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Design of a Light Stimulator for Fetal and Neonatal Magnetoencephalography

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Abstract

The design, safety analysis, and performance of a fetal visual stimulation system suitable for fetal and neonatal magnetoencephalography studies are presented. The issue of fetal, neonatal, and maternal safety is considered and the maximum permissible exposure is computed for the maternal skin and the adult eye. The risk for neonatal eye exposure is examined. It is demonstrated that the fetus, neonate, and mother are not at risk.

Keywords

fetus; light stimulation; magnetoencephalography; neonatal eye exposure

1. Introduction

The environment of the human fetus is well insulated from outside influences. Even so, the fetus responds to light stimuli applied trans-abdominally. As early as 1975, researchers reported fetal movement in response to light (Polishak *et al.*, 1975). Subsequent research demonstrated that a photographic strobe light can induce fetal state change (Kiuchi *et al.*, 2000) and that halogen light stimulation prompts a more rapid reactive fetal non-stress test result (Caridi *et al.*, 2004). Four commercially available light sources, halogen bulb, krypton bulb, photographic flash, and pen light, were compared to determine which would be best for fetal biophysical testing (Rayburn *et al.*, 2004). Fetal heart rate changes were observed after stimulus with a photographic flash and amnioscopy light (Peleg and Goldman, 1980) while some researchers report little or no response to photographic strobes (Boos *et al.* 1987). These studies utilized available broad spectrum light sources and ultrasound systems to observe changes in fetal heart rate or increases in body movements or eye movements. None of the above studies provide a detailed safety analysis for maternal exposure.

Using the superconducting quantum interference device (SQUID) technology, we reported the feasibility of performing magnetoencephalographic (MEG) recordings of visual evoked brain activity in the human fetus (Eswaran *et al.*, 2002). Since then we have improved the stimulus design and have recently reported fetal visual evoked response measurements with improved success rates (Eswaran *et al.* 2004, Eswaran *et al.* 2005, McCubbin *et al.* 2007). In this paper, we describe the design considerations, safety analysis, and the technical and practical problems

encountered in the development of a light stimulator system suitable for fetal MEG studies. Although our primary interest is the study of the fetal cerebral cortex, the same stimulus paradigm is applied to the neonate (premature and term) so that the fetal visual evoked response can be better understood. To that end, the safety analysis includes an estimate of the neonatal exposure.

2. Stimulator Design

2.1 Electromagnetic Considerations

SQUID systems suitable for MEG studies respond to magnetic fields that are on the order of a few femtotesla (fT) and are very sensitive to ambient electromagnetic fields (Vrba and Robinson, 2002). Practical MEG systems are typically housed in a magnetically shielded room. While some electronic equipment can be operated within the shielded room, commercial high intensity light sources can not be operated concurrently with the MEG data acquisition. These light sources utilize high electrical currents to produce light and the electrical currents in turn produce interfering magnetic fields much larger in amplitude than the fetal brain response. The only practical solution is to place the light source outside the shielded room and then use a light 'pipe' to deliver the light to the patient. The strength of the interfering magnetic field is then reduced by both the shielding and separation between source and SQUID sensors.

2.2 Light Guide

The original design used a long liquid core light guide fitted with a fiber optic dispersing head (Eswaran *et al.*, 2002). Although this system delivered sufficient light across the maternal tissue in order to evoke a fetal response, it was stiff and difficult to place and the fiber dispersing head did not transfer light efficiently to the maternal tissue. The second generation system reported on here utilizes a 340 cm long plastic fiber bundle fitted with a 5.1 cm by 8.9 cm by 0.56 cm woven illumination pad. The fiber optic system is a modified plastic fiber "back illumination" lighting component manufactured by StockerYale company of Salem, NH. The thin, flexible illumination pad may be easily placed between the patient and SQUID system and is sufficiently comfortable to allow 30 minute data collection paradigms. The plastic fiber construction is inherently non-magnetic and does not interfere with the SQUID recordings. The input end of the fiber bundle was divided into four smaller bundles of equal diameter to facilitate optical coupling to the light source described in the next section. Figure 1 is a photograph of the illumination pad and Figure 2 is a photograph of the illumination pad placed in position for a fetal study.

