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Sensory performances in the human foetus: a brief summary of research

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A growing body of evidence is available about the functioning of foetal sensory systems during gestation. This article aims at reviewing data concerning (i) the accession of sensory stimulation to the foetal sensory receptors, (ii) the sequence of functional development of the major sensory systems (iii) the physiological and behavioural responses of foetuses to various types of stimulation. Human data are confronted to data collected in other mammalian species. Most studies have investigated auditory and chemosensory (olfactory and gustatory) responsiveness of the fœtus in the second half of gestation. They demonstrate that (i) motor and autonomic (heart rate) responsiveness depends on gestational age and the properties of stimulations.

Keywords : foetus, newborn, sensory development, neural development, vestibular system, somesthetic system, touch, olfaction, gustation, audition, vision, foetal learning, behavioural states

Les performances sensorielles du fœtus humain : un bref résumé des recherches. Le nombre des recherches expérimentales sur le développement fonctionnel des systèmes sensoriels chez le fœtus s'accroît sensiblement. Cet article vise à passer en revue quelques-uns de ces résultats, en particulier en ce qui concerne 1) l'accès des stimulations sensorielles aux structures sensorielles qui les détectent; 2) la séquence du développement fonctionnel des systèmes sensoriels majeurs; 3) les réponses psychophysiologiques et comportementales des fœtus à différentes stimulations. A cette date, la majorité des recherches a porté sur la réactivité auditive et chimiosensorielle (olfactive et gustative) au cours de la seconde moitié de la gestation, aussi bien chez le fœtus humain que chez des fœtus de mammifères non humains.

Mots-clés : Fœtus, nouveau-né, développement sensoriel, développement nerveux, systèmes vestibulaire, somesthésique, toucher, olfaction, gustation, audition, vision, apprentissage fœtal, états comportementaux.

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INTRODUCTION

During the first half of the 20th century, developmental zoologists and psychologists demonstrated that the sensory systems of new-born animals and humans function at a quite good level of performance. Since it is not plausible that this sensory functioning has a sudden inception at birth, this observation raised interrogations about perceptual abilities in the foetus. During the 1970's, the development of ultrasound techniques (cardio-tocography, real-time ultrasonography) allowed the direct observation of foetal behaviour, and made more systematic investigations possible on the onset of responsiveness to sensory stimulation.

Foetal sensory functioning requires: (i) that there are potential sources of stimulation in utero, and (ii) that the sensory systems are mature enough, at both peripheral and central levels. These ecological and functional requirements for foetal sensory activation are surveyed below for each sensory system. The presentation of the different sensory entries will be ordered according to the developmental sequence in which they are known to develop among vertebrates (Gottlieb, 1971). Comparative anatomical investigations demonstrated indeed that sensory systems do initiate their structural differentiation and functional maturation in a given sequence in which somesthetic (tactile) systems are a bit developmentally earlier than the chemosensory (olfaction and gustation) and vestibular systems, the auditory and visual systems evincing delayed functional inception.

A. Somesthetic and proprioceptive systems

1. Potential sources of stimulation

Somesthetic and vestibular systems are generally co-stimulated, especially by foetal and maternal movements. It is quite impossible to determine to what extent each system contributes to an observed response. While the amniotic fluid should buffer the impact of fast maternal motions, the foetus is exposed to an increasing number of local contacts and general displacements as gestation proceeds. These contacts can be established with the uterine wall, but also with self (e.g., hand-body, hand-face, hand-mouth contacts) (Sparling, Van Tol, Chescheir, 1999). This last type of contact may induce sucking behaviour as it is often noted by ultrasonographists

2. Structural development of sensory transducers

*Somesthetic system:*_This complex and diffuse sensory system develops according to a cephalo-caudal pattern. Neuronal free-ending receptors can be found in the epithelium of the mouth and dermis of the peri-oral area as soon as 8-9 Gestational (G) weeks. Meissner and Pacini corpuscles develop soon after. Tactile receptors are to be found on the face, the palms and the soles by 11 weeks. By the 15th week they are found on the trunk and proximal zones of arms and legs, and on the whole skin by the 20th week (Humphrey, 1964). Their density, especially for the free-ending nerves, is then greater than in the adult.

*Vestibular system.*_By the 5th G week, the otic vesicle divides into two parts that will become the saccula and the utricula. The semi-circular canals stem out of the utricula by week 6. The vestibular apparatus is morphologically mature by 14 G weeks.

3. Evidence of foetal sensory functioning

Somesthetic systems. The tactile component associated with several obstetrical interventions elicit a significant heart rate (HR) acceleration in most foetuses. This has been described for either blood sampling at foetal scalp (Clark, Gimovsky & Miller, 1982), a 15-second manual pressure on the scalp (Clark, Gimovsky & Miller,1984) and intra-amniotic injection of fluid (Baxi, Randolf & Miller, 1988). Earlier data were obtained from aborted foetuses during their short extra-uterine life in a body-warm saline bath (Hooker,1952; Humphrey, 1964, 1978). These perinates responded motorically to a light touch on the upper lip as soon as G week 7, when nerve endings have not yet reached the dermis. The whole body surface (except the back of the trunk and the vertex) is responsive to touch stimuli by weeks 13-14. Stronger pressures on the foetal body through maternal abdominal tissues or vigorous shaking of the uterus evoke large HR accelerations that can be accompanied by motor responses (Bradfield, 1961; Issel, 1983). Finally, pressure at the foetal head may evoke HR accelerations (Aladjem, Feria, & Rest, 1977) as well as decelerations (Walker, Grimwade & Wood, 1973).

