The BabySQUID® Neonatal Biomagnetometer

A new way to evaluate neurological impairments of pre-term and full-term infants.

Introduction

BabySQUID®[1] is a novel instrument for evaluating neurological impairments of preterm and term infants. There is an increasing need to develop this kind of non-invasive tool for monitoring functions of human infants because more and more neurologically impaired infants are surviving today. A portable, non-invasive MEG system, babySQUID® can be used next to the bedside of any neonatal care unit without a cumbersome magnetically shielded room. The system is the size and shape of an examination table with a headrest in the form of a pillow case. Unprecedented spatial resolution and sensitivity is provided by a closely spaced array of superconducting MEG sensors housed just below the outer surface of the headrest.

Figure 1. Realistic size dummy of infant shown on cart with sensor cradle.

1. Significance: Increase in number of neurologically impaired infants

The need for finding useful diagnostic techniques is becoming increasingly urgent today in assessing brain functions of infants. With advances in medicine, more and more pre- and full-term newborns survive even with neurological disabilities. The number of newborns with neurological impairments are quite large. The incidence of perinatal asphyxia is between 2-47/1000. The 4-26% of those who survive such an event will have severe neurological deficits. The incidence of hypoxemic-ischemic encephalopathy in term or near-term infants is between 3-8/1000. Handicapped survivors may be as high as 42% in such cases. The incidence of infants with neonatal seizures is between 2-9/1000. The incidence of handicaps in the survivors is between 11-50%. The incidence of moderate-to-severe cerebral palsy in infants who survive the neonatal period is about 1-3/1000. The prevalence of severe mental

[1] BabySQUID® is a registered trademark of Tristan Technologies, Inc.

retardation is between 3-4/1000 school-age children. The incidence of mild mental retardation is 23-30/1000 in the same population. The percentage of preterm infants with proven periventricular white matter injury is 45% for those with birth weight of less than 1500g, 38% for those with gestational age of less than 33 weeks and 24% for those with gestational age of less than 38 weeks. The percentage of asphyxiated term infants with some form of CNS injury is as high as 62%, a common form of the injury being the parasagittal cerebral injury. Infants with germinal matrix hemorrhage is 23-32% of all births delivered through the vaginal route when the delivery lasts more than 6 hours.

Survival of neurologically impaired neonates raises an important responsibility for the health care community in this country. The NIH has recognized the importance of developing new non-invasive methods to measure the integrity of brain functions in the fetuses and neonates. The NIH also calls for the development of non-invasive methods to monitor electrophysiological functions of the infants for rehabilitation research (NICHD), for the development of a non-invasive method for assessment and monitoring of cerebral functions in the neonates (NINDS), and for the development of an improved pediatric brain imaging method to evaluate alterations in brain physiology produced by drugs (NIMH).

In response to the severe challenge for improved perinatal care, the quality of care has increased dramatically over the past twenty years. For example, the number of preterm infants with intraventricular hemorrhage has decreased by a factor of three (45 to 15%) in this period. This is in part due to the increased awareness for the need to carefully monitor blood pressure, especially the cerebral perfusion pressure which determines the level of oxygen supply to the brain. The improvements are also due to advances in the non-invasive methods to monitor the intracranial pressure, blood flow, cerebral oxygenation and electrical activity of the brain as well as advances in anatomical and functional imaging methods such as ultrasound, CT and MRI.

