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Fetal Brain Activity in Response to a Visual Stimulus

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Abstract: Previous studies have demonstrated the use of functional magnetic resonance imaging (fMRI) to assess fetal brain activity. To extend these studies, a fetal fMRI experiment using a visual stimulus has been performed at 0.5 T. This used a block fMRI paradigm with a bright, constant-intensity light source being shone at the maternal abdomen for 8 sec followed by 16 sec of darkness. This was repeated typically 40 times on nine subjects all of whom were greater than 36 weeks gestational age. Of these, one could not be analysed due to motion, three did not show significant activation, and five showed significant activation ($P < 0.0085$). In all cases, activation was localised within the frontal cortex. Exact localisation was difficult but this may correspond to the frontal eye fields and dorsolateral prefontal cortex. In no cases was significant activation present within the occipital region as would have been expected and was observed in 2/8 adult subjects. *Hum. Brain Mapp. 20:239–245, 2003.* © 2003 Wiley-Liss, Inc.

Key words: fMRI; fetal brain activity; visual stimulus; occipital and frontal regions

INTRODUCTION

Until recently, most magnetic resonance imaging (MRI) studies of the fetal brain have concentrated on structure rather than function [Levine et al., 1999; Levine and Barnes, 1999; Resta et al., 1998; Sonigo et al., 1998; Vimercati et al., 1999]. These have provided important information on neuro-anatomical development but limited information regarding the functional development of the fetal brain. The evaluation of fetal brain function should allow the characterisation of normal functional neurodevelopment and its disturbance in various pathologies. Until recently, the only methods available to assess fetal brain function in utero have been the indirect study of fetal heart rate responses [Vindla et al., 1997] and magnetoencephalography (MEG) [Blum et al., 1985; Eswaran et al., 2002]. Functional magnetic resonance imaging (fMRI) has become a well-established method for determining the patterns of brain activation following stimulus presentation in the adult. Preliminary work has also shown that fMRI can be used in the fetus, in studies to determine brain activation following the presentation of an auditory stimulus [Hykin et al., 1999; Moore et al., 2001]. However, auditory stimuli pose a particular problem for fetal fMRI, since it is difficult to ensure that the

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sound of the stimulus is louder than the noise from the scanner for the fetus.

The aim of the present study was to assess the fetal fMRI response to a light stimulus. This should provide additional information about neuro-development, particularly when compared to an auditory stimulus. It will also complement previous work on the response of the fetus and neonate to visual stimuli studying development [Johnson, 2002], behaviour (via fetal heart rate) [Kiuchi et al., 2000], and more recently MEG [Eswaran et al., 2002].

MATERIALS AND METHODS

Subjects

Twelve pregnant subjects at term (>36 weeks gestation) gave written consent to participate in the study, which had been approved by the local Ethics Committee. All the pregnancies were normal and singleton and the subjects were recruited following their routine attendance at antenatal clinics. Scanning was undertaken at this late stage of pregnancy as fetal motion is reduced once the fetal head is engaged within the maternal pelvis. To compare the sensitivity of the adult response to visual activation obtained using the same sub-optimal fMRI imaging parameters (i.e., with limited head restraint, in a whole body coil and at low field), eight adult subjects were also scanned.

Stimulus Design

The light stimulus was provided by a red LED cluster (Kingbright 50 LED cluster, 2.5 W, illuminated area 20 cm^2). To avoid magnetic field distortions due to current switching and susceptibility effects, the light was transmitted via a 30-cm light guide made from a cardboard tube lined with non-conducting aluminised plastic, resulting in a light intensity of 1,100–1,200 Lux at the maternal abdomen as measured with a hand-held light meter (RS 180-7133, 20 cm^2 sensitive detection area). It was established in phantom experiments that the light guide and the light source neither affected the images obtained nor created artefactual fMRI signals. During the "On" part of the cycle the light source had to be on continually, rather than being flashed, due to the difficulty in producing a high-intensity, flashing light source, capable of working within the magnet.

In order to confirm that the light source was potentially capable of penetrating the maternal abdomen, its intensity was compared to that of an endoscope (Olympus model Q30) light source. It is known that the endoscope light source is of sufficient intensity to penetrate the adult stomach and abdominal wall for a large proportion of the population undergoing endoscopies (a population that is generally more obese than the pregnant population) so that it is detected externally. For both light sources, the attenuation through tissue was determined by shining the light through various thicknesses of uncooked chicken breast (including skin) and recording the resulting light intensity (see Fig. 1). It should be noted that the attenuation response of the endoscope was greater due to the wide range of wavelengths present in it compared with the predominantly red LED source. It was found that an average intensity of 5 Lux over the light sensitive area of the detector after passing through chicken was readily detectable by the human adult eye and by examination of the attenuation responses (Fig. 1) it was determined that such intensities were reached following transit through 39 and 35 mm of chicken breast for the endoscope and LED light sources respectively. Such thicknesses are similar to those found for the abdominal wall at term and, therefore, it was assumed that the LED source was of sufficient intensity to be detected inside the uterus.