Regarding thermal and nociceptive sensitivities, several data are at hand. For example, a flush of cold water (4°C) on the foetal face during labor induces a motor response and a HR increase even when administered during a state of low responsiveness (quiet sleep) (Timor-Tritsch, 1978). Except HR changes induced by scalp blood sampling, and the startles evoked by contacts with the needle during amniotic fluid sampling, very little is known about foetal responses to nociceptive stimulation. Nevertheless, it has been shown that the blood concentration of endogenous opiates (β-endorphin and β-lipotropins) are higher after a breech delivery or a vacuum delivery than after a normal, presumably less stressful, delivery (Puolakka, Kauppila & Leppaluoto,1982). Comparing foetal umbilical blood sampling performed from a not innervated region, the placental cord insertion and from the intrahepatic vein, an innervated zone, Giannakopoulos et al. (1999) found a higher level of plasma noradrenalin level in the samples from this last zone. Since there was no correlation between maternal and foetal baseline these results indicate that the foetus can manifest an independent noradrenalin stress response to a needle from 18 weeks gestation.

*Vestibular system.*_Premature babies show Moro-like responses right after birth, by the 25th G week (Humphrey, 1978). Elliot and Elliot (1964) suggested that during the 5th month the foetus starts to orient itself *in utero* using kicking-like actions. A concurrent hypothesis has been raised suggesting central inhibition of vestibular responsiveness (Prechtl, 1985). This mechanism would prevent the foetus from responding to every maternal or self motion. Recent data from our group demonstrate that, by the end of gestation, foetuses display HR changes in response to maternal passive rocking and swaying, the nature and the amplitude of which depend on the duration of the motion (Lecanuet et Jacquet, 2002)

B. Chemosensory systems (olfaction and gustation)

1. Potential sources of stimulation

The amniotic fluid is the most obvious substrate mediating chemical stimulation for the foetal chemoreceptor systems. The fraction of this fluid which is in contact with the oral and nasal chemical receptors is continuously replaced due to frequent inhaling and swallowing activities. These receptors might also be stimulated by fragrant molecules that have entered the foetal blood stream. Such molecules may pass to the chemosensory neuroreceptors from the capillaries which irrigate them (Schaal, 1988). But so far this mode of activation has only been empirically ascertained in the adult.

The amniotic fluid carries a large number of potentially odorous or sapid substances (Schaal, Orgeur & Rognon, 1995). Its composition changes along pregnancy, and in the later stages shows daily variations depending on foetal micturition and maternal food intake. Animal studies demonstrate that olfactory substances which have not been metabolised at maternal, placental or foetal levels collect in the amniotic fluid (Schaal & Orgeur, 1992). The increase of placental permeability along gestation may elevate the placental transfer rate of such dietary odorants. It is well-known indeed by midwives and obstetricians that the amniotic fluid can be tainted with the dominant odour of the food that mothers have ingested shortly prior to delivery (e.g., Schaal & Orgeur, 1992; Schaal & Rouby, 1990). Several of such foodstuffs have been shown to be transferred into the foetal compartment in either animal (Nolte et al., 1992; Desage et al., 1995) or human pregnancies (Hauser et al., 1985; Mennella et al., 1995). In these experiments, the transferred aromas were qualitatively variable, including garlic, cumin, fenugreek or curry, indicating that a wide spectrum of odorigenic compounds may be involved. The transfer of odorants can be relatively rapid as it has been shown in the ewe that the major volatiles of cumin odour are detected in the foetal bladder after a 30-minutes delay from the ewe's intravenous injection with cumin extract (Desage, Brazier and Schaal, unpublished results). But much shorter delays have been described for other compounds, such as nicotine or various drugs, and it is not excluded that smelly substances are passed more quickly to the foetus, concurrently with the in-flow of all other metabolites.

2. Structural development of sensory transducers

Oral chemoreception. Oral chemoreception is mediated through a tacto-chemical pathway via trigeminal innervation of the mouth and through the specific gustatory pathway via the taste buds. These buds can be found as early as 12 G weeks and are morphologically mature by 13 weeks (Beidler, 1961). They are displayed all over the oral cavity at first and then, at birth, concentrate on the tongue, anterior hard and soft palate, epiglottis, pharynx and larynx (Beidler, 1961, Bradley & Mistretta, 1975).

Nasal chemoreception. Nasal chemoreception is performed by three subsystems: i) The main olfactory system, which is tuned to detects weak stimulations, ii) the intranasal trigeminal nerve endings, which mostly responds to stronger stimulations bearing tactile sensation or irritation, and iii) the accessory olfactory system, composed at the periphery by the vomeronasal organ (VNO). The olfactory system shows adult-like ciliated neuroreceptors by the 11th G week. The trigeminal system appears by the 4th G week and responds to stimulation by the 7th week. The VNO initiates its development by 5-8 G weeks and reaches its maximum development at the central projection region (on the accessory olfactory bulb) by the 20th G week. For some embryologists, the accessory olfactory bulb is considered, by this time, to decline (Humphrey, 1940). However, recent data indicate that the peripheral VNO subsists in new-borns and most adults (Johnson, Josephson & Hawke, 1985) in whom it has been suggested to be activated by specific compounds (Monti-Bloch & Grosser,1991). The foetal and neonatal responsiveness of this organ remains unknown.

