ENHANCEMENT OF CARDIO-RESPIRATORY FUNCTION AND NEUROLOGICAL DEVELOPMENT IN PRETERM INFANTS USING ACOUSTIC-VIBRO STIMULUS

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1. INTRODUCTION

In the UK annually approximately 44,000 infants are born preterm. This infant group have close links with cardiorespiratory abnormalities such as bradycardia and apnoea, hypoxemia and can experience delays in maturational development. Previous research has indicated that acoustic sensory processing may provide a controlling factor in cardiorespiratory function. Studies undertaken using various forms of acoustic stimuli, on diverse subjects and age ranges, have demonstrated that such stimuli can result in a reduction of bradycardia and central apnoea events. Whilst infants born at normal term gestation experience the natural intrauterine acoustic environment preterm infants will be exposed to the postnatal acoustic environment at an earlier stage in development. The spectrum characteristics of the postnatal environment as opposed to the intrauterine are quite different. This paper describes the potential importance of introducing an intrauterine acoustic stimulus to preterm infants for enhancement of cardiorespiratory function and neurological development.

Subgroup	Definition	Births / annum
Preterm	< 37 weeks	*36,000*
Very preterm	< 32 weeks	*5,500*
Extremely preterm	< 28 weeks	*3,000*

Figure 1. Approximate UK annual birth rates and groupings for infants born before term.

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2. PRETERM INFANTS AND ASSOCIATED ABNORMALITIES

The health of preterm birth and low birthweight babies is a central issue in perinatal health care. Worldwide, 20 million babies are born annually within this category accounting for approximately 17% of all births and no fewer than 75% of all infant deaths (Scottish Executive 98, HiS). In the UK preterm births (under 37 weeks gestation) account for 6.7% of all births, approximately 44,000 per annum (NHS Maternity Statistics) of which 8,500 are born 'very preterm' or 'extremely preterm', see Figure 1. Health problems in preterm infants includes poor control of cardiorespiratory function, hypoxemic events and delays in central nervous system function, maturation of sensory processing and cognitive development. Neonates born preterm are also at increased risk for sudden infant death syndrome (SIDS).

Cardio dysfunction such as bradycardia < or = 80 beats, and apneic respiratory pauses, > or = 20 seconds, and hypoxemia are closely linked in preterm infants (Poets, 1993). Di Fiore *et al* suggested that abnormalities in oxygenation and cardiorespiratory control may be markers for functional central nervous system abnormalities. Previous studies of SIDS infants has related SIDS to cardiorespiratory irregularities and data from the last minutes of life of three SIDS infants showed central apnoea and severe bradycardia (Meny *et al*, 1994).

Recent follow up studies on children aged between 7 and 10 years who were born at 28 weeks or less when compared with children born at normal gestation found that the low gestation group scored significantly lower on various cognitive tests (Scottish Executive HB 59/2).

3. AUDITORY DEVELOPMENT IN INFANTS

During the third trimester of pregnancy there is a gradual development of fetal behaviour states. These states are distinct and involve varied forms of neural activity and reflect a certain degree of maturity in the fetal brain (Visser *et al*, 1993). The hearing process depends on rapid, synchronised conduction in central auditory pathways. Prenatal hearing has been confirmed in fetuses at 34-40 weeks g.a. (gestational age) involving studies of fetal body movements and heart rate acceleration in response to sound stimuli (Dwanika *et al*, 1964, Barden at al, 1968, Goodlin and Schmidt, 1972). Birnholz and Benacerraf using ultrasound found that some fetuses could respond to auditory stimuli as early as the 25^{th} week g.a. and that by the 30^{th} week g.a. over 95% responded.

Moore *et al* investigated the development of myelin in the fetal auditory brainstem to determine the time of onset of hearing. Myelination of central pathways has traditionally been regarded as a marker for onset of function. They found myelinated axons occurring in auditory structures as early as the 26^{th} week g.a. and that human fetuses or preterm infants developed rapid axonal conduction during the 26^{th} to 29^{th} week. During the gestational age period 30-40 weeks, there is a rapid change in auditory neural function with increases in myelin density and axonal velocity running parallel (Moore

et al, 1995) These two factors have a slower change through the first and second postnatal years and generally mature between 18 months and 2 years.

