



## REPORT

## Developmental change in fetal response to repeated low-intensity sound

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### Abstract

*The aim of this study was to investigate developmental changes in heart rate response to repeated low-intensity (85 dB) sound stimulation in fetuses between 32 and 37 weeks of gestation. We measured amplitude changes in heart rate as our index of fetal response. At 35 to 37 weeks of gestation, the majority of fetuses showed a deceleratory response at the first trial. Amplitude decreased with further trials using the same stimulus before recovering when exposed to another type of stimulation. In contrast, responses in fetuses at 32 to 34 weeks of gestation were variable across trials and there was no recovery with exposure to another type of stimulation. Our results suggest that fetal habituation of cardiac response changes with developmental age.*

### Introduction

Sokolov (1963) defined two generalized reactions to stimulation: a defensive reflex (DR) and an orienting reflex (OR). DRs are evoked by high-intensity stimuli and limit effects of stimulation. ORs are evoked by novel stimuli below the intensity sufficient to evoke defense, and result in enhancement of the effects of stimulation. Habituation is defined as 'the decrement in response following repeated stimulation with the same stimulus' (Thompson & Spencer, 1966). A basic form of learning, habituation requires an intact CNS (Jeffrey & Cohen, 1971). Sokolov (1963) hypothesized that two anatomical centers are involved in habituation: The center that participates in habituation of the response to high-intensity stimuli capable of causing DRs differs from the center that participates in habituation of the response to low-intensity stimuli capable of causing ORs. Although it is not possible to say with certainty what structures are involved in mediating habituation of a DR, animal studies suggest that such habituation may be partially mediated by the midbrain (Capps & Stockwell, 1968; Jordan & Leaton, 1983). Sokolov (1990) considered work with ORs and concluded that the hippocampal system contributes to habituation, implying a different CNS center than that involved in habituation of DRs. Thus, developmental change in habituation may differ for habituation to low-intensity stimuli and habituation to high-intensity stimuli.

Observation of spontaneous fetal movement has made it possible to speculate when a given CNS level is beginning to function (Morokuma, Fukushima, Kawai, Tomonaga, Satoh & Nakano, 2004). In newborn infants, it is known that regular mouthing movements are observed exclusively during non-REM sleep (Watanabe & Iwase, 1972). Horimoto, Koyanagi, Satoh, Yoshizato and Nakano (1990) observed in fetuses that regular mouthing movements become concurrent with non-eye movement periods at 35 weeks of gestation or more, demonstrating functional maturation of the neural area rostral to the pons and implying the neural center that is related to non-REM sleep (Watanabe & Iwase, 1972; Wolff, 1968). Studies with DRs have shown that human fetuses are able to habituate (Leader, Baillie, Martin & Vermeulen, 1982; van Heteren, Boekkooi, Jongsma & Nijhuis, 2000; Morokuma *et al.*, 2004). In a study of fetal habituation of DRs to repeated vibro-acoustic stimulation at 32 to 37 weeks of gestation (Morokuma *et al.*, 2004), all fetuses at 32 to 37 weeks of gestation were able to habituate. In contrast, fetuses at 32 to 34 weeks of gestation took significantly more trials to show habituation than fetuses at 35 to 37 weeks in whom non-REM sleep was observed. These findings established that there is a certain relationship between CNS development and habituation. It appears that 35 weeks of gestation is a pivotal age for learning ability, suggesting that the midbrain may function at this time, providing important inhibitory input

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capable of modifying the rate of habituation in humans (Morokuma *et al.*, 2004).

The cardiac deceleratory response has been used as a physiological correlate of infant ORs (Graham, 1984). However, fetuses do not necessarily show deceleratory responses to stimuli that do not induce startle reflex or gross body movement, and instead may show an acceleratory response (Lecanuet, Granier-Deferre, Jacquet & Busnel, 1992; Kisilevsky, Hains, Jacquet, Granier-Deferre & Lecanuet, 2004). Turkewitz, Moreau, Birch and Davis (1970) argued that acceleration might be an OR in newborns, which would mean that the definition of ORs in fetuses and newborns has been obscure. In this study, we evaluated habituation and developmental change in habituation using repeated low-intensity acoustic stimuli, which do not induce DRs causing body movements at 32 to 37 weeks of gestation.

Kisilevsky, Pang and Hains (2000) evaluated functional development of the fetal auditory-response system and showed that the response occurred at 30 weeks. However, the stimulus was high-intensity sound, which induces cardiac acceleration and body movement at that age and thus did not evaluate habituation. Although Lecanuet *et al.* (1992) evaluated fetal response at term to repeated vocal stimuli, they did not examine possible developmental change. No reports have examined a possible developmental change with increasing gestational age in habituation pattern of the response to low-intensity sound.