2.3 Light Source

The duration of the light pulse for fetal studies was a major consideration in the selection of the light source. Flash durations of 33ms, 100ms, and 500ms have been used for fetal visual evoked response (Eswaran *et al.* 2004). The rationale for longer flashes is to account for the lower degree of myelination of the cortex in the early gestation fetuses. A high flux red LED illuminator, model OTLH-0040-RD manufactured by Opto Technology, Inc, Wheeling, IL, was selected as the light source for the stimulator system. These modules have 50 high output LEDs mounted in a 0.71 cm by 0.84 cm area which in turn is mounted in a standard TO-66 electronic package. The LEDs are protected by a transparent glass window. One module can continuously produce 110 mW @ 630 nm. The most effective method found for launching the light from the LED module into the fiber was to place the fiber bundle directly in contact with the optical window. To maximize transmitted power, the fiber bundle was subdivided into four equal diameter bundles of 0.64 cm diameter, each fitted to an LED module, so that the area of a single LED array was larger than the numerical aperture of the fiber bundle, thus filling its input field with high intensity LEDs. The four LED modules were mounted onto a 1.27 cm

(0.5 inch) thick aluminum plate fitted with a cooling fan. Each of the four fiber bundles were also secured to the aluminum plate, each positioned against a corresponding LED module.

2.4 Electronics

Each LED module is powered by a separate voltage controlled current source capable of supplying 0 to 1.5 amperes to the LED module. The control inputs of all four currents sources were connected to the output of a single 5-bit digital to analog converter (DAC) constructed using an R-2R ladder circuit. The digital input to the DAC is provided by a logic port of a PIC18F442 8-bit embedded microcontroller. The light output is controlled in the software. The microcontroller is programmed to monitor a single logic input pin and to use the logic state of that input as a command to activate or deactivate the LEDs. A logic 'true' gives activation at full power and a logic 'false' gives deactivation with a delay of only a few microseconds. An LED current monitor output is provided so that the actual LED activation may be recorded during experiments. Figure 3 is a photograph of the interior of the electronics cabinet. The LED modules are mounted on an aluminum plate in the upper left of the photograph.

3 Safety Analysis

For the mother and experimenters, we compute the maximum permissible exposure (MPE) as set forth in the ANSI Z136.1-2007 standards for the light stimulus system described above. The ANSI standards were derived by committees composed of experts in ophthalmic biophysics and occupational health who incorporated all available animal and human injury data and an understanding of light/tissue interaction to develop criteria for the safe use of lasers (Sloney *et al.*, 2002; Sloney 1995; ANSI 2007; McKinlay and Harlen 1984). The MPE is an exposure level that is deemed to be well below the threshold of tissue damage for all individuals. However, subthreshold exposures may cause biochemical perturbations which may alter visual acuity for some time.

In our safety analysis, we assume continuous exposure. This assumption addresses two practical concerns. First, should there be an electronic component or software failure so that the LEDs are accidentally activated continuously the resulting exposure will be within safe limits. This makes the stimulator inherently safe and eliminates the need for inclusion of failsafe circuitry in the design. Second, typical fetal research paradigms require light flashes that are on the order of one second duration to induce the maximum fetal cortical response. For simplicity and safety, we set the MPE base on continuous exposure. If the continuous MPE criterion is met, any pulse sequence can be implemented without having to perform a new hazard evaluation.

It must be noted that in the cited literature, photometric units are often employed to quantify the output of the devices used for fetal stimulation. Radiometric measurements must be used for safety analysis since photometric meters are weighted by the photonic eye response and are therefore blind to ultraviolet and infrared light. Because the spectral output of the LED modules falls between 600 nm and 700 nm, there is no photochemical hazard for the eye or skin and only thermal effects need be considered. The computation of the MPE(s) in the following subsections are valid only if the following criteria are met: 1) spectral output falls between 600 nm and 700 nm, 2) the radiant flux density of the illumination pad is always below the constant exposure MPE when activated, and 3) the active area of the illumination pad is equal to or less than 100 cm².

3.1 Skin Exposure

For exposures up to $3 \cdot 10^4$ sec (8.33 hours) the skin MPE irradiance is 0.20 W/cm², subject to an adjustment if the area of exposure is greater than 100 cm². Since the illumination pad has

an area of 45.4 cm², no adjustment is needed. Because the illumination pad is placed in direct contact with the maternal skin, the radiant emittance of the illumination pad, Θ_{pad} in W/cm², must always be less than the MPE for the skin. The limiting safe value of Θ_{pad} for the maternal skin is simply:

$$\Theta_{\text{pad}} = 0.20 \text{ W/cm}^2. \quad (1)$$

3.2 Adult Eye Exposure

The computation of the MPE for the adult eye is dependent upon the angular extent of the light source (α). A light source with an angular subtense below 1.5 mrad (α_{min}) is considered a point source; otherwise it is an extended source. Further, α_{max} is the angular subtense of an extended source beyond which additional subtense does not contribute to the hazard and need not be considered. For retinal thermal effects, $\alpha_{\text{max}} = 100$ mrad (ANSI 2007, p5). When a light source subtends any visual angle, the maximum permissible irradiance for a point source is adjusted by a correction factor, C_e . The factor C_e is defined below over three ranges:

$$\begin{aligned} C_e &= 1 && \text{for } \alpha < \alpha_{\text{min}} \\ C_e &= \alpha / \alpha_{\text{min}} && \text{for } \alpha_{\text{min}} \leq \alpha \leq \alpha_{\text{max}} \\ C_e &= \alpha^2 / (\alpha_{\text{min}} \alpha_{\text{max}}) && \text{for } \alpha > \alpha_{\text{max}}. \end{aligned} \quad (2)$$

A second dimensionless parameter, T_2 , is also determined by the angular extent of the source.

$$\begin{aligned} T_2 &= 10 && \text{for } \alpha < 1.5 \text{ mrad} \\ T_2 &= 10 \cdot 10^{(\alpha - 1.5)/98.5} && \text{for } 1.5 \leq \alpha \leq 100 \text{ mrad} \\ T_2 &= 100 && \text{for } \alpha > 100. \end{aligned} \quad (3)$$

In terms of the illumination pad radiance, L_p (W/sr-cm²), the MPE for a continuous radiant exposure to the adult eye is given by (ANSI 2007, p75–76, p174–175):

$$L_p = 1.8 \cdot C_e \cdot T_2^{-0.25} \cdot 10^{-3} / \Omega \text{ W/sr-cm}^2, \quad (4)$$

where Ω is the solid angle of the source as seen from the observer's eye. To find the maximum allowable radiant emittance of the illumination pad, Θ_{pad} , for eye exposure, we assume that the cosine law (Lambertian surface) holds. Thus,

$$\Theta_{\text{pad}} = \pi \cdot L_p \text{ W/cm}^2, \quad (5)$$

and then the MPE for the eye, expressed in terms of the radiant emittance of the illumination pad is simply:

$$\Theta_{\text{pad}} = 1.8 \cdot \pi \cdot C_e \cdot T_2^{-0.25} \cdot 10^{-3} / \Omega \text{ W/cm}^2 \quad (6)$$

Evaluating (6) for the case worst case MPE ($\alpha = 100$ mrad), we find that the limiting safe value of Θ_{pad} for an eye exposure is 15 (W/cm²).

3.3 Neonatal Exposure

Experts generally agree that the adult MPE should not be applied to the neonate or infant (McKinlay and Harlen 1984). However, the thermal mechanisms of eye damage from light exposure have been studied for many years (Sloney *et al.*, 2002; Sloney 1995; Welch 1984; Takata *et al.* 1974). Our approach is to use the MPE for the normal adult eye as a starting point and adjust the MPE as dictated by the physiology of the neonatal eye.

The MPE computations for the adult eye assume that visible eye exposures activate protective reflexes: the blink reflex and pupil constriction so that the full exposure to continuous sources is limited to about 0.15 to 0.25 seconds. In addition, such exposures usually elicit instinctive head turning as an aversion response adding further protection. In contrast, the pupillary reflex is absent in all neonates of less than 30 weeks gestational age, however, the blink reflex is present in neonates of 26 weeks or more (Robinson and Fielder 1990). For cases where the pupil is fully dilated by means of drugs and the eye is completely immobilized so that there is no blink reflex or aversion reflex, the ANSI 2007 standard provides the following adjustment factor:

$$C_p = 1/10^{0.0074(700-\lambda)} \quad (7)$$

For 630nm light, $C_p = 0.3$ so that the MPE should be reduced by about 1/3. Considering that the neonatal natural defensive response may not be fully developed and that the neonatal experiments are carried out in a dimly lighted room, we apply C_p to the adult MPE.

The optical geometry of the neonatal eye and transmissivity of the ocular media varies with gestational age (Mactier *et al.* 2008) and may differ significantly from the eye of an adult. The retinal irradiance, E_R , in W/cm^2 can be expressed in terms of the source radiance