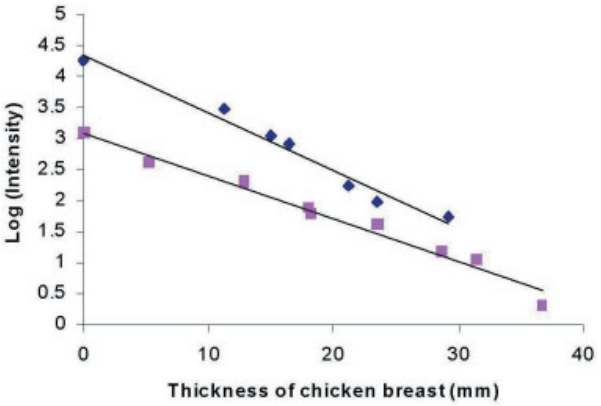

Figure 1.
Attenuation of intensity of endoscope and LED light sources with varying thickness of chicken breast. Diamonds, endoscope; squares, LED cluster.

Before performing MRI, an ultrasound scan was carried out to determine the orientation of the fetus. Only in those cases where the fetal head was approximately facing the front was the subject included within the study and light stimulation undertaken. The light guide was positioned so that it overlaid the fetal eyes although in practice the light would be greatly scattered in the tissue, giving a diffuse illumination inside the uterus rather than a spot source.

fMRI Paradigm

All imaging was performed on a 0.5 T purpose built scanner at the University of Nottingham. Imaging was performed in a whole body bird cage coil, giving a signal-to-noise ratio of approximately 25:1. The Modulus Blipped Echo-planar Single-shot Technique [Mansfield et al., 1990] was used to encode an image in 130 ms, with the switched gradient sinusoidally modulated at 0.5 kHz and the echo time to the centre of k-space of 70 ms, chosen to match the long T2* of the fetal brain. In-plane resolution was 4.0 × 4.0 mm with a data matrix of 128 × 128. The imaging slice was 10 mm thick and transverse to the mother but typically oblique to the fetus. A 10-slice volume was sampled every 4 sec. All scanning conformed to NRPB guidelines [National Radiological Protection Board, 1991]. One hundred and

eighty images were acquired prior to the presentation of the paradigm. Light was applied for 8 sec (2 volumes) interleaved with 16-sec periods of darkness (4 volumes), and the sequence was repeated typically 40 times.

Three control studies were also performed in which the experimental parameters were identical to those described above, except that the light tube was blocked with black foam so that no light was incident upon the maternal abdomen.

For the adult subjects, the light source was suspended horizontally above the subject resulting in the subject being exposed to a diffuse light pattern. The rate of switching of the light source, scanning protocol, and all analyses were otherwise identical to those used with pregnant subjects.

The most significant problem encountered in fetal fMRI is movement. Conventional motion correction techniques cannot be applied directly, due to the independent contributions of mother and fetus to the total movement. Consequently, a number of additional analysis steps were required compared to those conventionally used for adult data analysis. If a scan displayed large-scale movement, the whole associated cycle was removed from subsequent analysis. For the remaining volumes it was first necessary to mask the maternal signal prior to motion correction (Fig. 2). Thus, for each image a trace was obtained around the *fetal skull*, with all signal outside of this trace area set to zero. Subsequent motion correction was undertaken using AIR within Medx. The success of the process was assessed by viewing the sequence as a movie. In the event of significant motion remaining, the process was recommenced with additional cycles removed followed by masking and motion correction.

Images were then filtered within Medx using a Gaussian profile of 5 mm full width half-maximum followed by global intensity normalisation. Temporal filtering was undertaken using a matched bandpass filter.