The present study investigated heart rate response to repeated low-intensity acoustic stimulation in fetuses of 32 to 37 weeks of gestation.

## Methods

### *Fetal population*

A total of 27 normal singleton fetuses between 32 and 37 weeks of gestational age (GA) were recruited at the Fetal Medicine Unit of St George's Hospital between June 2005 and January 2006. Of that number, six subjects were excluded from the study because the fetus did not enter a non-eye movement period before onset of maternal fatigue. We divided the remaining 21 fetuses into two groups by GA: 32–34 weeks ( $N = 9$ ) and 35–37 weeks ( $N = 12$ ).

The study was approved by the Local Research Ethics Committee, and all mothers gave written informed consent to participate in this study. The women had no medical or obstetric complications and no use of alcohol, drugs, or medication other than vitamins and/or iron. GA was calculated from the date of the last menstrual period and confirmed by ultrasonographic measurement of fetal crown–rump length between 11 to 14 weeks of gestation. After birth, none of the neonates was found to have any abnormalities and each had a 5-minute Apgar score  $> 8$ . For the two experimental groups (32–34 and 35–37 weeks GA), average birth weight was 3081

g ( $SD = 407$ , range 2610–3800 g) and 3375 g ( $SD = 345$ , range 2850–3775 g) respectively; all had a birth weight above the tenth percentile. Seven (33%) fetuses were male. Distribution of study sample by infant gender and birth weight was not significant.

### *Procedure and data analysis*

#### Stimuli

The stimuli were two types of computer-generated, pulsed white noise. Pulsed sound stimulus 1 lasted 4.75 sec, alternating 250 msec sound with 250 msec quiet; sound stimulus 2 lasted 4.5 sec, alternating 500 msec sound with 500 msec quiet. Each period of sound onset and offset was linear for sound intensity, with a rise time of 20 msec to full amplitude and a fall time of 20 msec. The sound was played through an amplifier (1706II, Bose Corporation, Framingham, MA, USA) and a loudspeaker (101TR, Bose Corporation) positioned 15 cm above the mother's abdomen. The amplifier was adjusted to provide an intensity of 85 dB SPL at a distance of 15 cm (A scale, AS ONE sound level meter, type SM325, Osaka, Japan), prior to the mother's arrival to the examination room.

#### Procedure

Each study was initiated approximately 60 min after the mother completed her meal, with all studies performed between 2 pm and 5 pm. All examinations were performed in a quiet room. We checked that background sound pressure level was less than 50 dB before examination. Mothers were placed in a semi-recumbent position on a bed, and each mother wore earphones and listened to relaxing music during fetal testing. We conducted procedures from a position that was not visible to the mother. For all trials, the loudspeaker was held approximately 15 cm above the maternal abdomen over the site of the fetal head as determined by ultrasound. In order to obtain fetal heart rate (FHR) data, each fetus was examined using an external cardiocograph (MT-333U, Toitu, Tokyo, Japan) with a pulsed-Doppler ultrasound transducer of 1.1 MHz. FHR values were stored on an online personal computer (VAIO VGN-T70B, Sony, Tokyo, Japan). We evaluated fetal behavior in terms of fetal non-eye movement period: The period was equivalent to fetal behavioral state 1F as originally defined by Nijhuis, Prechtel, Martin and Bots (1982), using real-time ultrasound (SSA-340A, Toshiba, Tokyo, Japan). For ultrasound observation of eye movements, the standard plane used was the coronal facial view as previously described (Horimoto, Koyanagi, Nagata, Nakahara & Nakano, 1989). The ultrasound image was stored on a video cassette recorder (Model WV-DR9, Sony, Tokyo, Japan). After a period of non-eye movement lasting more than 2 minutes, each fetus received a total of six consecutive trials including five trials of sound

stimulus 1 and a final trial of sound stimulus 2. The minimum inter-stimulus interval was 20 sec to allow for return of FHR to baseline. Fetal eye movements were not assessed with ultrasound during the 30-second pre-stimulus and stimulation periods to avoid any ultrasound effect. Alternatively, each trial began only when heart rate was judged to be stable with a narrow oscillation bandwidth and no gross body movements were seen on the cardiocotograph; this was done to standardize fetal state at time of stimulation. No-sound control trials were performed before or after the stimulus period using the same procedure but without sound as a stimulus. Each fetus was tested only once.

