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Review article

Correlation between human nervous system development and acquisition of fetal skills: An overview

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Abstract

Understanding the association between fetal nervous system structure and functioning should be an important goal in neurodevelopmental sciences, especially when considering the emerging knowledge regarding the importance of prenatal onset. Intrauterine development of the human central nervous system consists of specific processes: neurogenesis, neuronal migration, synaptogenesis, and myelination. However, as extensively shown by the neurobehavioral studies in the last century, the development of the central nervous system involves both structure and functioning. It is now recognised that the developing motor and sensory systems are able to function long before they have completed their neural maturation and that the intrauterine experience contributes to neurobehavioral development. This review analyzes the recent literature, looking at the association between the human nervous system maturation and fetal behavior. This article will follow the development and skill acquisition of the anatomical nervous system across the three trimesters of the gestation period.

Keywords: Fetus; Development; Nervous system; Learning; Behavior

1. Introduction

The emerging knowledge regarding prenatal human neurodevelopment [e.g. 1] highlights the complexity of the progressive functional maturation in the fetal nervous system. Changes in behavior and in the electrical activity of the fetal brain clearly reflect this complexity.

From a neuroanatomic point of view, the intrauterine development of the human central nervous system consists of four developmental processes: neurogenesis, neuronal migration, synaptogenesis, and myelination [2]. However, neurobehavioral and embryological studies in the last century have shown that the development of the central nervous system involves both structure and functioning in human and other vertebrate species as fish, amphibians, birds and mammals [3,4]. It is now

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recognised that developing motor and sensory-perceptual systems are able to function long before they have completed their neural maturation and that various contributions of experience to behavioral development can operate pre- as well as post-birth [4]. Graven and Browne [5] suggested that brain development is influenced by different factors such as the genetic endowment and the epigenetic effects from the environment, the endogenous or spontaneous neural activity, and the stimulation of the sensory and motor organs by the physical and chemical stimuli reaching the human fetus [4,6] and other animal species [6].

Architectural framework and functional capacities of the major neurotransmitter systems are established quite early in gestation, even though their functioning in early cortical development is, at present, poorly understood in humans. Their functional expression consists of a variety of behavioral patterns from fetal to neonatal life as the nervous system matures [2]. Currently, the moment in which the human fetus is able to respond to a stimulus not just as a reflex is still open to debate [e.g. 7,8]. Some authors maintain that the maturation of the neuroanatomical apparatus is necessary in order to allow perception at a cortical level. Recent noteworthy research highlights the development of neural network connectivity in the third trimester as useful for a complex elaboration of stimuli. This has been extensively demonstrated by various studies on the human fetus learning skills [9].

The present review analyzes the recent literature investigating the correlation between nervous system maturation and fetal behaviour, integrating the authors' competences in both the psychological field and neuroanatomy [e.g. 10–17]. The development of the human nervous system and the acquisition of skills will be presented using a temporal subdivision of gestation in three trimesters (Fig. 1).

2. First trimester of gestation (from 0 week to 13 weeks + 1 day)

2.1. The development of the nervous system

The development of the nervous system starts at gestational age (GA) weeks 2–3 with the folding and fusion of ectoderm to form the neural tube [18]. At GA week 4, the rostral portion of the neural tube forms three vesicles (prosencephalic, mesencephalic and romboencephalic vesicles) which will become the forebrain, the midbrain, and the hindbrain [18]. The prosencephalic vesicle then forms two vesicles that are destined to become the diencephalon (thalamus, hypothalamus, and other structures) and the telencephalon (cerebral cortex). The structural development of the telencephalon has been detailed in Fig. 2 [19,20].

By GA weeks 5–6, neuroblasts, or neuronal precursors, proliferate rapidly [21,22] within the ventricular and subventricular zone (germinal matrix) and, at about GA week 5, the neurons located in the first recognizable cortical layer, known as the preplate, form the earliest synaptic connection. The preplate is the initial synaptic target for neuronal projections from the developing thalamus and brainstem and forms a functionally active primitive cortical circuit [e.g. 2,23,24].