3. Evidence of foetal sensory functioning

Oral chemoreception. Behavioural data on foetal gustation remain scarce and those who exist are inconsistent. Several studies have attempted to assess the foetal functionality of taste by studying premature infants shortly after birth. The application of sweet stimuli (including glucose, sucrose or saccharin solutions) consistently elicited sucking motions which all experimenters interpret as indices of acceptance (e.g., Stirnimann, 1936; Tatzer et al., 1985). Conversely, bitter tastants tended to inhibit sucking, while sour and salty tastants elicited a less clear pattern of response. From these studies, premature infants of gestational age situated between 6 and 9 months can be considered to express differential responses to taste stimuli, especially sweet and bitter.

Other experimental attempts conducted directly in the foetus capitalised upon such taste-elicited stimulation of neonatal swallowing. In accordance with the data on premature newborns, the injection of saccharin into the amniotic fluid of chronic hydramnios gestations led to a reduction of the maternal abdominal volume that was attributed to increased foetal intake of the fluid (De Snoo, 1937). However, spontaneous fluctuations of the amniotic volume in this syndrome make the conclusions at best tentative (among the two concepti observed after intra-amnionic infusion of sweet stimuli, one increased in amniotic volume, while the other decreased) (Liley, 1972). But, conversely, intra-amnionic injections of a bitter solution seemed to elicit more consistent reductions in foetal swallowing (Liley, 1972).

Otherwise, electrophysiological recordings from foetal lambs have established that gustatory receptors are clearly functional *in utero*. Their responsiveness to various tastants are similar to that of late-gestation foetuses, of newborn lambs or of adult sheep (Bradley & Mistretta, 1973; Mistretta & Bradley, 1978). Nevertheless, foetal responses become larger and more stable as a function of gestational age. Although a large inter-individual variability was noticed, responsiveness to acid and bitter stimuli seems to be elicited earlier than to salty stimuli (Beidler, 1961).

Nasal chemoreception. From the third trimester of gestation all chemosensory systems of the nose seem ready to be functional: the nostrils have become patent and allow amniotic fluid-borne stimulations to flow through the nasal pathways. So far there is no direct evidence of foetal olfaction in the human species. However, numerous studies in various animal models (rat, sheep, rabbit) indicate that such responses are clearly effective (cf Schaal and Orgeur, 1992, for review). In the foetal rat and sheep, for example, intranasal infusions of odorants induce marked HR changes, while a control solution has no such effect (Smotherman et al., 1991). In addition different qualities of odour solutions can elicit opposite directional effects in the autonomic responses

Several indirect demonstrations of olfactory function in the foetus have been provided in examining the responsiveness of premature infants. A sample of prematurely-born infants whose age ranged from less than 28 to 36 G weeks was screened for responses to the odour of mint (Sarnat, 1978). The following results were raised: for the <29 week-, 29-32 week- and 32-36 week-olds, 16% (n=6), 73% (n=11) and 100% (n=15) respondents were recorded, respectively. This latter group of subjects did not differ in response frequency from term new-borns, indicating that during the last G month, the chemosensory pathways are ready to detect (in aerial conditions) a concentrated odorant bearing tactile properties (mint). Subsequent, more refined, assessments of premature olfactory abilities indicate that other odorants are efficient stimuli at high and low concentrations (e.g., Pihet et al., 1996, 1997). It might thus be considered that olfactory abilities derived from premature infants tested right after birth predict comparable abilities in the foetus of equivalent GA (Schaal, Orgeur & Rognon, 1995).

So far, evidence for chemoreceptive function in the human foetus can be drawn from studies examining neonatal responses to stimuli to which the foetus has been exposed in utero, several hours or days before birth. We first investigated whether newly-born infants would make discriminative responses to the odour carried in the fluid which bathed their chemoreceptors during late gestation. Choice tests opposing the odours of amniotic fluid differing in familiarity (own and 'alien' fluid) and a control odorant (water) first indicated that the infants were positively responsive to any amniotic fluid. But when they were facing the more tricky test opposing their own amniotic fluid and the same fluid from another, unrelated foetus, they oriented more quickly and for longer periods toward the most familiar stimulus (Schaal et al., 1995, 1998). Thus, amniotic fluids from different concepti are endowed with idiosyncratic odour qualities that 3-day old new-borns are capable of processing in a selective way.

The nature of the odour cues that mediate that neonatal responsiveness is at present unclear. The idiosyncratic fraction of amniotic fluid may depend on numerous sensory facets (differential intensity, a complex sensory pattern, a unique note) or odour sources (e.g., aromas derived from the mother's diet, from maternal metabolic functioning, or from genetically determined odour types). We have begun to investigate whether an aroma introduced into the foetal compartment through the mother's diet in late pregnancy would affect the odour responsiveness of the new-born (Schaal et al., 2000). Olfactory responsiveness was compared in infants born to women who had or had not consumed anise flavour during the last two weeks of pregnancy. Both groups of infants were followed-up for behavioural markers of attraction and aversion when simultaneously exposed to a pure anise odour and a control odour right after birth and at day 4. Infants born to anise-consuming mothers evinced a stable preference for anise odour over this period, whereas those born to anise-nonconsuming mothers displayed aversion or neutral responses. Another paper recently related the frequency of maternal alcohol drinking during pregnancy with the infants' increase in motor activation when alcohol odour is presented to them at age 1-2 days (Faas et al., 2000). Thus foetal experience with certain odorants fosters memories upon which newborns can rely in the direction of their neonatal behaviour.

C. Auditory system

1. Potential sources of stimulation :

This section surveys some representative results on the auditory properties of the spontaneous environment of the foetus, the extent to which incoming sounds are attenuated by the passage through the maternal tissues, and specifically how human speech can be acoustically detected *in utero* and affect foetal and neonatal behaviour.