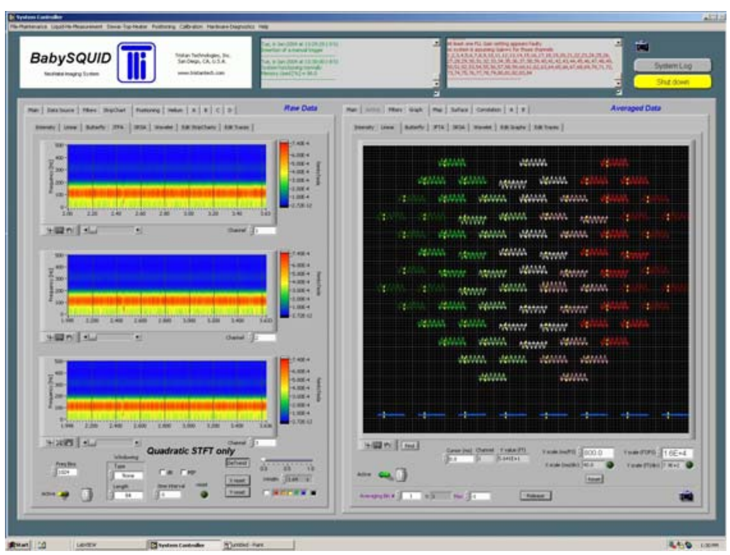

Figure 2: Data display. Time frequency plots (left) and sensor layout display (right)

2. Background

Currently, Electroencephalography (EEG) is being used to monitor electrical activity of the brain of newborns. The use of EEG for perinatal monitoring was started in the late 1950's. Its use is increasing in recent years due to its usefulness in staging the development of the nervous system, in detecting the presence of hypoxic and intracranial injuries, in providing the prognosis of recovery and in differential diagnosis of seizures from non-seizures in paroxysmal motor behavior. The staging is useful in detecting a delay or an arrest in brain development. The waveforms and spatial topography such as hemispheric asymmetry of spontaneous EEG are also useful for detecting the presence of a tumor or a necrotic area in the brain.

The babySQUID® will also have unprecedented spatial resolution and sensitivity. A closely spaced array of sensors will be located 2 mm below the outer surface of a headrest. The sensor noise will be less than **10 fT/√Hz** for the 6-mm diameter pickup coils. The short sensor distance combined with the improved sensor noise provide unprecedented sensitivity and spatial resolution for infant studies. babySQUID® is about one order of magnitude better in sensitivity than the conventional whole-head MEG sensors. Its sensitivity will be sufficiently high to measure not only spontaneous neuronal activity, but also evoked activity of the cortex of the newborns in real time without signal averaging. Its spatial resolution will be greater by a factor of about four in comparison to the existing whole-head MEG sensors. The babySQUID® takes advantage of the fact that the infant's scalp and skull are thin. This make it possible to measure MEG signals at a distance of only about 5-6 mm from the brain surface. This shorter distance will result in a very large increase in amplitude of MEG signals from the newborns, since the magnetic field is inversely proportional to the square of the distance. The shorter distance and a high density of detectors planned for the babySQUID® will also result in higher spatial resolution.

a. Portability, Capability to function in unshielded ordinary clinical setting

In order for MEG to become useful as a clinical electrophysiological monitoring technique, complementing EEG, a viable MEG instrument must be quite different from the conventional whole-head MEG instruments. To be competitive with the existing EEG instrumentation, a useful MEG instrument must be portable and functional in any ordinary clinical rooms without any special cumbersome electromagnetic shielding such as a large and expensive, special purpose magnetically shielded room being used today.

The babySQUID® is designed to be portable (Fig. 1). It is cart the size of an ordinary examination table with a mattress on top shaped as a cradle and a headrest. The infant can be placed on the cart with a minimum of preparation. The acquisition of brain signal should be very quick, since there is no need to attach electrodes as in the case of EEG. The measurements of MEG signals can start immediately after placing the infant in the cradle and the head in the headrest. Placing electrodes on the scalp is time consuming and often troublesome since the infant may easily resist. The infant may wake up if not sedated. This practical problem limits the number of electrodes to be used in any diagnosis, thereby severely limiting the inference that can be made regarding the nature of brain abnormality.