By GA week 8, the laminar structure of the cerebral cortex is defined; the initial cortical neurons migrate and form the cell-dense cortical plate [23,25]. The cortical plate together with the marginal zone (above it) and the pre-subplate (below it) forms a trilaminar anlage of the early fetal cortex, in which the first synapses appear in a bilaminar fashion above and below the cortical plate [26]. Thus, an important question is whether these early synapses are present only in an intrinsic cortical circuit or also in an extra-cortical circuit established with subcortical afferent inputs. Kostović et al. [27]

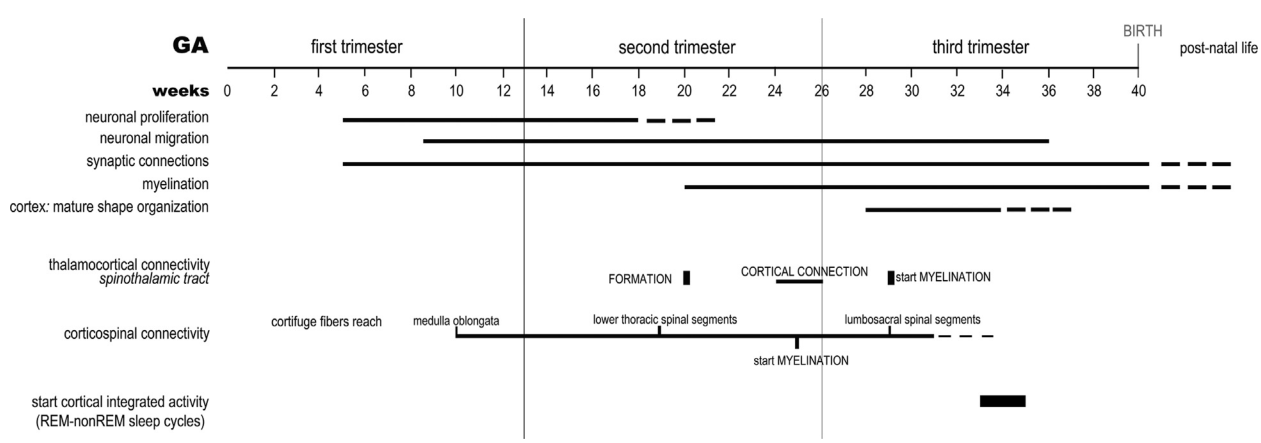

Fig. 1. Timeline of the neurobiological processes in the telencephalon and the sensitive/motor connectivity during human ontogeny. The weeks of gestational age (GA) are reported and related to the major events during fetal neural development: neuronal proliferation [21,22]; neural migration [9,21,67]; synaptic connections [2,9,23,24,52,53]; myelination [51]; cortex (mature shape organization) [51]; thalamocortical connectivity (spinothalamic tract) [9,44,52,53], cortico-spinal connectivity [31–33,64–66]; start cortical integrated activity (REM-nonREM sleep cycles) [50].