$$E_R = A_p \cdot \tau_\lambda \cdot L_p / d^2 \quad W/cm^2, \quad (8)$$

where, A_p is the area of the pupil (cm^2), τ_λ is the transmissivity of the ocular medium (dimensionless), L_p is the radiance of source ($W/cm^2\text{-sr}$), and d is the posterior nodal distance (image distance in cm). If A_p , τ_λ , and d are known for both the neonate and adult, then the relative irradiance at the retina may be computed. Though τ_λ changes significantly with age at short wavelengths, it is almost constant with age at 630 nm (van de Kraats and van Norren 2007). However, A_p/d^2 was highly variable in the pre-term neonate, ranging from 0.15 to 0.53 during the preterm period and ranging from 0.27 to 0.6 at 50 postmenstrual weeks. By comparison, the full term neonate and adult A_p/d^2 ratio was just less than 0.2 with much less variation (Mactier *et al.* 2008). Taking the worst case measurement of Mactier *et al.*, we apply another safety factor of 0.33 (which is $.2/.6$) to allow for the case of the preterm neonate. This number is rather conservative since in this study the pupils were dilated to their maximum extent by means of drugs.

In the spectral range between 600nm and 700nm, the dominant light absorber in the human eye is melanin. The human retinal pigment epithelium (RPE) is about 12 microns thick and contains a thin layer of densely packed melanin granules. The vascular choroid layer lies below the RPE and contains some sparsely spaced melanin granules (Welch 1984). The melanin in the RPE absorbs the majority of the light thereby heating the immediate tissue. Experience indicates that the most susceptible area for damage is at the macula which has a thick RPE and thus absorbs more light energy (Barkana and Belkin 2000). Weiter *et al.* (1986) studied the melanin concentration in the RPE and choroid in 38 eyes varying in age between 2 weeks and

90 years. Their findings indicate that an individual's melanin concentration is fixed during fetal development and declines only slightly over one's life. The melanin concentration of the neonate is then similar to that of the adult so that the rate at which heat energy is deposited is similar.

For continuous exposure, the heat flowing out of the RPE and choroid must come into equilibrium with the heat being deposited. On one side, the RPE is in contact with the vitreous humor which acts as a large heat sink. On the other side, the RPE is in contact with the choroid which also conducts heat away from the RPE. But unlike the vitreous humor, the choroid is rich in blood flow. The nasal retina is vascularised at about eight months gestation while the temporal retina is not fully vascularised until just after term (Fielder *et al.* 1988). The neonatal blood flow to the choroid (30 mL/min/g) is equal to or greater than that of the adult (Hardy *et al.* 1997). The only difference between the adult and neonate heat flow considerations is that the neonatal eye may not have a fully developed vascular system on the temporal retina. In the finite difference thermal damage model developed by Takata *et al.*, the effects of blood flow were included, but it was limited only to the choriocapillaries, yet the model gave results comparable to experimental data (Takata *et al.* 1974). In the numerical model developed by Clarke *et al.* (1969), the RPE and choroid were simply modeled by assuming that these tissues had the thermal characteristics of water and no heat transport due to blood flow was assumed. Since the results of the simulations with and without the inclusion of blood flow were similar, and in view of the high perfusion in the choroid and the identical heat dissipating capacity of the vitreous humor, we choose to make no adjustment to the MPE due to heat flow considerations.

After applying the factors stated above, we estimate that the MPE for the pre-mature neonatal eye should be about (1/10) that of the MPE for the adult eye. The lowered MPE for the neonate presumes no protective behavior such as blinking or eye aversion, assumes the eye is maximally dilated, and takes a conservative position for the A_p/d^2 ratio. Because of the lack of experimental data, we take the modified adult MPE to be a guide rather than a working value for the maximum neonatal eye exposure.

3.3 Fetal Exposure

In the analysis presented in the preceding sections, light reaches the respective tissue by traveling through transparent, non-scattering media (air or tissues of the eye). In contrast, light that penetrates into the uterine cavity must traverse one or more centimeters of tissue undergoing scattering and absorption. Such diffuse light can not be focused by the fetal eye. To demonstrate safety, one must show that the fetal irradiance (W/cm^2) is at a safe level. However, there are no standards for fetal exposures and we must make a rational estimate. First, the MPE for maternal skin is $0.2 \text{ W}/\text{cm}^2$. Further, the adult skin is assumed to be exposed to air, a poor thermal conductor, whereas the fetal skin is in contact with amniotic fluid, an excellent thermal conductor. Second, we can compute the maximum permissible retinal irradiance of the neonate by using (8), (6), (5), and applying the correction factor developed for the neonate eye. This value is $0.29 \text{ W}/\text{cm}^2$, which is comparable to the acceptable skin exposure. It would be reasonable to argue that the fetus could be directly exposed to $0.2 \text{ W}/\text{cm}^2$ without harm, but this argument isn't necessary. Direct measurements made during routine laparoscopy examination show that it is possible to transmit light through 1 to 4 cm thick abdominal wall but with attenuations ranging from 3 to 5 orders of magnitude (Bearden *et al.* 2001), with the uterus providing even more attenuation. Therefore, the fetal irradiance exposure will be many orders of magnitude below the maternal exposure. We argue that if the system is safe for the mother, then it will necessarily be safe for the fetus.