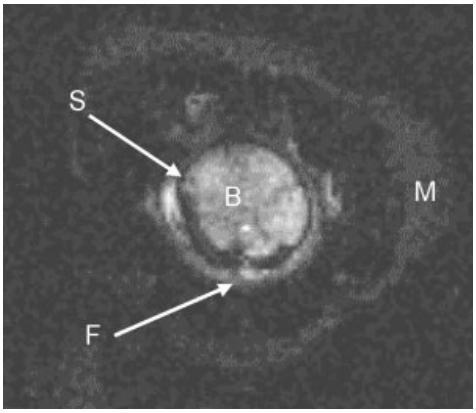

Figure 2.
A raw transverse MR image showing the maternal abdomen with the fetus within it. The long echo time (chosen to match the T2* of the fetal brain) is responsible for the low signal in the rest of these T2* weighted images. S: fetal skull around which the mask is drawn; B: Fetal brain; F: amniotic fluid; M: maternal subcutaneous fat (shifted 4 pixels downwards on these images, because of the narrow bandwidth per pixel of these EPI images).

TABLE I. Summary of activation determined within fetal subjects

Subject no.	*P* (corrected)	Activated region	Cycles
1485	No activation	Not analysable-movement	21
1484	<0.0085	Central/upper left	19
1483	<0.00009	Upper frontal	13
1463	<0.00003	Upper frontal	5
	<0.00001	Centre/back	
1462	<0.001	Upper central	23
1461	No activation		24
1431	<0.012	Upper central/right	15
1382	<0.025	Frontal	11
1330	<0.00004	Upper right	14
	<0.0005		

In-house software was used to correlate the data against the stimulus time-course convolved with a Poisson function of width 6 sec designed to model the haemodynamic response. The calculated correlation coefficient for each pixel was converted to a *Z* score to express the statistical significance of activated regions, taking into account the reduced degrees of freedom resulting from temporal filtering. Using the theory of Gaussian Random Fields, corrected *P* values for the statistical significance of activated regions were determined. Activation maps were subsequently overlaid on base images to generate statistical parametric maps showing the anatomical sites of activation. Only regions with $P < 0.0085$ (corrected) were considered significant. SPMs were resliced to generate slices transverse to the fetal head with Analyze software and the positions of activated regions within the fetal brain determined.

RESULTS

For the nine fetuses that received light stimulation, one was not analysable due to excessive motion and activation was not found ($P > 0.01$, corrected) in another three. For the remaining five, activation ($P < 0.0085$, corrected) was found with individual *P* values listed in Table I. Representative signal time courses are shown in Figure 3. Due to the lack of landmarks in the fetal brain, areas of activation were difficult to determine and varied between individual patients. However, in four of five cases an area of activation was found within the frontal region with no significant activation detected within the visual areas as shown in Figure 4. None of the three control subjects showed activated regions with $P < 0.1$. For 2/8 of the adult subjects, activation was found in the anatomical region corresponding to the primary visual cortex ($P < 0.005$, corrected). Activation was not found elsewhere ($P > 0.01$, corrected) (see Table II).

DISCUSSION

This study suggests that it is possible to use fMRI to detect fetal brain activity in response to a visual stimulus.

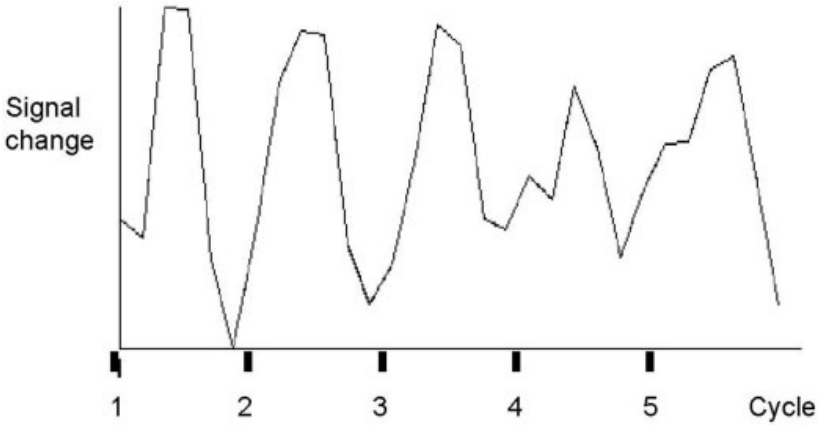

Figure 3.
Representative raw signal time course (subject 1463).

The most significant feature of the fetal activation was its location. We initially hypothesised that activation would be detected in the visual cortex as was found in the adult subjects. However, activation was consistently detected in the frontal lobes. Significant activation was recorded for more than 50% of the fetuses, which is similar to the sensitivity of previous fetal fMRI studies using acoustic stimuli [Hykin et al., 1999; Moore et al., 2001]. A very low sensitivity was found in adults. However the use of a low field (0.5T), a whole body coil, no head restraint, and a static light stimulus (not flashed) to which habituation would rapidly occur in the adult, would all be expected to reduce the BOLD (blood oxygen level-dependent) signal. However, unexpectedly large signal changes on activation have recently been reported at low field strength, probably due to a local change in proton density [Stroman et al., 2003]. The fact that a larger proportion of fetuses than adults displayed activation despite having a smaller number of motion-free cycles may indicate either a greater fetal response to this specific stimulus or a more general elevation of BOLD signal in the fetus relative to the adult. This is consistent with our previous fetal fMRI findings [Fulford et al., 2003; Moore et al., 2001].