The foetal sound environment. The first series of human intra-abdominal recordings was performed using microphones covered with rubber membranes which were (i) vaginally inserted close to the uterus in either pregnant (Bench, 1968, Walker, Grimwade & Wood, 1971, Murooka, Koie & Suda, 1976) or non-pregnant women (Walker, Grimwade & Wood, 1971, Tanaka & Arayama 1969, Busnel, 1979), or (ii) inside the amniotic cavity after rupture of the membranes during or after delivery (Walker, Grimwade & Wood, 1971, Murooka, Koie & Suda, 1976, Johansson, Wedenberg & Westin, 1964, Henshall, 1972). Except for the acoustic band analysis of Murooka et al. (1967) and Busnel (1979), only global measures were performed in these studies. Taken together, they described a very noisy womb (72-96 dB SPL) with only very loud external low frequency sounds being transmitted into the amnion. The considerable background noise was interpreted as originating from the maternal cardio-vascular system.

But more recent investigations using better adapted hydrophones and narrow-band analyses indicate that the womb is a relatively quiet place. When the mother is in a calm environment and when there are no abdominal gurgles, the mean sound pressure levels (SPL) are comparable to those generally encountered in the external environment (Querleu, Renard, Versyp, Paris-Delrue & Crépin, 1988, Gerhardt, 198, Graham, Peters, Abrams, Gerhardt & Burchfield,1991, Benzaquen, Gagnon, Hunse & Foreman, 1990). The recorded intra-uterine background noise is a composite of: (a) intrinsic noise from the hydrophone and amplifiers, (b) ambient external noise and (c) various biological noises from the mother and the foetus (of respiratory, motor, gastro-intestinal, cardio-vascular, or laryngeal origins); it is mainly composed of low frequencies under 500-700 Hz. Pressure levels show a regular and significant decrease as frequency rises. Frequency band analyses have demonstrated that the important global pressure levels previously obtained were due to infra-sounds and/or very low frequencies below 50-60 Hz (Benzaquen, Gagnon, Hunse, & Foreman, 1990, Querleu, Renard, Boutteville & Crépin, 1989) for which human auditory thresholds are very high. Therefore, contrary to a long-held opinion, this high energy does not have a biological origin.

Low-pitched pulsations recorded at frequencies above 50-60 Hz and under 500-700 Hz, and interpreted as originating from vascular activity, were identified either as the beat of the maternal heart (Walker, Grimwade & Wood, 1971, Murooka, Koie & Suda, 1976, Querleu, Renard & Versyp, 1981), the umbilical artery (Graham, Peters, Abrams, Gerhardt & Burchfield,1991), the uterine artery (Bench, 1968), or the utero-placental blood flow (Querleu, Renard, Versyp, Paris-Delrue & Crépin, 1988, Benzaquen, Gagnon, Hunse & Foreman, 1990, Querleu, Renard, Boutteville & Crépin, 1989). Recent data suggest that vascular sounds are not always present at the same SPL everywhere inside the human amniotic cavity. Querleu et al. (1988, 1981), placing transducers at variable distance to the placenta, measured mean SPLs from 65 to 28 dB (the lowest value being obtained far from the placenta with only 20 dB SPL at 500 Hz and no more than 10 dB at and above 700 Hz); an overall 25 dB emergence from background noise was found for the maternal heartbeat. Thus, noises from the placenta may probably have a higher masking effect than those from cardiac origin. Clearly, these data indicate that the foetal sound environment is highly heterogeneous.

In utero attenuation of auditory stimuli. The *In utero*-attenuation of airborne broad- and narrow-band noises and pure tones emitted in proximity (less than 2 meters) of the maternal abdomen varies as a function of the relative position of the sound source and the microphone (Gerhardt et al., 1989; Nyman et al., 1991; Lecanuet et al., 1996). Namely, the intrauterine noise level decreased with increasing distance from the sound source in pregnant ewes (Lecanuet et al., 1996; Peters et al., 1993). Other, less clearly-defined sources of variation of sound attenuation can be summarized as follows (data mainly from the ewe model): (1) The SPL of long wavelengths and low frequency sounds (<300 Hz) generally were similar *in* and *ex utero*. (2) The attenuation of external sounds is heterogeneous along the sound spectrum. *In utero* SPL loss in the ewe is moderate between 400 and 1,000 Hz and grows between 1,000 and 8,000 Hz, peaking at 20 dB (Peters, 1993). But in all recent studies and in both ovine and human species, the maximum attenuation never exceeded 30-35 dB SPL up to 10 kHz. Finally, (3) at higher frequencies, a shift has been found in the ewe, the *in utero* SPL increasing and becoming even higher than the *ex utero* SPL. Using sweeping pure tones Lecanuet et al. (1999) have found such increases at 4,000 Hz. These increases were represented as a series of pressure peaks of resonance and anti-resonance probably due to standing waves caused by reflection of the short waves on the internal walls of the uterus. Their functional significance is not known.