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Another process requiring rapid synchronised axonal conduction is evoked auditory brainstem response (ABR). ABR is a group of waves identified as the short latency response (Jewett at al, 1970, Sohmer Feinmesser, 1967) and include up to seven peaks that normally occur within about 8*msec* following a click stimulus. Measurement of the inter-wave latencies between these seven peaks can be used to determine the maturation of the central auditory pathways. Gelfand notes "it is tempting to attribute the peaks to successive sites along the auditory pathway. However, it appears that the first two peaks are produced by the auditory nerve, the subsequent peaks have multiple generators, meaning that they are due to combined electrical activity of several nuclei in the auditory brainstem". The ABR's are present in preterm infants and with developmental age the latency of the waves shorten and eventually reach adult characteristics by 18 months of age. Myelination has been presumed to underlie both the onset of the recordable ABR and the subsequent changes in wave latencies (Inagaki *et al*, 1987; Matschke *et al*, 1994).

Hearing threshold during the 30-40 week g.a. period has been found to be 60-40dB in very preterm infants to 20dB in some term infants (Lary S *et al*, 1985) and that there is no apparent difference in threshold level whether maturation occurs inside or outside the uterus. Other studies have found that the threshold level during this period may decrease from 70dB to 40dB and that over the first two years the rate of decrease is slower reducing to 10-5dB (Gelfand, 1996)

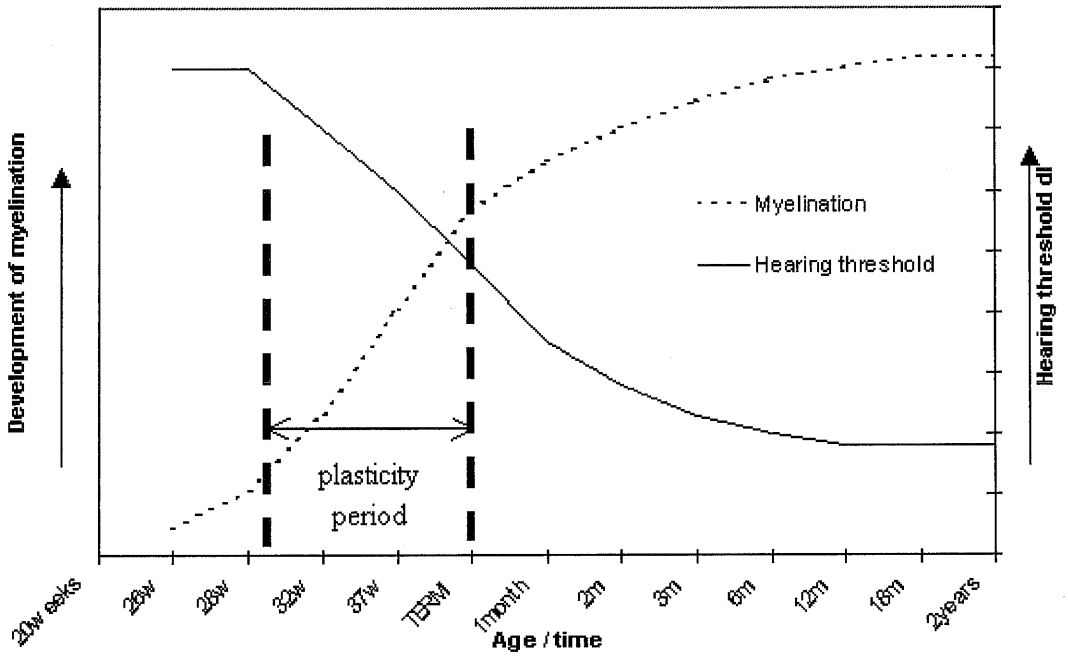

Figure 2. Development of myelination (- - -) and hearing threshold (___)