#### Data analysis

The magnitude of HR change to each stimulation was determined by comparing the HR response in the first 10 seconds following stimulus onset to pre-stimulus HR variability using the method of Lecanuet *et al.* (1992) (Figure 1). First, the interquartile ranges (IQR) were calculated for the 10 seconds immediately preceding stimulus onset in order to establish lower and upper ranges in pre-stimulus HR: the lower range (q1) was defined as the mean HR for 1 sec before stimulation minus IQR, and the upper range (q2) was defined as the mean HR for 1 sec before stimulation plus IQR. Next, the lower (Q1) and upper (Q2) quartiles in HR were calculated for the first 10 seconds following stimulus onset. Q1 and Q2 are, respectively, conservative estimates of the lowest and highest HR during stimulation. HR change was categorized as a deceleration if  $Q1 < q1$  and an acceleration if  $Q2 > q2$ . If both criteria were satisfied, HR response was categorized based on the direction of the larger change; if neither criterion was satisfied, the HR response was categorized as no change. The amplitude of an HR acceleration or deceleration was calculated as the difference between Q1, Q2, and the HR 1 sec before

stimulation, respectively. These calculations were performed between trial 1 and trial 6 for each fetus. The same calculations were also performed for no-sound control periods for the same fetuses. Each fetus was tested only once.

#### Statistical analysis

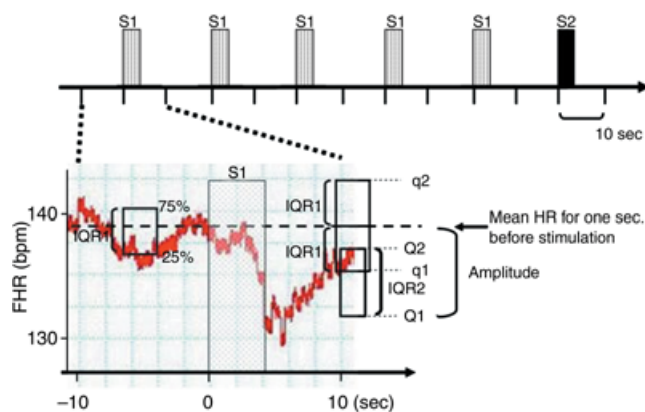
Differences in pre-stimulus HR between the GA groups or across trials were calculated using Student's *t*-test and the paired *t*-test.

Regarding response to first stimulation, comparison of acceleratory or deceleratory response and no change frequency between stimulus and control periods was made using the McNemar test. Irrespective of type (acceleration or deceleration) of HR reaction, the absolute value was also examined to investigate the change tendency of reaction to repeated stimulation. Regarding amplitude and the absolute value of amplitude, comparison between stimulus and control periods was made using the paired *t*-test. Regarding the change tendency of each group, both amplitudes and the absolute values of amplitudes across the first to fifth trials were analyzed using repeated measures analysis of variance (ANOVA). Comparison between HR change amplitudes following the fifth and sixth stimulation was made using the paired *t*-test. *All differences* were considered significant at  $p < .05$ . The distributions of dependent variables were not statistically different from the normal distribution. Therefore, HR amplitude data were compared using Student's *t*-test, the paired *t*-test, and ANOVA. The proportions of acceleratory and deceleratory responses and no change were compared using the McNemar test.

## Results

Differences between groups classified by GA or across trials in pre-stimulus HR were not significant (Table 1).

The frequency of HR changes in each 10-sec period following stimulus onset is summarized in Figure 2 (stimulation and control periods). At 35 to 37 weeks GA, fetuses exhibited a significant deceleratory HR change (67%) only after the first stimulation when compared with the control period (17%) ( $p = .031$ ). In contrast, at 32 to 34 weeks, deceleratory HR changes occurred in only two cases (22%) (Figure 2). Among fetuses between 35 and 37 weeks, the amplitude and absolute value of HR change following the first stimulation was  $3.6 \pm 4.1$  (mean  $\pm$  SD) and  $4.3 \pm 3.4$  (mean  $\pm$  SD) beats per minute (bpm), respectively; these were significantly higher than those obtained in no-sound controls ( $0.2 \pm 1.7$  bpm (mean  $\pm$  SD),  $1.0 \pm 1.4$  bpm (mean  $\pm$  SD)) ( $p = .029$ ,  $p = .010$ ). At 32 to 34 weeks, the amplitude was  $0.62 \pm 3.42$  bpm (mean  $\pm$  SD) following the first stimulation; this was not significantly different from the no-sound control ( $0.29 \pm 1.3$  bpm (mean  $\pm$  SD)) ( $p = 1.0$ ). However, the absolute value ( $3.6 \pm 1.8$  bpm