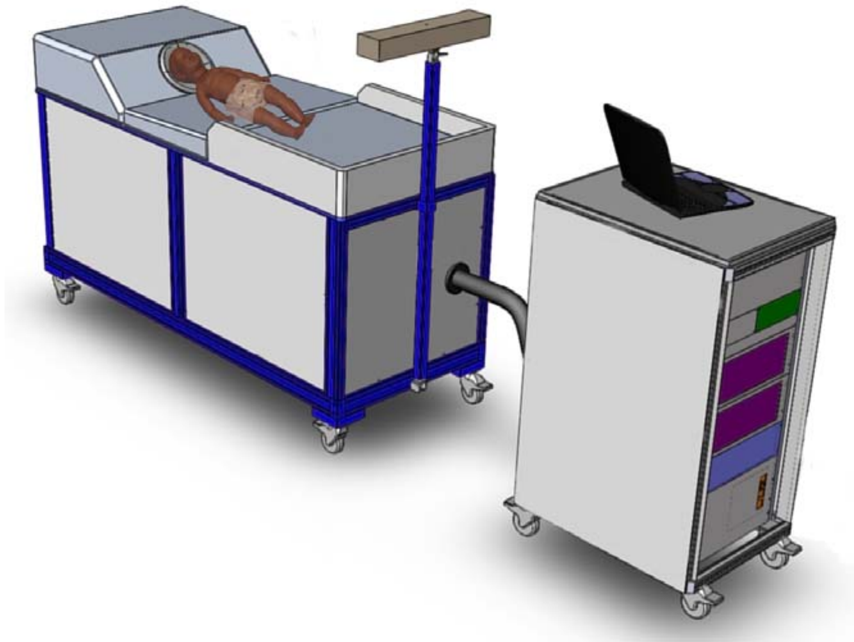

Figure 1. Rendering of cart with its cradle and patient positioning unit, connected to the data processing/electronics cart.

A clinically useful MEG instrument must be also able to function in any clinical room without magnetic shielding. An ideal system should function without interference from the ambient magnetic field, line frequency and rf noises. The babySQUID® will be equipped with SQUID control electronics with an effective dynamic range of 32 bits that resolve magnetic fields between 10 μT and <1 fT. It also has a fast slew rate that can follow magnetic field changes as fast as 10 μT/ms which is fast enough to follow changes in the line frequency noise without loosing the lock on the flux-locked feedback loop. This fast slew rate enables us to maintain the SQUIDs operating continuously in the midst of low frequency magnetic field changes and line frequency noises.

b. Sensitivity and spatial resolution.

The above features make the babySQUID® useful in an ordinary clinical setting. In addition to these features, an ideal MEG system must have a sufficiently high level of sensitivity and spatial resolution to provide new information. The babySQUID® does satisfy this essential requirement by taking advantage of several unique features of the head of infants. First, the skull and scalp of a newborn are quite thin (about 1.7-2.0 mm thick at birth). The scalp are also 1-2 mm thick in the first several months of age. Thus, MEG sensing coils can be placed as close as 5-6 mm from the cortical surface if an MEG system is built with a 2 mm distance between the outer surface of the pillowcase and the sensing coils. Thus, the measurement distance for a cortical source 3 mm below the surface of the brain would be 8 mm and 30 mm for the babySQUID® and a conventional whole-head MEG system. This implies that the signal may be more than 10 times stronger when measured with the babySQUID®. Therefore, it may be possible to monitor cortical activity in real time without signal averaging.

The sensing coils are tightly packed in the babySQUID® to maximize the spatial resolution. Its spatial resolution is about four times higher than that of the conventional whole-head MEG systems. All the coils are assembled below the pillowcase (headrest), so that there is no need to position each sensor precisely as it would be required by EEG if one were to carry out a quantitative EEG analysis. The high-density packing of the sensors in the babySQUID® will make it possible to delineate the abnormal cortical region such as the bilateral strip of cortical tissue along the anterior-posterior direction expected in the case of parasagittal cerebral injury typical of term infants who have suffered a temporary ischemia or anoxia.

c. Effects of fontanels, sutures, dynamically changing skull thickness and conductivity on MEG and EEG.