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From a variety of studies of the myelination process, axonal conduction and ABRs there appears to be a critical period of auditory neural development during the 30 - 40th week g.a. period. Whilst hearing threshold may not differ markedly in maturation between preterm and normal term infants the ability to detect a signal does not reflect the ability to perform higher acoustic sensory processing and the relationship with motor and autonomic functions. Figure 2 shows the time relationship for myelination of the central auditory pathways, which can act as a marker for the onset of function, and the relationship between developmental age and hearing threshold.

It has been well documented that the primary hearing frequencies of a neonate are low frequencies and that high frequencies are the last to be accurately distinguished (Fisch, 1983). The neural spike rate varies for stimulus level, direction of excitation and frequency spectrum. Considering that myelination is in part dependent upon auditory neural stimulus and the neural spike rate is dependent upon the frequency spectrum of source stimulus, it is suggested that during the early developmental period 30-40th week gestation the pattern of neural spike rate may play a 'design' role in the myelination and junctional characteristics of the higher auditory pathways. If the predominant frequencies which penetrate the womb are low frequencies and the predominant hearing sensitivity of the neonate is towards low frequencies are these functions inter-related?

4. AUDITORY NEURAL INPUT AND PRIMARY FUNCTIONS

The auditory neural network is an extremely complex system of "series-parallel" neural connections. As such, immaturity of several connections may not lead to loss of hearing sensitivity as the signal may be represented along an alternative route. However, immaturity of connections may result in a loss of sensory processing in higher auditory nerve fibres involving second order or third order neurons. Of particular interest is the termination of third order neurons at the medial geniculate body of the thalamus. The thalamus is housed in the diencephalon with the hypothalamus. The thalamus and hypothalamus both carry out further processing of neural activity from a variety of sense organs. The hypothalamus has a major role in control and integration of the autonomic nervous system and exhibits properties of a self-sustained oscillator and acts as a pacemaker to drive many biological rhythms. Immaturity in the early post natal period may restrict the quantity and quality of auditory neural input received by the central nervous system and it is suggested that this may affect primary functions such as cardio-respiratory control.

Preterm infants are more at risk of increased central apnoea and bradycardia, with an exponential increase in incidence of apnoea with decreasing gestational age at birth (Henderson *et al*, 1986). From ABR studies on preterm infants this group experience longer ABR wave latencies possibly related with delayed auditory neural development. Several studies have demonstrated a relationship between central apnoea and/or bradycardia and prolonged ABR latency.

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Previous studies using a variety of different stimuli have demonstrated a relationship between cardio-respiratory function and auditory neural input. McKenna found that very young infants appear to be particularly responsive to external stimuli. In sleep cycle studies introduction of acoustic stimulation increased respiratory tidal volume (Carley *et al*) and in animal studies respiratory rate has been increased (Stewart and Stewart) and central apnoea has been dramatically reduced by counter-conditioning stimulus (Strohl and Thomas, 1997). Auditory neural input has also been related to SIDS (Stewart et al, 2000).

Studies involving aminophyllin or caffeine citrate (Larsen *et al*, 1995) have demonstrated positive changes to respiratory and cardio functions in very preterm infants. Aminophyllin is a stimulant that enhances auditory neural pathways and leads to increased auditory evoked potential amplitude. Chen *et al* monitored ABR latency for preterm infants compared with normal control's ABR and found that the use of aminophyllin enhanced conduction along auditory neural pathways resulting in normal ABR responses for the preterm group.

Anday *et al* suggested that abnormalities in the respiration patterns of preterm infants may be related to acoustic sensory processing due to alterations in brainstem neuronal function and organisation. Studies of acoustic sensory processing and neurobehavioural development were carried out by Thoman *et al*. They reported that preterm infants exposure to a mild acoustic stimulus facilitated neurobehavioural development at follow-up five weeks after the expected date of birth and recently Strohl and Thomas suggested that the brainstem of the neonate contains a degree of developmental plasticity which is experience dependent and modifiable.

