectable in 80% of the fetuses. These cortical responses occurred at latencies around 200 ms after stimulus onset and have been shown to decline with advanced gestational age (GA). Shorter latencies are believed to indicate more mature brain responses (Holst et al., 2005;

Schleussner & Schneider, 2004). In addition to auditory stimulation, a light flash has been used to successfully elicit visual evoked fields in 80% of the participating fetuses (Eswaran et al., 2002b; Eswaran et al. 2004). Figure 3 shows the setup for the presentation of the light stimulus in a prenatal study. In subsequent studies, fetal spontaneous brain activity has been investigated (Preissl et al., 2004) and characteristic activity patterns, such as trace alternates have been described (Eswaran et al., 2007). Lowery et al. (2003) conducted fMEG with the SARA system. The authors successfully detected fetal heart signals and identified different segments of the fetal heart beat by means of fMEG (see Kisilvelski & Hains, 2009). More recently, Govindan et al. (2007) showed the fetal heart rate, recorded with fMEG, could differentiate between high- and low-risk conditions.

Since basic evoked responses to sensory activation as well as spontaneous brain signals have been successfully detected in the prenatal stage of life, the next step was the assessment of more advanced, higher-level processes that could be precursors for cognitive development. One of the most commonly used definitions for the term cognition was published by Neisser (1967):

“Cognition refers to all processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used ... cognition is involved in everything a human being might possibly do ...” (p. 4).

Thus, cognition stands for higher-level functions of the brain, such as working memory and speech development. As yet, early developmental precursors for cognitive functions are not well understood. This is mainly because they are not established until cortical maturation is in a more advanced stage. However, previous studies have used certain study paradigms to investigate basic cognitive processes. One of the original paradigms used to assess cognitive functioning is classical conditioning, which was first studied in fetuses by Ray (1932) and Spelt (1948). Another paradigm used to measure precursors for cognitive development is commonly referred to as habituation (see James, 2009, Kawai, 2009), which is considered to be one of the primary phenomena used to assess neurological integrity of the central nervous system in the fetus (Leader et al., 1984; Madison et al., 1986a). Sheridan et al. (2008) carried out a study using fMEG technology and reported response decrement in fetuses and neonates as early as 30 weeks GA.

Other approaches for studying higher-level cortical functions in fetuses and neonates include the investigation of the mismatch response (MMR) as well as rapid temporal processing (RTP). The MMR is the physiological correlate of a participant's ability to discriminate auditory information. In the so-called oddball paradigm, sequences of frequent standard stimuli are intermixed with rare deviant stimuli. A participant's ability to differentiate between these two stimuli is reflected in the so-called discriminative response, or MMR. This difference wave is obtained by subtracting the response to the standard from the one to the deviant stimulus (Näätänen, 2001; Näätänen, Gaillard, & Mäntysalo, 1978; Sams et al., 1985). Several studies have shown the MMR to be evident in preterm and fullterm neonates (Alho et al., 1990; Cheour, Leppänen, & Kraus, 2000; Cheour et al., 2002; Cheour-Luhtanen et al., 1996; Dehaene-Lambertz, & Baillet, 1998; Dehaene-Lambertz, & Dehaene, 1994; Huotilainen, et al., 2003; Kushnerenko et al., 2001; Tanaka et al., 2001). Huotilainen et al. (2005) investigated auditory discriminative skills in a prenatal study on fetuses and prematurely born infants. The authors successfully recorded fetal discriminative responses using MEG, indicating that the auditory change-detection is functional even prenatally. By means of fMEG, Draganova et al., (2005) found MMR in 60% of the fetuses between 33 and 36 weeks GA. And in a more recent study, it was detected in 66% of the fetuses, starting at 28 weeks GA (Draganova et al., 2007).

A more recent phenomenon to investigate higher-level processes is the processing of rapidly presented auditory stimuli. This rapid temporal processing (RTP) has been shown to be predictive of later speech performance (Benasich, & Tallal, 2002). It is believed to facilitate sufficient perception of sounds and to therefore constitute a precursor for the development of speech perception. RTP has been successfully recorded with fMEG technology. Sheridan et al. (submitted) showed that neonates successfully processed rapidly presented tones at about three weeks after delivery. Younger newborns and fetuses as well, showed only one response to the presented tone-pair, which indicates immature processing in these early developmental stages.