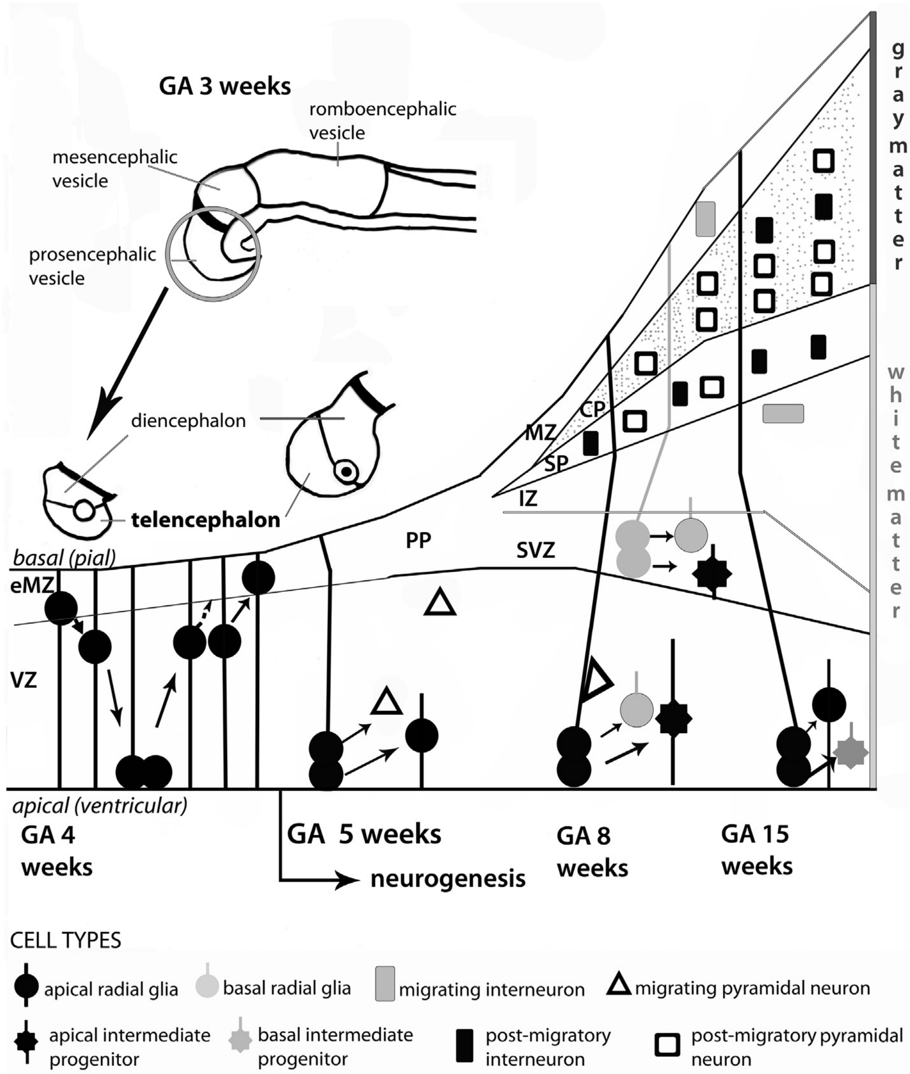

Fig. 2. The neuro-ontogenic process starts at gestational age (GA) weeks 2–3 with the constitution of the neural tube. At GA week 4, the rostral portion of the neural tube forms the prosencephalic, mesencephalic and romboencephalic vesicles. The prosencephalic vesicle then forms two vesicles that are destined to become the telencephalon and the diencephalon (thalamus, hypothalamus, and other structures). The schematic diagram represents the development of telencephalon [19,20]. Initially, the telencephalic primordium is constituted by dividing neuroepithelial cells (often called neural stem cells), characterized by interkinetic nuclear migration, which form the ventricular zone (VZ). There, one type of cells, the radial glial cells, is particularly prominent and distinctive. At GA week 4, they undergo to an early exponential proliferation increasing the number of progenitor/intermediate progenitor cells and the thickness of VZ. Early born neurons are interneurons which move within the marginal zone (MZ) and intermediate zone (IZ). The MZ will eventually form cortical layer I and, for some authors, MZ could be identified also before the cortical plate (CP) formation as early MZ (eMZ). The IZ is a cell-sparse compartment and exists before the appearance of the CP. Radial glial cells and intermediate progenitor cells can be classified in two distinct subpopulation: apical, resident in VZ with bipolar fibers, and basal, which delaminate from VZ with unipolar basal fiber. Apical progenitor cells in the VZ and basal progenitor cells in subventricular zone (SVZ) are considered the main source of pyramidal neurons. Around GA week 5, the neurogenesis begins and the neuronal precursors proliferate rapidly within the VZ. The neurons located in the first recognizable cortical layer, known as the preplate (PP), form the earliest synaptic connections. PP is a transient structure present before the appearance of the CP. Around week 7, the PP cells contribute to the subplate (SP) which remains below the CP after its formation and contains post-migratory pyramidal neurons and interneurons. Moreover, the accumulation of basal progenitor cells creates a distinct new compartment above the VZ, the SVZ. Here, they divide and are considered an additional source of intermediate progenitor cells. By GA week 8, radially migrating neurons from VZ and SVZ initiate the development of the layered CP forming from inside to outside. For example, pyramidal neurons eventually migrate outward along the radial glial cells.