There have been a limited number of previous studies of fetal responsiveness to visual stimulation. It has been shown that the switching of a light in front of the maternal abdomen results in induced fetal heart rate accelerations [Smyth, 1965] and fetal movements [Polishuk et al., 1975]. It has been shown that the response to light depends on the initial behavioural state [Kiuchi et al., 2000]. Furthermore, the introduction of a light during an amnioscopy results in fetal heart rate changes [Peleg and Goldman, 1980]. More recently, a magnetoencephalography study has recorded visual evoked brain activity in 4 out of 10 fetuses. No localisation within the fetal brain was reported [Eswaran et al., 2002].

The absence of activation within the occipital lobe in the fetus could result from either (1) the light not being of

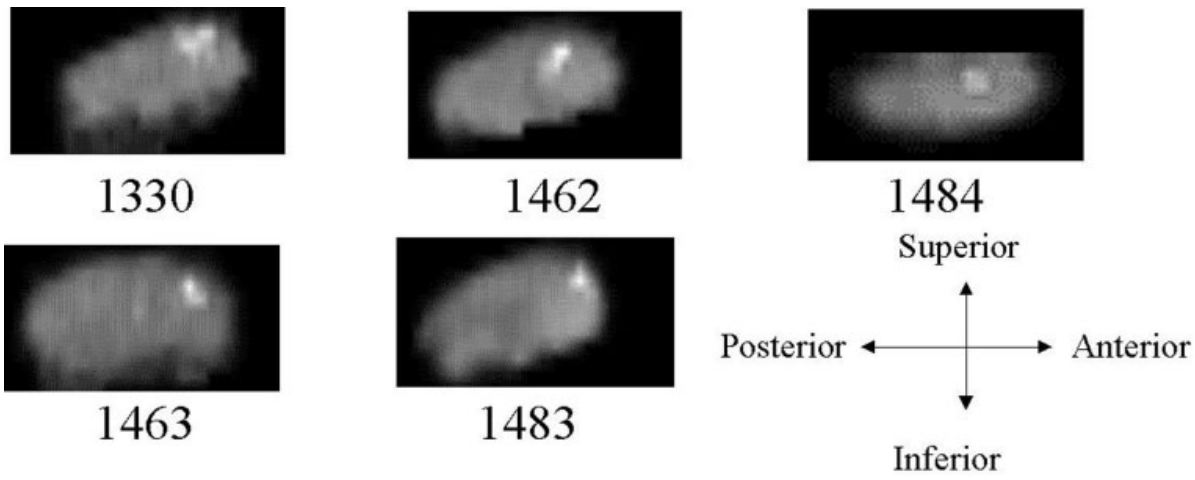

Figure 4.
Illustration of fetal activation in sagittal, masked slices.

TABLE II. Summary of activation determined within adult subjects

Subject no.	Occipital activation	Cycles
8	0.026	11
7	0.0003	18
6	0.004	16
5	No activation	23
4	0.02	31
3	No activation	20
2	No activation	16
1	0.3	31

sufficient intensity, (2) a low sensitivity of the developing visual cortex to the constant, relatively low level light applied, (3) differences in activation in the immature (and largely visually unstimulated) brain relative to the adult, in particular resulting from the slow maturation of the visual pathway and V1, and (4) low sensitivity of the fetal fMRI technique generally. However, given the results of the preliminary light attenuation experiments and the fact that activation was detected elsewhere in the fetal brain, it seems likely that the light was of sufficient intensity to penetrate the abdomen. Furthermore, we believe that the fetal fMRI technique generally has adequate sensitivity as we detect activation to auditory stimuli in approximately 50% of fetuses [Hykin et al., 1999; Moore et al., 2001]. Hence, it is possible that the lack of activation within the occipital region may be due to the way that the immature brain responds to this particular visual stimulus.