Current limitations and ongoing developments in the use of fetal MEG

The above summary constitutes an outline of studies conducted with fMEG over the last few years. Advances range from the conduction of basic stimulus-response studies and the recording of spontaneous brain activity to the investigation of higher cognitive functioning. This section provides insights into current limitations of fMEG technology and the latest attempts designed to address these challenges.

Artifacts

Even though body tissue does not affect the detection of fetal magnetic cortical fields, MEG recordings face a different kind of challenge. Environmental artifacts such as the terrestrial magnetic field (10^{-4} Tesla) or other environmental noise (10^{-7} Tesla), are much larger than the small magnetic fields generated by the fetal brain (10^{-12} – 10^{-15} Tesla). In order to detect cortical activity without distortion from such artifacts, MEG recordings are typically conducted in magnetically shielded rooms.

Source determination

A further challenge with MEG recordings is the source determination. MEG has a high temporal but a limited spatial resolution (Vrba et al., 2004). The spatial resolution is mainly determined by the signal-to-noise ratio, which is low for fetal recordings (McCubbin et al., 2008). Therefore, it can be difficult to determine the exact source of a recorded signal. In general, reconstruction of the signal sources, the so-called inverse problem, is possible only if an adequate model of the investigated structure is available. In the case of fetal recordings, this information is obtainable with the help of additional imaging systems, such as ultrasound (Gutierrez, Nehorai, & Preissl, 2005).

Monitoring of fetal position during recordings

Presently, among other things, ultrasound is used to determine fetal positioning directly before and after a recording. Consequently, changes in the fetal position can be monitored. However, it remains unclear when exactly the fetus changes position over the course of the recording. Nijhuis et al. (1982) categorized four different fetal states by combining fetal heart rate variability with body movements: quiet asleep (F1), active asleep (F2), quiet awake (F3) and active awake (F4). Every fMEG recording contains fetal heart rate acceleration and body movements. Therefore, these signals can be extracted and visually inspected for determination of fetal postural changes. The exact reconstruction of the fetal position, however, remains difficult. In order to address these challenges, one of our ongoing projects assesses the possibility of continuous ultrasound recordings during fMEG studies. The use of additional imaging methods might be helpful in validating the detected magnetic fields. The parallel use of both devices might also allow fetal cortical signals (direct evidence for responses) to be validated with the observation of fetal body movements (indirect indicator for responses).

To date, fMEG is the only non-invasive brain imaging method that allows direct assessment of prenatal cortical development. It is a promising approach, despite its limitations. Ongoing technological as well as methodological advancements might propel its applicability to become an important tool for the assessment of precursors to cognitive development and prenatal diagnostics.

An outline of future projects

Using brain imaging for prenatal studies is a fairly new approach that has only really emerged within the last decade. As a consequence, the needs and possibilities for future projects are extensive. An overview of suggestions based on previous investigations with fMEG is given below.

Clinical studies

So far, cognitive fMEG studies have been conducted mainly on low-risk participants. This is crucial in order to set a baseline standard and to investigate the usefulness of study paradigms. However, controlled clinical studies are essential to establish fMEG technology as a useful tool for prenatal diagnostics. Paradigms that have been successfully applied in previous cognitive studies could be used as a starting point in order to investigate high-risk groups. Assessing differences in cortical development between high- and low-risk populations might contribute to an early detection of deficits. This could trigger the derivation of intervention methods for mother and/or the unborn child and therefore prevent further deficits. One of the first studies that compared high-risk and low-risk groups has been conducted by Kiefer et al. (2008). They compared growth restricted fetuses with a group of fetuses whose weight was normal for their GA and found that growth restriction is associated with a delayed maturation of evoked responses.