Experimental evidence from a variety of paradigms such as manipulation of auditory stimulus to pharmacologically enhancement of auditory neural pathways carried out on preterm infants suggests

that this infant group may experience delayed maturational development of the auditory neural pathways. Several studies on the ABR response of preterm infants compared to normal term control infants support the assumption that there is developmental delay in acoustic sensory processing.

It is suggested in this study that the critical period, 30-40th week g.a., when acoustic sensory processing rapidly changes, may be a high "plasticity period" for development. The sensory processing signals are related to neural firing rate which is dependent upon sound pressure level, frequency spectrum of noise source and frequency intervals of stimulus. Thus, the stimulus environment during this "plasticity period" is suggested as being a critical component of neural development.

5. INTRAUTERINE 'versus' POSTNATAL ACOUSTIC ENVIRONMENT

The fetus is provided with consistent stimulus within the intrauterine environment. The stimulus sources may be exogenous, endogenous or a combination of both. Stimuli penetrating the womb environment are predominantly low frequencies because the mother's body tissue and amniotic fluid attenuates high and mid frequencies (Bench, 1968)

Exogenous sources of stimulus involve ambient noise and the frequency spectrum will be highly dependent on the location of the mother. Endogenous sounds include noise sources such as respiratory and cardio functions, gastric tracts and circulations of fluids. The mother's voice is an example of a combination of both endogenous source stimulus (transmitting through the body) and

exogenous (transmitting through the air to the womb). The endogenous source of the mother's voice has been found to have priority (DeCaspar and Fifer, 1980) over other noise sources and by resonating primary organ functions its transmission path is less attenuated than exogenous stimulus sources. The low and mid frequencies of the mother's voice are transmitted to the fetus and some of the mother's lower frequencies are actually amplified (Vivalda *et al*). The amniotic fluid and tissues provide considerable attenuation protection for the in-utero infants from loud noises and sources of high frequency noise spectrum.

The postnatal acoustic environment whilst rich in all frequencies lacks the low frequency emphasis as experienced in-utero. In addition, most infants born during the early preterm 'plastic' period may be placed in incubators and under intensive care. The temperature, fluids, ventilation and constant electronic monitoring of these infants exposes them to various noise sources which are significantly different from the in-utero environment. Furthermore, when the electronic monitors detect an abnormality in breathing, temperature, oxygen saturation or cardio function various high pitched alarms automatically are sounded. As a result the infant whilst already stressed has to deal with sudden or high levels of noise, which are outwith the normal acoustic spectrum of the in-utero environment. Figure 3 shows a typical noise spectrum of two neonatal units, spectrum A illustrates the Leq ambient noise level in the vicinity of an incubator and spectrum B details the noise level when an alarm is switched on, 3150Hz. Spectrum C shows the characteristic frequency weighting within the womb environment (Vivalda *et al*). As can be seen there is much greater emphasis on low frequencies and lower mid frequencies for the womb environment than post natal environment. Peak noise levels in intensive care units from such alarms can generate 80-85dB within the immediate

vicinity of the infant and at frequencies of 1,600 - 4000Hz. In addition, the enclosed and cavity dimensions of an incubator amplify these noise levels even higher.