There are still several other considerations which strengthen our argument for the use of an MEG system for neonatal brain assessment. The babySQUID® is designed to be capable of measuring cortical activity as if its sensing coils are placed a few millimeters above the cortical surface without the intervening scalp and skull, that is as if the scalp and skull are removed and the sensors lie very close to the exposed cortical surface. The magnetic field above the head is essentially the same as the field present at the cortex except for an attenuation of signal amplitude and spread of the spatial distribution of the magnetic field merely due to the slightly larger distance of measurement. This means that an MEG signal above the scalp should be quite similar in information content to the signal just above the cortex. This capability is based on the fact that MEG signals are transparent to the scalp and skull, unlike EEG, even in the presence of skull defects created by the fontanels and sutures. It has been argued that the skull is "transparent" to MEG. This conclusion is supported by simulations studies, by measurements of MEG signals outside the head of a cadaver with a hole in the skull and by a careful comparison of the topography of the somatic evoked magnetic fields before and after a hole is introduced in the skull in an *in-vivo* piglet study.

In comparison, EEG signals are significantly distorted by skull defects that are unique to the human neonates. The fontanels are present at the midline junctions of the bregma and lambda. The skull is not present within the fontanels; instead the brain is protected by a thick dura filling the windows. They are small during the delivery, but become larger in the first several months, up to about 3-4 cm along the coronal suture, and then eventually they close. The anterior fontanel may be large enough to admit an adult's thumb. The unclosed sutures can be quite wide near the fontanels. The mean width of the coronal and lambdoidal sutures at their midpositions is 3-4 mm for infants between 0 and 60 days after birth. In abnormal cases such as hydrocephalous, the sutures may change its width with the development of the disease and become as wide as 10 mm or more. Moreover, the sutures do not close for many years. The earliest age for complete closing of the sagittal and coronal sutures are 6 and 11 years, respectively. Thus, EEG signals may be profoundly affected by the fontanels and sutures since they create paths of low conductivity for the volume currents in the brain and funnels the currents through these openings in the skull.

Some might argue that the skull defects are not a disadvantage for EEG, but on the contrary, are an advantage. Although the breech provided by fontanels improves the sensitivity of the EEG in diagnosing seizures, for example, those skull defects can also obscure the asymmetry of the signals, especially when the generator is deep, making it difficult to determine the epileptiform tissue when it can not be easily visualized by CT or MRI.

The conductivity of the skull is also expected to change with age and across individuals. The skull thickness increases rapidly within the first three years of age from about 2 mm at birth for term newborns to about 5 mm at 3 years of age for boys, then the growth slows down. The skull thickness reaches a mean of 8.3 mm and 9.5 mm for 25 year-old women and men, respectively. These changes in skull thickness are associated with thickening of the dense, poorly-conducting inner and outer bony tables of the skull relative to the spongy middle layer containing blood and with a decrease in effective conductivity of the skull with age. Also important is the variability in skull thickness. The 10th-90th percentiles are 2.4-4.6 mm and 3.0-4.9 mm for 1-1/2 year old girls and boys. That is, the range is 50-60% of the means. At the age of 25, the 10th-90th percentile range is 40-50% of the means for women and men.

d. Differential attenuation of EEG signals from shallow and deep active tissues.

EEG signals are distorted not only by skull defects, but also by the brain-skull and scalp-air boundaries of EEG waveforms. Goff et al. (1978) have shown that the attenuation of scalp potential is highest for focal cortical sources and lower for extended cortical and subcortical sources. The attenuation of potential may be as much as 50 times greater for a 6^o cortical source compared to a focal source at the center of the brain and as much as 100 times greater for such a shallow focal source compared to extended sources subtending a solid angle between 72^o and 180^o regardless of depth. This large variation, depending on source depth and extent, implies that the EEG signals on the scalp would be most likely different or deformed in comparison to the signals on the cortex. The components due to focal cortical sources should be small relative to deeper sources and thus some of the cortical components may be difficult to be identified or distinguished, being overshadowed by signals from extended cortical or deeper subcortical sources.

3. Summary

The babySQUID® will become a very useful non-invasive clinical tool for monitoring physiological functions of pre-term and full-term neonates born with possible neurological disorders. Advances in perinatal care are making this non-invasive technology more and more critical. The babySQUID® and its succeeding generations of instruments will easily and quickly assess possible pathophysiology in the neonates. It will enable routine screening of all infants leaving any neonatal unit, and should become the screening device of choice for all neonates suspected of having ante- or intrapartem trauma or hypoxic/ischemic episodes.