Response decrement

Habituation has not only been shown to be a possible predictor of postpartum cognitive development (Gaultney, & Gingras, 2005; Madison, Madison, & Adubato, 1986b), but also to be an indicator for developmental delays. Maternal characteristics such as smoking (Leader, 1987), depression (Allister et al., 2001), diabetes (Doherty & Hepper, 2000) and stress (Sandman et al., 2003) have been shown to affect prenatal habituation in a negative way. Previous fetal habituation studies relied on outcome measures observable with ultrasound technology. Fetal body movements have been used in many studies as indirect measures for fetal responses. The fetuses were presented a tone or vibroacoustic stimulus and a response was noted if fetal body movements were observed. A decrease in fetal body movements with repeated stimulation is believed to show habituation (Doherty & Hepper 2000; Groome et al., 1993; Madison et al., 1986b; Van Heteren et al., 2001a; Van Heteren et al., 2001b). In addition to body movements, other studies observed the blink-startle reflex (Bellieni et al., 2005) and/or heart rate acceleration (Goldkrand & Litvack, 1991; Smith et al., 1991) by means of ultrasound. Both measures have been concluded to be indicators for cortical stimulus perception (Bellieni et al., 2005; Hepper, 1995; Morokuma et al., 2004). Thus, such fetal reactions are indirect observations of cortical responses. Since it is not clear whether fetal body movements are influenced by motor development in general, these studies need to be interpreted carefully (Hepper, 1997). With fMEG recordings, on the other hand, direct detection of cortical responses is possible. In case a paradigm does not fulfill all the criteria to distinguish habituation from receptor fatigue (Thompson & Spencer, 1966), it is more appropriate to call the phenomenon 'response decrement' (Kuhlman et al., 1988). This has been investigated in a previous fMEG study (Sheridan et al., 2008). To achieve the assessment of fetal response decrement with fMEG technology, the paradigm needs to be

adjusted accordingly. Subsequently, the differences in fetal response decrement between high- and low-risk groups could be investigated.

Interventions

Intervention methods could also be developed and their effects evaluated by means of fMEG technology. They could be targeted to benefit fetal development.

Adverse maternal conditions—Previous studies have revealed that maternal depression or anxiety during pregnancy can contribute to detrimental neonatal, fetal and perinatal outcomes (Alder et al., 2007). Increased maternal anxiety or stress during pregnancy has been shown to result in higher levels of cortisol, not only in maternal plasma, but also in the amniotic fluid (Glover et al., 2008; see Di Pietro, 2009, Van Den Bergh, 2009 this issue). Diego et al. (2006) found that prenatal cortisol significantly predicts fetal weight. Other authors state that elevated stress levels during pregnancy can lead to a wide variety of problems for the developing child. These include psychological symptoms as well as adverse general health, such as heart disease, eating disorders, personality disorders and a negative self-image (Dowling, 2007). In a recent meta-analysis, Beddoe and Lee (2008) evaluated the usefulness of prenatal mind-body interventions during pregnancy. The studies included measures of obstetrical outcomes, maternal mood and/or perceived stress. The interventions ranged from progressive muscle relaxation to yoga, meditation and multimodal psycho-education. The effectiveness of these treatments was shown by outcome measures such as "...higher birthweight, shorter length of labor, fewer instrument-assisted births, and reduced perceived stress and anxiety" (Beddoe & Lee, 2008, p. 1). Thus, future studies could apply such interventions for the expecting mothers and assess their effects on fetal wellbeing with fMEG technology. This might help to determine the effects different interventions have on the offspring's brain development during prenatal life and even allow determination of so-called critical periods for recovery. Such interventions could include maternal social support (especially by her partner) and relaxation techniques. As physiological indicators for fetal/infant well-being habituation, MMR and/or spontaneous brain activity could be used. In addition, delivery outcomes and birth records, such as length of labor, complications, infant head circumference and weight, etc. should be included. This might help to determine whether, for example, a habituation deficit was evident prenatally or whether complications during delivery could have caused such an adverse development. Furthermore, comparisons between experimental groups and placebo and non-treatment control groups would enable one to determine which treatment was the most beneficial for which group and during which developmental stage.

Speech development—Another area of interest is the prenatal development of speech. By incorporating established paradigms such as the recording of rapid temporal processing into fMEG studies, their usefulness for infants and fetuses at risk for delayed speech development could be assessed. Subsequently, studies could address prenatal differences between high- and low-risk groups. This could be a first step towards the prenatal detection of speech delays. Training programs for language impaired children (e.g., Fast ForWord) have been shown to successfully improve their deficits (Merzenich et al., 1996; Tallal et al., 1996). Such programs could be developed for the prenatal stage of life and potentially prevent further delays in a non-invasive way.