supposed that it is probable that no thalamocortical connectivity exists to provide the interaction between the somatic periphery and cortical neurons during the early fetal period, which likely corresponds to oscillatory models of spontaneous, endogenous circuitry described in experimental studies [28]. Nevertheless, the earliest cortical activity can most probably be modulated by early monoaminergic afferents originating from the brainstem [29] and cholinergic afferents from the basal forebrain [30].

The corticospinal system (or pyramidal system) is the principal motor system for cortical mediated movements. The first corticofugal projections originate in the first embryonic period of cortical development [31,32]. Therefore, the corticospinal tract arises in a very immature cortical plate. The corticospinal tract reaches the caudal medulla (medulla oblongata) at GA week 10 [31,33].

At GA 12 week neuronal migration begins to peak until 20 weeks together with the second phase of synaptogenesis, which takes place at around GA week 12–17 in the cerebral cortex and follows an inside-out gradient of density similar to neuronal migration [9].

2.2. The development of sensory and motor skills

The sensory system's basic structure develops early in gestation. Neuroembryological studies showed that in a wide variety of species, particularly in mammalian and avian species, sensory systems start developing at the embryonic stage following a fixed sequence: the somesthetic system (tactile and nociceptive sensitivity), the chemosensory system (smell and taste), the vestibular and the auditory systems and finally the visual system. Humphrey [3] reported evidence, from histological studies, for perioral cutaneous sensory receptors at GA week 7.5, for palmar cutaneous receptors at GA week 10 and for abdominal cutaneous receptors at GA week 15. Lee and colleagues [34], in their systematic review on fetal pain perception, confirmed Humphrey's data reporting a spinal reflex arc in response to tactile stimuli at GA week 8. An outline of a primitive olfactory bulb is seen at GA week 4.5 [35]. Humphrey's [36] histological studies suggested that indications of a sector arrangement of the mitral cell layer first appears at GA week 11 and, by GA week 15.5, the sectors are most clearly defined. A study examining human embryonic/fetal tongues by means of transmission electron microscopy, documented the taste bud cells formation around the GA week 8 and the presence of taste pores by the GA week 14 [37]. By this age, chemical stimuli are likely to be received from the amniotic fluid since synaptic contacts between taste bud primordium cells and afferent nerve fibers are fully developed [37].

In the auditory system, the inner ear and vestibular organs start to differentiate as soon as GA week 4 [38]. The middle ear starts its development at GA week 8; the eardrum membrane begins at GA week 11 continuing its development until the 8th month. The development of the organ of Corti, seat of the auditory receptors, in the inner ear starts at GA week 10. At GA week 12, the hair cells are visible and, by GA week 15, the synapses and stereocilia of inner hair cells are developed [39]. Regarding the visual system, electron microscopy studies have shown that by the end of the GA 8 week the early corneal endothelium is formed, and the development of Descemet's membrane begins with the formation of a lamina below the corneal endothelium, which is completed during the third and fourth month [40].