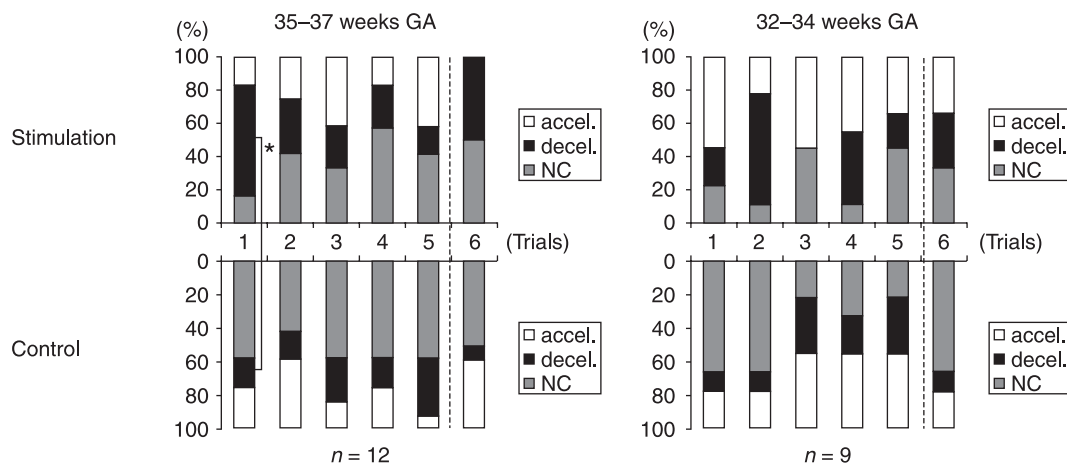


**Figure 1** Schema of heart rate data analysis. S1: Stimulation 1, S2: Stimulation 2. Q1: Interquartile range for 10 sec before stimulation, Q2: Interquartile range for 10 sec after stimulation. Reproduced from Lecanuet *et al.*, 1992.

**Table 1** Heart rate characteristics in the 10-sec pre-stimulus period

GA in weeks	32–34	35–37	significance
Number of Subjects	9	12	
Pre-stimulus period			
10 sec			
Mean (bpm)	135.3	134.7	$p = .88$
Standard deviation (bpm)	7.5	9.8	
IQR (bpm)	1.8	2.1	$p = .59$
Standard deviation (bpm)	0.7	1.4	
1 sec			
Mean (bpm)	134.5	134.7	$p = .95$
Standard deviation (bpm)	7.5	9.9	
significance (10-sec mean VS 1-sec mean)	$p = .82$	$p = .99$	

GA: gestational age.

**Figure 2** Frequency (response ratio out of total cases) of fetal heart rate change (accel., decel. and no change [NC]) following each stimulation. We used stimulus 1 for trials 1–5 and stimulus 2 for trial 6 (see Methods); accel.: acceleration, decel.: deceleration, NC: no change. \*  $p < .05$ .

(mean  $\pm$  SD)) was significantly higher than the no-sound control ( $0.76 \pm 1.1$  bpm (mean  $\pm$  SD)) ( $p = .01$ ) in the younger fetuses (Figure 3).

At 35 to 37 weeks GA, fetuses exhibited response decrement across the first to fifth trials and there were significant tendencies of both HR amplitude and absolute value across trials ( $F(4, 44) = 2.85$ ,  $p = .035$ ,  $F(4, 44) = 2.75$ ,  $p = .039$ ). Among fetuses 32 to 34 weeks, there were no significant tendencies ( $F(4, 32) = 1.78$ ,  $p = .15$ ,  $F(4, 32) = 1.31$ ,  $p = .28$ ) (Figure 3).

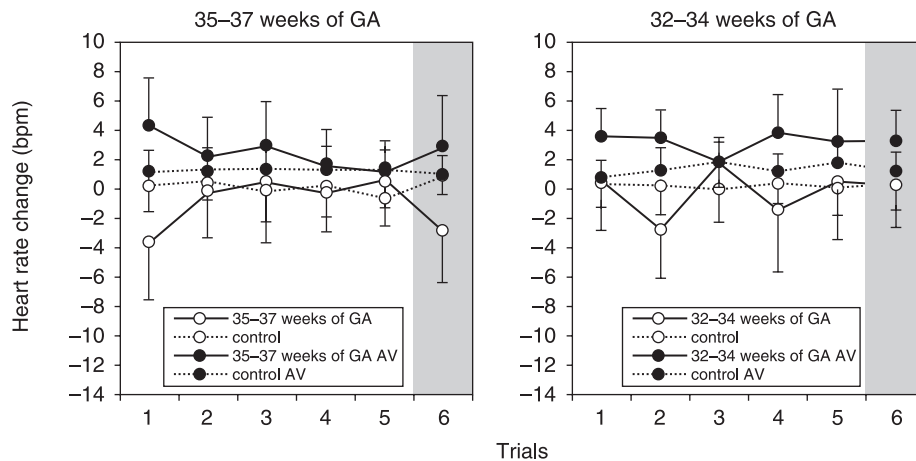
Finally, at 35 to 37 weeks there was a significant change in HR amplitude between the fifth trial (stimulus 1) and the period following the sixth trial (stimulus 2) ( $p = .048$ ), but this difference was not observed in younger fetuses ( $p = .93$ ) (Figure 3).