Differentiation of speech from the background noise. Data on voice differentiation and attenuation *in utero* agree with the above data on attenuation of artificial sounds. Recent acoustical recordings revealed that the maternal voice as well as external speech emitted close to the mother clearly emerged from the uterine background noise components over 100 Hz. Various recordings (Busnel et al., 1979, Querleu et al., 1988) have shown that both maternal and another speaker's speech (a) was muffled and significantly attenuated in the high frequency components, but (b) had well preserved prosodic characteristics, and (c) was somewhat intelligible since some phonemes (up to 30%, Querleu, 1988) and words could be recognized by adults when the recordings were performed far from the placenta. This was also true for external voices recorded within the womb of a pregnant ewe (Gerhardt, 1989, Vince, et al. 1982; Vince et al., 1985). Analyses of transmission of stimuli composed of syllables (Vowel, Consonant, Vowel: VCV) showed that "voicing" information was better transmitted *in utero* than "place" or "manner" information, which were less preserved for a female than for a male speaker. *In utero* speech recording, in certain recording conditions, may even be clearly intelligible in the human (Benzaquen et al., 1990, Smith, 1990) or the ewe (Lecanuet et al., 1996, at 90 dB SPL).

Human studies of *in utero* speech transmission performed with a hydrophone placed near the foetal head during delivery have all shown that there is a significantly better transmission of the maternal voice than of any external voice. Querleu et al. (1988) and Benzaquen et al. (1990) measured an overall 20 dB Smith SPL attenuation of external voices, with no significant difference between male and female voices. In contrast, there is only an 8 dB SPL attenuation of the maternal voice. Richards et al. (1992) recorded the maternal voice (external 72 dB SPL level) 5 dB SPL louder *in* than *ex utero*.

The higher *in utero* SPL of the maternal voice compared to the SPL of externally-emitted voices spoken at the same level can be readily explained by the particular mode of transmission *in utero* via two different pathways. On the one hand, the maternal voice is airborne and is transmitted like any other close external sound and may thus be affected by the same acoustic modifications. On the other hand, the maternal voice is internally transmitted via body tissues and bones (Petitjean, 1989).

What sounds reaches the foetal ear? The transmission of external sound pressures to the foetal ear is constrained by two factors (1) the attenuation due to the amniotic cavity and (2) the transformation of the *in utero* pressures into cochlear displacements. While factor 1 has been described above, factor 2 remains unknown. The proportion of the *in utero* SPL that reaches the foetal internal ear depends of the transduction pathway at foetal head which is made either directly through the fluids bathing the external and middle ear or indirectly via bone conduction in the foetal head. Experimental manipulations of the ear channel in the foetal sheep indicates that the principal mode of transmission to the foetal inner ear is through bone conduction (Gerhard et al, 1996). As a consequence of this mode of transmission, the opportunity to localise sounds is probably not available to the foetus

2. Structural development of auditory transducers

In the inner ear, the cochlea develops from the otocyst which appears around the 28th G day. It reaches its full morphological development by G month 5. The organ of Corti, which bears the auditory receptors, develops within the cochlea from the 8th week onwards. The first auditory cells (inner hair cells) and the three rows of outer hair cells are differentiated by G week 11. Neither inner nor outer ciliary cells are functional at this age, nor on the 14th week when the cell positioning on the basilar membrane has reached its final stage (Pujol, 1993). Outer hair cells are located in a typical W shape organisation The number of cells (inner hair: 3,500, outer hair: 2,500) is very small if we compare it to the millions of chemo- or photo-receptor cells. Since these cells have their last mitosis before they differentiate, this number is defined early in gestation (10 weeks) and, if damaged, is not replaced.

Based on comparative evidence, Pujol and Uziel (63), suggested that the human cochlea may be functional by weeks 18-20, despite histological studies have shown that auditory receptors are not completely mature by this time. The first cochlear potentials were recorded at the same developmental stage in animal studies. By week 20 the efferent innervation of the outer hair cells grows out, mature synapses being found in the cochlea between weeks 24 and 28 (Pujol et al., 1964). The maturation of the inner ear probably ends during the 8th month with the organisation of afferent and efferent synaptic connections.

At the onset of cochlear functioning, auditory abilities of animal foetuses are poor: electrophysiological responses can only be recorded for medium frequencies (1,000 to 2,000 Hz, depending on the species); auditory detection thresholds are high (around 100 dB) and frequency discrimination and temporal coding is weak. However, these abilities improve gradually: auditory thresholds decrease, temporal coding begins, and frequency sensitivity widens first in the low range, then in the high range (Rubel, 1983)

3. Evidence for foetal auditory functioning

Studies in several mammalian species have brought electrophysiological and neurochemical demonstrations of foetal auditory function. In the human, cardiac and motor responses to various vibro-acoustic and acoustic stimulations have been examined and some electrophysiological measurements have been performed during labour.

Electrical brain responses. Brainstem and cortical auditory evoked potentials (AEP) have been extensively studied *in utero* in the foetal guinea-pig (Scibetta & Rosen, 1969) and lamb (Woods & Plessinger, 1989). These AEP display the same characteristics and developmental course as those recorded *ex utero*. In the human, they have been recorded with electrodes placed on the foetal scalp during labour (Barden, Peltzman & Graham, 1968, Staley, Iragui & Spitz, 1990). In premature infants, short-, middle- and late-latency AEP have been first detected from G weeks 24-25, and they stabilise by weeks 30-32 (Starr, Amlie, Martin & Sanders, 1977, Pasman, Näätanen & Alho, 1991). Brainstem responses are more reproducible, but with very high thresholds (100 dB SPL) at 25 weeks. Thresholds gradually decrease with development so that by G week 35 they differ only of 10-20 dB Hearing Level from the mature threshold.