Considering the motor development, Preyer's [41] pioneering studies highlighted that autogenous motility can be observed even before the establishment of the neural sensorimotor reflex arcs. Ultrasonographic studies show that, as early as GA week 7, movements of the whole embryonic body are evident matching the formation of the first synapses and brain's electrical activity; by GA week 16 almost the entire repertoire of movements characterising the full-term fetus already exists [3,42–44]. Some investigations indicate that facial reflexes in response to somatic stimulation begin at GA week 7 and are fully present at GA week 11 [45]. These reflexes seem to be coordinated by subcortical systems and probably reflect the development of these lower brain circuits [46]. From a functional point of view, the hands show reflex activity around GA week 10, while the lower limbs start these reflexes around GA week 14. Then the number of synapses significantly increases between GA weeks 13 and 15. At this stage fetal movements include: general body movements, startle and twitch movements, isolated limb movements, breathing movements, hiccups, isolated head and neck movements, sucking the thumb and swallowing, jaw movements (including yawning), hand-face contact, stretch and rotation [43]. Evidence of a right-side handedness bias in the human fetus has been found since GA week 10 (for a review see [47]) and more recent research supports this conclusion and suggests a more stable handedness can be detectable from GA week 18 [48].

3. Second trimester of gestation (from 13 weeks + 2 days to 26 weeks + 2 days)

3.1. The development of the nervous system

At the beginning of the second trimester, the subplate zone becomes visible as a cell-poor/fibre-rich layer situated between the intermediate zone and cortical plate. The subplate is a transient though important embryonic cortical layer and represents a key connectivity compartment of the neocortical anlage [49]. Between GA weeks 18 and 22, neurons in these portions of the subplate receive preliminary afferent inputs from the visual and somatosensory thalamus, cholinergic afferents from the basal forebrain, and monoaminergic afferents from the brainstem [21]. In particular, cortical electrical activity has been observed at GA week 19 while spinothalamic tract is formed at GA week 20 [44].

Regarding the development of descending pathways, the influence of the supra-spinal structures on fetal motor behavior during the period between weeks 17 and 20 is confirmed by studies in anencephalic fetuses [50]. Moreover, the pyramidal decussation of the corticospinal tract is completed by GA week 17. An increase in the number of pyramidal tract fibers occurs at cervical levels between GA week 16 and 17. Lower levels of the spinal cord is reached by GA week 19 (lower thoracic cord) [31,33].

Between GA weeks 20 and 28, mature myelin is detected first in subcortical regions and later in cortical regions [51]. The thalamic-cortical connections penetrate into the cortical plate between GA weeks 24–26 and the spinothalamic tract is myelinated around GA week 29 [44]. The synaptic refinement begins [52,53], and the third phase, which was called the synaptic 'big bang' by Jean-Pierre Bourgeois, starts ending 8 to 12 months after birth [9].

3.2. The development of sensory and motor skills

In the second trimester, the somesthetic system and the chemosensory system complete their development. Taste buds have an adult-like morphology and distribution before the end of the 4th gestational month [54] and, by the end of the 2nd gestational trimester, the olfactory mucosa is well developed [55]. Histological studies show that neurons for nociception are present at GA week 19 while thalamic afferents reach the subplate zone at GA weeks 20–22 and the cortical plate at about GA week 23 [27,34]. Therefore, there is a debate whether fetal perception of pain starts at this stage or before (see [56,57]).

The cochlear structures are mature and start functioning by GA weeks 18–20 [58]. At GA weeks 18–20, vestibular reflexes are first elicited and by GA weeks 23–24, the auditory startle reflex has been observed [38]. The auditory nerve pathways are active at GA weeks 24–25, well before completing the myelination process, which continues up to two years after birth. The onset of a sudden body movement in response to vibroacoustic stimuli is observed at GA weeks 24 to 26, with the amount of movement increasing gradually as gestation progresses [59]. The low frequency sounds (below 250 Hz, which is where the human voice lies) are more easily transmitted in utero. There is substantial agreement that the nature of the stimulus, its frequency and intensity, and the stage of fetal development modulate the latency and magnitude of the response [60].

The visual systems show important developmental steps in the second trimester, with most of the retinal structures starting to form around GA week 24 in absence of visual stimulation [61,62]. At about GA week 16 the first slow changes of eye position can be observed with the aid of real time ultrasonography. At GA weeks 18–20, more rapid eye movements are detectable.

Maternal sensation of movement usually commences after GA weeks 16–18 [43]. Motor response to vibroacoustic and acoustic stimuli are consistently reported by the end of the second trimester [59] and anecdotal maternal observations report fetal responses to mother's stimulations [60].