## Discussion

At 35 to 37 weeks GA, the majority of fetuses showed a deceleratory response at the first trial. Amplitude decreased with further trials using the same stimulus, followed by recovery when exposed to another type of

stimulation. The findings suggest that these fetuses have the ability to generate an orienting response, habituation, and dishabituation. On the other hand, at age 32 to 34 weeks, the frequency of a deceleratory response was low following the first stimulation, responses were variable across trials, and responses showed no significant trends and no recovery with another type of stimulation. This second set of findings cannot be due either to an inability to detect the stimulus or to an absent functional response mechanism because the fetuses showed significant response to the first stimulation.

Regarding stimulation intensity, we thought that a sound intensity of 90 dB or less was optimal for testing of ORs in fetuses because this level of sound intensity causes HR change but not body movement (Groome, Mooney, Holland, Bentz, Atterbury & Dykman, 1997; Kisilevsky *et al.*, 2000). We chose amplitude and absolute HR value as indexes of fetal response because inter-fetal responses in HR could differ in direction (acceleratory, deceleratory, or no change) and would therefore be inappropriate for analysis of mean group differences (Graham & Jackson, 1970). Thus, it was necessary to design a quantitatively based procedure that would determine



**Figure 3** Change of fetal heart rate response following repeated stimulation. Means and SD for heart rate amplitude and absolute value of amplitude for all subjects (35–37 weeks:  $n = 12$ , 32–34 weeks of GA:  $n = 9$ ) across six trials in both stimulus period and control period. Stimulus period: solid line, Control period: broken line, Amplitude: open circle, Absolute value (AV) of Amplitude: filled circle.

whether an individual fetus did not react to a stimulus or to change in stimulus. We chose a measure that was intentionally quite conservative in order to increase its reliability and validity. We used the measure described by Lecanuet *et al.* (1992), which takes into account ongoing level of HR variability, which is known to modulate the amplitude of HR reactivity in newborns and near-term fetuses (Berntson, Bigger, Eckberg, Grossman, Kaufmann, Malik, Nagaraja, Porges, Saul, Stone & van der Molen, 1997; Lecanuet *et al.*, 1992).

Some studies have reported that human fetuses at term can respond with HR deceleration to a low-intensity stimulus (Groome *et al.*, 1997; Lecanuet *et al.*, 1992). However, even among term fetuses, about 10% show an acceleratory HR change (Lecanuet *et al.*, 1992). In that study, term fetuses exposed to low-intensity sound exhibited an HR change of approximately 4 bpm. We showed similar results for fetuses of 35–37 weeks. In the study by Kisilevsky *et al.* (2004), fetuses from 28 weeks to term showed some HR response when exposed to music at an intensity of 95–110 dB. Their study showed no body movement responses until 35 weeks GA even at an intensity of 95–110 dB. At 32 to 34 weeks, our fetuses also showed some HR response (acceleration or deceleration). Regarding response following first stimulation, our findings are similar to those of other reports.

A previous study of habituation using a DR suggested that fetuses have an ability to habituate by 32 weeks GA and that fetuses over 35 weeks that show observable non-REM sleep periods are able to habituate earlier during exposure to the stimulus (Morokuma *et al.*, 2004). The present study shows that fetuses over 35 weeks were able to habituate rapidly to repeated low-intensity stimuli, whereas fetuses under 35 weeks were not able to habituate to the same test stimulus. Sokolov (1990) reported that repeated presentation of less intense stimuli results in

selective habituation of novelty detectors in the hippocampus, higher than midbrain level.

Although fetuses at 32–34 weeks GA responded to a sound stimulus as reported in other papers, their lack of habituation is important in explaining the anatomical correlates of behavior: The center that participates in habituation of the response to high-intensity stimuli differs from the center that participates in habituation of the response to low-intensity stimuli. We conclude that the neural center involved in habituation of response to low-intensity stimuli starts to function around 35 weeks of gestation.

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