Local metabolic responses of the brain. The labelled 2-Deoxyglucose method, which allows to target glucose utilisation in the brain as a function of local metabolic changes triggered by sensory activation, has been used in the foetal guinea-pig (Servieres, Horner, Granier-Deferre, 1986; Horner, Servières and Granier-Deferre, 1987) and sheep (Abrams, Peters, Gerhardt and Burchfield, 1993) Pure tones (guinea-pig), and vibro-acoustic stimulation (sheep) induce a marked increase in 2-DG uptake in the auditory pathways. In the guinea-pig foetus, frequency-specific auditory labelling has been obtained to loud, external pure tones up to 20 kHz. The location of the labelling in the cochlear nuclei and in the inferior colliculi is a function of the frequency of the tones. Thus, the tonotopic organisation of the structures processing auditory information is already evident *in utero*.

Further demonstration of prenatal auditory activation was recently obtained with brain imaging techniques (*viz*., fMRI) (Hykin, Moore, Duncan, Clare, Baker, Johnson, Bowtell, Mansfield, & Gowland (1999). The recording of a nursery rhyme uttered by the mother was presented 18 times to three foetuses aged 38-39 G weeks (at a level of 100dB for periods of 15 sec alternated with 15-sec periods of silence). In two foetuses whose results could be processed a significant activation could be detected in the cortical auditory region. Up to now this study brings the only direct *in vivo* evidence of foetal hearing.

Behavioural studies. Abundant research has been conducted on the foetal responses to external sounds. These investigations are methodologically diverse in that they used variable sounds transmitted by various techniques, focused on different response variables at different periods of foetal development and in different receptivity states of the organism.

Structure of stimulations and their mode of administration. The first investigators of foetal perceptual abilities were guided by maternal testimonies about their infant moving in response to a very loud noise. Thus, fœtal responses were first analysed with complex, realistic stimuli, such as warning horns (Peiper, 1963/1925; Fleischer, 1955) and wood claps (Forbes & Forbes, 1927; Ray, 1932; Spelt, 1948). Later, experimenters used more carefully defined acoustic stimulation, such as pure tones and band noises, emitted through loudspeakers located at various distances from the maternal abdomen. Still later, this airborne mode of stimulation was abandoned in favour of stimulation directly applied on the mother's skin, near the foetal head, so as to minimise sound attenuation. Two procedures were used: a) Stimulation was directly transmitted to the maternal abdomen by a vibro-acoustic source (bone vibrator, tuning fork, electric toothbrush or Electro-Acoustic Larynx, EAL). The EAL delivers broad-band noises at a fundamental frequency of 87 Hz with multiple harmonics up to 20,000 Hz (Gagnon, Hunse, Carmichael et al, 1986; Gagnon, 1989). Intrauterine pressure estimation during EAL application varies between 95 dB (Grimwade, Walker, Bartlett, Gordon & Wood, 1971) to 138 dB (Gagnon, Benzaquen & Hunse, 1992; Gerhardt, Abrams, Kovaz, Gomez & Conlon, 1988). b) Stimulation was air-coupled, and in most cases the loudspeaker was isolated from the mother's abdomen with a rubber or foam ring.

Both above methods introduce shortcomings. Vibro-acoustic devices propagate sound pressure more efficiently through tissues and fluids than through air. Thus, such devices may activate foetal cutaneous receptors and also possibly the vestibular system. The air-coupled procedure is likely to result in important stimulus alterations if the loudspeaker is applied against the mother's abdomen. The loudspeaker membrane is then partially blocked and produces frequency distortions. Therefore, the acoustic conditions produced by these two procedures are very different from those of foetal auditory activation by external everyday sounds. This is probably why, in the 1980's, investigators came to use airborne stimulation by placing loudspeakers at various distances from the maternal abdomen (1 to 0,1 m) (Querleu, Renard, Boutteville & Crépin, 1989; Querleu, Renard, Versyp, 1981; Granier-Deferre, Lecanuet, Cohen & Busnel, 1983; Lecanuet, Granier-Deferre & Busnel, 1988).

Since foetal studies began, the variety of stimuli used via the different administration modes - airborne, air-coupled or vibratory is considerable, including pure tones, various bandwidth frequency noises, high-pass filtered or unfiltered pink or white noises, and the EAL stimulation. In addition, the SPL varied across a wide spectrum (from 65 to 123 dB SPL), but most studies were performed at or above 100 dB SPL.

*Nature of foetal responses***.** The first systematic observations of the fœtus quantified motor responses and concomitant heart rate changes in response to various acoustic stimuli.

Motor responses. In the early studies, motor responses were classified either as isolated, strong, and sudden (startles), or as sustained. Inhibition of ongoing movements (Tanaka & Arayama, 1969; Fleischer, 1955; Vecchietti & Bouché, 1976; Bouché, 1981) and habituation to the stimulus (activity cessation or decrement) were regularly observed in many studies (Johansson, Wedenberg & Westin, 1964; Sontag & Wallace, 1934; Ogawa, 1955). In order to detect foetal startles, early investigators relied either on visual or tactile estimation of foetal movement or on mother's descriptions. As maternal perception of movement is poorly reliable (Kisilevsky, Killen, Muir, and Low, 1991) various transducers were designed to more objectively record foetus-induced changes on the maternal abdominal wall (Ray, 1932; Sontag & Wallace,1934; Sontag & Wallace, 1936; Goupil, Legrand, Breard, Le Houezec & Sureau, 1975). But the analysis of foetal motor responses was clearly boosted with the advent of real time ultrasound scanning systems. A great number of studies produced startle response estimates by looking at a transverse view of the foetal trunk and lower limbs.