4 Results and Discussion

The radiant emittance (W/cm^2) of the illumination pad was measured by placing the sensing element of a laser power meter (Thor Labs model 520MM) in direct contact with the illumination pad while the pad was activated. The total optical power delivered to the 0.787 cm diameter sensor was $3.8 \cdot 10^{-4}$ W which gives a measured radiant emittance of $7.8 \cdot 10^{-4}$ W/cm^2 and the total radiant flux delivered to the patient is 0.035 W. In the safety analysis, the MPE for the mother's skin was found to be the most restrictive case, requiring that the illumination pad radiant emittance be less than $0.2 \text{ W}/\text{cm}^2$ for safe operation in the intended application. The measured illumination pad emittance of $7.8 \cdot 10^{-4}$ W/cm^2 is only 1/256 of the MPE for adult skin with higher safety margins for eye exposures.

Evaluation of (6) as a function of distance indicates that the eye hazard is constant for viewing distances of 51 cm or less, reducing at distances greater than 51 cm so that exact placement of the illumination pad for neonatal studies is not critical from a safety standpoint. Using (5), (8), and the measured radiant emittance of $7.8 \cdot 10^{-4}$ W/cm^2 , the nominal retinal exposure of the neonate from the illumination pad can be computed. Assuming worst case A_p/d^2 of 0.6 for a preterm neonate, the actual retinal irradiance from the illumination pad is at most $1.49 \cdot 10^{-4}$ W/cm^2 , which is comparable to the typical retinal exposure from room lighting in a neonatal intensive care unit (Fielder and Moseley 2000, p 292).

In the neonatal experiments, the illumination pad is placed at a distance of approximately 50 cm from the neonate. Using (5) and (6) to get L_p , the radiant power falling on 1.0 cm^2 of neonatal skin may be computed by $(L_p \cdot \Omega_1 \cdot A_s)$, where Ω_1 is the solid angle encompassing 1.0 cm^2 at a distance of 50 cm and A_s is the area of the illumination pad. The neonatal skin exposure is typically 1/173 of the maternal skin exposure for the same illumination pad radiant emittance.

Separate from the safety analysis is the necessity to estimate the effectiveness of the light stimulator for fetal visual stimulation. The human eye can detect on the order of 100 photons/sec @ 507 nm entering the pupil (Hecht *et al.* 1942, Baylor *et al.* 1979). Correcting for the lower sensitivity of the eye to longer wavelengths, approximately $3.7 \cdot 10^4$ photons/sec @ 630 nm are required for perception. The illumination pad emits $1.1 \cdot 10^{17}$ photons/sec resulting in just over 12 orders of magnitude more photons being emitted than needed to cause an evoked response. Three to five orders of magnitude are absorbed while penetrating the abdomen and possibly four orders of magnitude (but likely less) are absorbed penetrating the uterus (Bearden *et al.*). Because of diffusion, the remaining photons will be spread over some area larger than the illumination pad and would have to penetrate the fetal eyelid if closed (Fielder and Moseley 2000). The latter two factors are estimated at three and one order of magnitude reduction, respectively. It is easy to see that inter subject variability could result in several orders of magnitude difference in the level of light reaching the fetal eye and in the worst cases the light reaching the fetus would be insufficient to elicit an evoked response. In practice, the success rate for acquiring a visual evoked response from the fetus varies between 63% and 89%, depending upon the stimulus protocol, gestational age, and population studied (Eswaran *et al.* 2004, Eswaran *et al.* 2005, McCubbin *et al.* 2007).

5 Conclusion

The design and development of a visual stimulation system suitable for fetal and neonatal MEG experimentation is presented. A safety analysis of the system indicates that the exposure from the system is well below the MPE for mother, neonate, and fetus. In looking to the future, it is reasonable to consider developing a light stimulation device of considerably higher light output to improve the success rate of fetal evoked responses. The limiting factor is the MPE for

maternal skin allowing the photon flux density delivered to the fetal light environment to be safely increased by about two orders of magnitude.

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Figure 1.
The woven fiber illumination pad and fiber optic cable.

Figure 2.
The illumination pad placed in position for a fetal study.

Figure 3.
Interior of the electronics cabinet. The LED modules are mounted on an aluminum plate in the upper left of the photograph.