fMRI studies of the responses of neonates and young children to visual stimuli have produced some reports of little or no activation close to or before term [Born et al., 1998, 2000; Martin et al., 1999]. However a recent study of neonates from 34–40 weeks GA found activation in 6 out of 7 infants [Erberich et al., 2003]. Clearly, any differences between fetuses and neonates may be due to the fact that fetuses have not been exposed to bright light. After term, a positive signal change is generally observed up to about 60 days and a negative signal change is observed from about 60 days to 40 months. Thereafter, an adult-like, positive signal change is observed [Born et al., 1998; Martin et al., 1999; Morita et al., 2000; Yamada et al., 2000]. However, it should be stressed that these time points are only approximate; the literature demonstrates that there is considerable individual variability, and this is likely to be further complicated by the varying degrees of sedation that are used in different reports and at different postnatal ages. There is also some evidence that the activated areas are located more anteriorly within the occipital lobe in younger infants, although this may be a result of the type of stimulus used [Born et al., 1998; Morita et al., 2000]. Nonetheless, it seems that the significant developmental changes taking place within the visual processing system during the first few months are responsible for these variations in the fMRI signal.

The negative signal change observed postnataly is consistent with infrared spectroscopy, which has shown that activation causes an increase in blood volume and both oxy- and deoxy-haemoglobin concentrations, in contrast to adults where deoxy-haemoglobin decreases on activation [Meek et al., 1998]. However Born et al. [2002] have detected a decrease in perfusion on activation in sedated children aged 4–71 months (in contrast to the increase observed in adults and usually assumed to be related to the increase in blood volume). It has been suggested that the change from positive to negative response is due to increased oxygen consumption during stimulation as a result of increased synaptic density, and the results of fitting neonatal data to mathematical models of the BOLD effect are consistent with this [Moramoto et al., 2002].

It is possible that the activation that was detected in the frontal lobes was the result of false positives. However, activation occurred within a consistent area of the fetal brain with low P values. No significant activation was found either in phantoms or for the control subjects for whom the current flowing through the light source was identical, excluding the possibly of artefacts from the light source. A large number of additional areas outside of the occipital lobe may be activated following various types of light stimulation in adults. Therefore, the frontal lobe activation found without occipital lobe activation might reflect the non-homogeneous maturation of the fetal brain. There have been no reports of frontal lobe activation in infant fMRI.

The human visual system develops progressively during gestation. The optic vesicles, from which the retina develops, appear at approximately 30–32 days gestation. The major retinal morphogenic events occur between 8 and 17 weeks gestation, but the development of photoreceptor cells is not completed before birth with the macula not being fully developed until a few months after birth. The eyelids typically can open around 20–22 weeks (although they do not open for prolonged periods), reducing the potential attenuation of the light before it reaches the fetal retina.

Johnson [2002] suggested that four visual pathways predominate within the newborn: (1) a direct pathway from the retina to superior colliculus involved with the movement of the eyes towards simple easily discernible stimuli, (2) cortical pathways to the superior colliculus from the primary visual cortex and middle temporal area, (3) a cortical pathway involved with processing within the frontal eye fields, (4) a pathway controlling eye movements via the basal ganglia. The primary visual cortex within the occipital lobe is somewhat undeveloped at birth with the deeper layers showing greater myelination and dendritic branching than the more superficial layers [Huttenlocher, 1990]. This leads to the conclusion that in term fetuses, such as in this study, only the deeper levels of the primary visual cortex are likely to be involved in the processing of visual inputs.

The exact area of activation was difficult to determine in the present study because of the lack of landmarks above the temporal lobes in the fetal fMRI data sets due to the long T2 of the fetal brain. However, activation was found within the frontal region in an area that may correspond to the frontal eye fields, supplementary eye fields, and dorsolateral prefontal cortex, an area associated with visual orienting and attention. Thus, although a visual stimulus may not invoke activation within the occipital region due to the immature state of V1, there are sufficiently developed pathways elsewhere that might result in detectable activation within other components of the visual processing system, possibly via the superior colliculus and thalamus [Schall, 1991]. This is supported by work examining visual evoked potentials in neonates with abnormalities in the occipital region [Dubowitz et al., 1986]. Even in the event of an infant having a complete absence of visual cortex, a visual evoked waveform was generated. Thus, from both behavioural and electrophysiological standpoints there is evidence that early visual function is not dependent upon the cortex but instead may be mediated through subcortical pathways. It should be noted, however, that in the present study there is insufficient resolution to identify activation within sub-cortical structures.

CONCLUSION

Functional MRI has the potential to study the development of the visual pathways in the fetal brain. The current study should be repeated with a different light source, possibly flashed, and with the inclusion of anatomical fetal brain scans such as HASTE images. To further assess development, studies must be extended to undertake equivalent fMRI in the newborn and for the first 3 months post-natally, a time-span that is known to coincide with rapid visual development [Johnson, 2002].

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