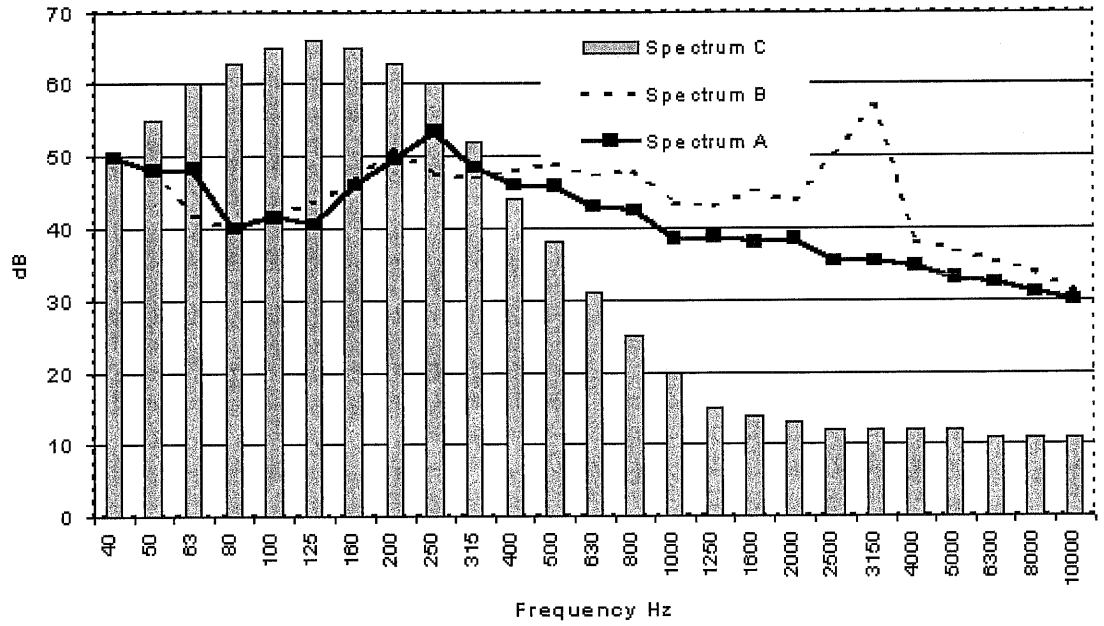

Figure 3 – Frequency spectrums of neonatal units (A and B) and in-utero spectrum (C).

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There are significant variations between the intrauterine acoustic environment and postnatal acoustic environment and as such preterm infants exposed to the postnatal acoustic environment too early, i.e. during the "plasticity period", may result in changes to the development of the higher auditory neural network. Thus, it is suggested that this may have a detrimental effect on the maturational development of preterm infants.

6. DISCUSSION

The 30-40th week g.a. period appears to be a critical period of development for acoustic sensory processing development. Infants born preterm may experience noise levels and frequency spectrum

characteristics significantly different from the in-utero environment. We suggest that the lack of appropriate acoustic environment in this "plasticity period" may be detrimental to the higher order neural functions and maturational development of the infant and as a result lead to increased incidents of central apnoea and bradycardia amongst the preterm neonatal population. The resultant lack of appropriate stimulus may result in delays to ABR development and prolonged latency time intervals. As a result of increased incidences of central apnoea amongst this group, as opposed to term infants, would lead to increased episodes of hypoxia. The consequences of increased hypoxia are delays to cognitive and sensory development and in some cases brain damage. The very preterm and extremely preterm infants groups may never fully experience any of the in-utero acoustic environment and as such are more at risk of abnormal cardiorespiratory function.

Whilst absence from the in-utero environment and low birthweight associated with preterm births may have multi causal implications for other health factors of the infant the significance of the acoustic environment should not be underestimated. The human infant at birth displays a generally low level of sensorimotor development, but its auditory sophistication contrasts sharply with the poorly developed neonatal hearing of most other altricial mammals (Moore *et al*, 1995). Moore *et al* stated "it is not clear why the human auditory system is so singularly precocious, or what biological function could be served by hearing in the weeks preceding birth".

We would suggest that from the various previous experimental paradigms and evidence to date of the role of acoustic sensory processing in cardiorespiratory function that the early and rapid development of the hearing mechanism in the prenatal period is to facilitate the neonate's central auditory pathways for future higher order neuronal pathways. It is proposed that the immediate neonatal environment for preterm infants within hospital units could be altered to account for the absent intrauterine acoustic environment. Such stimuli and frequency spectrums provided may enhance the cardiorespiratory function of these infant groups and assist in neuro-behavioural development.

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