Components of the startle response have been ultrasonographically analyzed as head rotations and/or retroflexions, extension/flexion of upper and lower limbs, and hand or mouth opening (Divon, Platt, Cantrell, Smith, Yeh, Paul, 1985; Visser, Mulder,Wit, Mulder & Prechtl, 1989). Tongue protrusions, cheek movements and hand-to-face movements, the simultaneously occurrence of which is rare, have also been reported (Kuhlman, Burns, Depp & Sabbagha, 1988). In the very first study performed using a vibroacoustic stimulus, Birnholz and Benacerraf (1981) observed the eye-blink.

Stimulus-response latency for specific movements (isolated leg movements, eyeblink) has not often been measured. Hepper and Shahidullah (1992) found an average latency of 0.34 sec in 34-35 week foetuses (evoked by a pure tone 250 Hz stimulation delivered at 80-100 dB), a value close to those recorded in term newborns.

Looking at leg movements during a 5-sec airborne 105-110 dB broad band noise, Granier-Deferre and Lecanuet et al. (Granier-Deferre, Lecanuet, Cohen & Busnel, 1985; Lecanuet, Granier-Deferre, Cohen, Le Houezec & Busnel, 1988) defined three types of fast movements: (i) a leg flexion/extension, (ii) a double flexion at hip and knee levels, and (iii) leg movements induced by a global body displacement. Median latencies of these movements ranged from 0.73 to 2 sec depending on the acoustical structure of the noise. These values are longer than the acoustic startle latencies recorded in the newborn: from 0.16 to 0.67 sec (Peiper, 1963/1925; Irwin, 1932; Monod & Garma, 1971; Steinschneider, Lipton & Richmond,1966; Weir, 1979).

Some very intense acoustical stimuli (>110 dB) and most vibroacoustic stimuli induce long lasting (up to 30 min., 18) increases in the number of movements compared to the pre-stimulation period. This increase usually reflects a change in foetal state.

Heart rate response. Cardiac responses are mostly composed by phasic Heart Rate (HR) accelerations, but also sustained HR modifications, such as tachycardia, or a change in HR variability. Some authors studied both motor and cardiac responses and showed that the rate of motor response was lower than the rate of cardiac acceleration (Tanaka & Arayama, 1969). Most studies on foetal audition have used loud stimuli for two reasons: the long-held, false conception that the fœtus is acoustically insulated and the feasibility of fœtal auditory testing. The use of these startling, loud stimulations led to interesting insights into the developmental timing of sound-elicited responsiveness and sensory keenness.

Studies using broad band vibro-acoustic noises have shown that motor responses were evoked in some foetuses as early as 24 G weeks (Grimwade, Walker, Bartlett, Gordon & Wood, 1971; Leader, Baillie, Martin & Vermeulen, 1982; Crade & Lovett, 1988) and in all subjects at 26 weeks (Kisilevsky, Muir and Low, 1992), 28 weeks (Querleu, Renard & Versyp, 1981; Grimwade, Walker, Bartlett, Gordon & Wood, 1971; Birnholz & Benacerraf, 1983) or 30 weeks GA (Divon, Platt, Cantrell, Smith, Yeh, Paul, 1985; Leader, Baillie, Martin & Vermeulen, 1982; Crade & Lovett, 1988; Druzin, Edersheim, Hutson, Bond, 1989). According to Leader et al. (1982) only 7% of foetuses responded by 23-24 weeks, while 89% responded by 27-28 weeks. The onset of the response occurred earlier in females than in males (by 25-26 weeks, 75% of the 12 females responded compared to only 33% of the 15 males; all females responded by the 28th week, whereas 80% of the males responded at this age level). This fits in with neurophysiological data indicating that females mature earlier than males (Singer, Westphal & Niswander, 1968). Concerning cardiac responses, a 5-sec EAL stimulation induced first an acceleration followed by a delayed response consisting in an increased occurrence of HR accelerations during a 20-min post-stimulus period. The appearance of the first HR response seems delayed by 2-3 weeks compared to motor responses (Jensen, 1984; Druzin, Edersheim, Hutson & Bond, 1989; Gagnon et al, 1987a; Kisilevsky et al. (1992) did not find reliable HR accelerations before 29 weeks. In a recent article Kisilevsky et al (2000) comparing foetal responses to airborne sound (pulse white noise filtered <800Hz) of high and low risk foetuses stimulated at various intensity levels found that the first cardiac acceleration and body movement occurred at 30 weeks for a 110 dB stimulus in both groups. Threshold decreased from 110 to 105dB at 33weeks and from 105 to 100dB at 36 weeks GA.

Airborne stimulation of low SPL (between 85 and 100 dB SPL *ex-utero*) do not induce startle responses or cardiac accelerations, but rather evoke moderate HR deceleration without movements. For example, Lecanuet et al. (1988) found that a 500 Hz octave-band noise emitted at 100 dB elicited only HR deceleration and that the deceleration had the same amplitude in quiet and active sleep (<10 bpm). This more shallow response had been mentioned by many authors (Tanaka & Arayama, 1969; Vecchietti & Bouché, 1976; Dwornicka, Jasienska, Smolarz & Wawryk, 1964; Bernard & Sontag, 1947; Goodlin & Schmidt, 1972; Goodlin & Lowe, 1974). These HR decelerations could be reliably elicited in foetuses in quiet sleep by various types of continuous or rhythmic airborne stimuli. These responses quickly habituated to stimulus repetition, which made them suitable to examine auditory discrimination in the 36-40 week-old foetus using an habituation procedure.