Spontaneous brain activity—A further area of application might be the use of prenatal spontaneous brain activity for clinical and intervention purposes. For example, fMEG technology could help in the detection of epileptic seizures in utero. This would require thorough analysis of continuously recorded data. With fMEG recordings, seating time is limited by maternal comfort or discomfort. To this point, the longest continuous fMEG

recordings conducted were 30 minutes in length (Sheridan et al., 2008). However, it might be possible to conduct recordings several times a day with adequate breaks in between. This might reveal the usefulness of fMEG technology as a screening tool for prenatal seizures. Every epileptic seizure could damage basic cortical functions and lead to severe irreversible handicaps. Prenatal diagnosis and adequate medication could help to prevent subsequent brain damage.

Preterm delivery—The combined investigation of different fetal signals by means of fMEG (fetal magnetocardiography, fetal state determination, evoked responses and spontaneous brain activity) might allow for a better insight into the general wellbeing of the unborn child. This, in turn, could facilitate decisions on whether an infant should be delivered before term. In some cases, this can be a crucial decision because preterm delivery brings with it severe risks for the infant. Even one more day in utero could improve the child's long-term development. But sometimes, preterm delivery is inevitable in order to save the offspring's life. For example, placental insufficiency could lead to fetal undersupply of essential nutrients, which in turn can lead to brain damage and prove to be fatal. Determining the right time to deliver such babies – not too early, but just in time to prevent harm – is still difficult due to the lack of adequate screening methods. Thus, additional insight into cognitive as well as physiological wellbeing during gestation could facilitate decisions that maximize the best possible outcome for the infant's health.

Familial risk—Another addition to future studies addressing populations at high familial risk for clinical conditions could be the inclusion of MEG or EEG recordings for family members as well. The carrier of the condition that puts the unborn at risk, as well as the family members with no such diagnosis, should be asked to participate in at least one measurement. For example, precursors for speech perception could be investigated via the recording of responses to rapidly presented auditory stimuli. The experimental group would consist of fetuses at high familial risk for dyslexia such that one or both biological parents and/or siblings have been diagnosed with this condition. Fetuses with no known risks or complications would constitute the control group. This might give better insights into how the clinical condition of concern is reflected in the recorded cortical responses. Moreover, it might reveal additional information regarding the severity of the condition. However, the appropriateness of a prenatal paradigm for adults is still to be determined. With increasing age, people typically develop coping strategies or learning mechanisms that could mask the detection of certain impairments (McArthur & Bishop, 2001). For a more detailed discussion on this issue, see Tallal and Gaab (2006). In such instances, a paradigm that detects prenatal delays might not be appropriate for studies with older infants or adults. Therefore, the application of an equivalent paradigm that is appropriate for the carrier's age group should be considered.

Longitudinal study design

The clinical studies proposed above should be longitudinal in design. This is important in order to determine the accuracy and specificity of the observed phenomena, such as precursors for cognitive development, spontaneous brain activity and speech development. The length and number of the follow-up intervals depend on the clinical condition of interest. For example, onset of depression can extend well into adulthood, whereas delays in speech development typically become evident when the child enters school.

Demographic data

Last but not least, future studies should include demographic data, such as parental socioeconomic status and age as well as maternal body mass index, nutrition evaluation, depression values, anxiety and stress. These data could be obtained via questionnaires,

interviews or clinical records. Insight into such data is fundamental in order to avoid confounding effects on fetal development due to differences in these areas. Clinical and control groups should be matched accordingly.

Conclusions

A better insight into early functional brain development, preferably during prenatal life might be an important step towards the prevention of maturational delays and deficits. Technological advances in brain imaging, such as fMEG, enable the direct investigation of the human brain in uterus. And even though this technology is still in its infancy and faces multi-faceted challenges, it is to date the only non-invasive method for prenatal brain imaging. Recent studies, however, have shown promising results and suggest that fMEG-based research is worth the effort to further advance this technology. The number of suggested future projects is quite extensive and their respective outcomes could be first steps towards prenatal diagnosis, prevention, and eventually intervention.

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Figure 1.

Figure 2.

Figure 3.