Foetuses exposed every 3.5 sec to a pair of syllables ([ba]-[bi], or [bi]-[ba]) uttered in French by a female speaker, and emitted at the same pressure level (95 dB) displayed habituation of the decelerative HR response (Lecanuet, Granier-Deferre, DeCasper, Maugeais, Andrieu & Busnel, (1987). Reversing the syllables whithin each pair after 16 presentations reinstated the initial decelerative response, suggesting that the foetus discriminated both stimuli. This discrimination may have been performed on the basis of an intensity difference between the [ba] and the [bi], since the equalization of these syllables was done on the basis of the SPL, not the hearing level.

To further assess fœtal discrimination, a more conservative analytic procedure was used which took into account each subject's pre-stimulus HR variability (Lecanuet, Granier-Deferre, Jacquet & Busnel, 1992). This procedure quantified for each subject whether the stimulus presentation and its acoustic modification: (i) induced a HR change, (ii) the direction of this change, and (iii) its amplitude. The results indicate (1) that near-term foetuses exposed to the short sentence « Dick a du bon thé » uttered by a male voice (minimum fundamental frequency (Fo) = 83 Hz) or a female voice (minimum Fo = 165 Hz) at the same hearing level (90-95 dB SPL) and at 3.5 sec intervals, reacted with a high proportion of decelerative responses (77 and 66% to the male and female voice, respectively) within the first 10 sec of stimulation compared to a group of non-stimulated subjects. After return to a stable HR pattern, the initial voice (male or female) was either replaced by the alternative voice or continued (control condition). A majority (69%) of the experimental subjects displayed a HR deceleration to the stimulus change, while 43% of the control subjects displayed a weak acceleration (Lecanuet, et al., 1992). This pattern of response is interpretable in terms of response to novelty and indicates that near-term foetuses may perceive a difference between the vocal properties of two speakers, at least when they are highly contrasted in Fo and timbre. These results cannot be generalized to all female and male voices and for all utterances, however. It should be emphasized that in this experiment HR change occurred within the first seconds of exposure to the novel stimulus, thus suggesting that only a short speech sample is needed for the foetal auditory system to detect an acoustically relevant change in stimulus. Since the most obvious acoustic cues for discrimination are fundamental frequency and timbre, near-term foetuses in quiet sleep may perform pitch discrimination between two piano notes C4 and D5 separated by a diminished seventh (Lecanuet et al., 2000).

Foetal responses to maternal speech

It was mentioned above that maternal speech was efficient in inducing foetal HR decelerations. Unpublished data from our group suggest that this response is most frequently elicited in low HR variability state and when the mother speaks with a 70 dB Leq[1] level. Recent work by Masakovsky and Fifer demonstrated that near term

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[1] Leq: equivalent continuous sound level: average sound level. The level of a steady sound which, in a stated time period and at a stated location, has the same A-weighted sound energy as the time varying sound.

foetuses tested in quiet sleep, showed a HR decrease from baseline during the last 5 sec of a 10 sec episode of loud maternal speech (Masakovski & Fifer, 1994). Silence or mother whispering episodes did not evoke a significant HR change. Such changes are commonly expected to be easily evoked, maternal voice being 8 to 12 dB louder *in utero* than any other female voice measured at the same *ex utero* level. But the fact that maternal prosodic cues are a constant element of the foetal environment, foetal responsiveness (HR one) may be reduced by such factor.

D. Visual system

1. Potential sources of stimulation :

In utero visual stimulation appears to be very limited; however Liley (1972) recalls that - in a dark room - the amniotic cavity may be illuminated with a torch light, especially in the case of polyhydramnios. Measurements performed during rat and guinea-pig gestation have demonstrated that if only 2% of incoming light was transmitted in utero below 550 nm, this value increases with the wavelength of the signal to reach 10% around 650 nm (Jacques, Weaver & Reppert, 1987). Thus, a limited portion of external light may reach the human foetal retina when eyelids are open (by G week 20) or through the eyelids.

2. Structural development of sensory transducers

The optic vesicles in which the retina originates appear by 30-32 days of gestation. Major retinal morphogenetic events occur between months 2 and 4 of gestation. Rods and future cones can be found by the end of the 3rd month, but the development of photoreceptor cells is not completed before birth.

3. Evidence of foetal sensory functioning

The presumed restricted amount of visual input *in utero* has not stimulated the investigation of responsiveness to this type of sensory stimulation. A few studies have been conducted which suggest that : (a) switching on a bright light bulb in front of the abdomen of a pregnant woman induces foetal heart rate accelerations (Smyth, 1975); (b) an increase of foetal motor activity may be obtained after a sustained exposure to light (20 min.) but not after a series of “on and off ” switches (Polishuk, Laufer & Sadovsky, 1975). However, HR changes induced by a cold light introduced during an amnioscopy represent more convincing data (Peleg & Goldman, 1980) since they reflect an immediate response to the stimulus and not a differed change in activity that could be due to a shift in behavioural state occurring spontaneously. The ontogeny of visual evoked potentials has been described in the foetal sheep (Lecanuet, Granier-Deferre & Busnel, 1991). Stimulation was delivered by a tiny light source secured close to the eye.

CONCLUSION

Among the numerous questions that may arise from this review the following ones emphasize major issues.

- ☐ What is recorded *in utero* with artificial sensors? Can it be equated to what is effectively sensed by the fœtus? We are unfortunately not able to verbally recall memories from the *in utero* period and thus to evoke the nature of foetal perceptions.
- ☐ What is the effect of prenatal sensory experience on the development of cognitive abilities? Which abilities are present *in utero*? Which are prepared by fœtal experience? How is sensory integration processed in the flow of all modalities?
- ☐ What is the postnatal adaptive function of prenatal sensory, motor and integrative exercise?

The “foetal behaviour science”, enters now in a stage where some of these questions could start to find some answer.

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