4. Third trimester of gestation (from 26 weeks + 3 days to 40 weeks)

4.1. The development of the nervous system

From about GA week 24, thalamocortical axons grow into the somatosensory, auditory, visual and frontal cortices [63].

Myelination of the corticospinal tract usually starts at the end of the second or the beginning of the third trimester and it is already in progress at the level of the pyramidal decussation at GA week 25; it is complete at the age of two to three years [64–66].

By GA weeks 26–29, neuronal migration is largely concluded [21,67]. As neurons complete their migration, they extend axons and dendrites to appropriate synaptic partners for the synaptic connections, which are often transient.

Around GA week 28, the refinement of synaptic connections causes the start of the subplate dissolution, even if it remains present (as a recognizable architectonic compartment) under the prefrontal and other association cortices up to 6 postnatal months [23]. Transient connections now yield to more stable patterns of neural connections for generating goal-directed activity. The cortical plate increasingly acquires the organizational features of the mature cortex [51].

Thus, the available evidence suggests that the human fetus can receive a thalamic input through the transient subplate zone at the end of the midfetal period [63,68]. In fact, around GA week 29, the spinothalamic tract is myelinated and the functional connection between the periphery and functioning cortex is established, as demonstrated by different studies on pain perception [69,70].

Regarding the development of descending pathways, the corticospinal tract reaches the lumbosacral tract of spinal cord by GA week 29 [33].

By GA week 32, the developing cortex has a full adult feature [2] containing afferents of all the major neurotransmitter systems [71]. At GA weeks 34–35, there is a synchrony between the two hemispheres [63].

Between GA weeks 36 and 40, the proportion of total brain volume that contains myelinated white matter increases from 1 to 5% [72]. Patterns of connectivity in human fetal brain networks have been found using resting-state functional magnetic resonance imaging in a study on fetuses between GA weeks 24 and 38 [73]. The fetal brain demonstrates cerebral-cerebellar and cortical-subcortical connectivity. Many forms of cerebral connectivity, motor, visual, default mode, thalamic, and temporal networks are present by the third trimester. Default mode network connections are evident in fetuses older than 35 weeks. Long-range functional connectivity is more prominent in older fetuses. From GA week 38 to the term, there is maturation of long intrahemispheric (associative) and interhemispheric (callosal) cortico-cortical connectivity [68].

4.2. The development of sensory and motor skills

The third trimester is the period in which the fetal sensory systems show functionality and integration. Literature has proved that at this stage the fetus is able not only to feel and react to environmental stimuli but also to learn and recognize them before and after the birth [74–76].

Mistretta and Bradley [77] reported ultrasound observations of fetal increased swallowing when saccharine was injected in the amniotic fluid and decreased swallowing in presence of an unpleasant flavor by GA week 34. Experimental data show that new-borns in the first post-natal hours recognize and prefer their mother's amniotic fluid smell independently from the type of feeding [55].

The auditory system is already well developed; the onset of hearing has been established at about GA week 29 and at this time the auditory system is similar to the postnatal one (unless for higher threshold and slower latency of response) [59]. At this stage, a new kind of response to auditory stimuli is evident: a modification of cardiac frequency in response to sound [78]. Using a classical habituation paradigm, a fetal heart rate acceleration response decline and recovery were shown using an airborne noise and a vibroacoustic dishabituating stimulus [59]. In a study examining controlled exposure to a passage of speech spoken out loud by the mother from 28 to 34 weeks gestation, fetuses showed an orienting cardiac response when listening to the passage of speech they were exposed before but not when listening to a control passage of speech [75].

With the onset of hearing, it is supposed that experiences with environmental sounds are available for adjustment of the cortical circuits. Kisilevsky and Davies [79] suggested that this can be considered the 'experience-dependent' phase of maturation. More recently, fetal functional response to sound and light (from GA week 27 onwards) have been confirmed using functional magnetic resonance imaging and magnetoencephalography [80].

At the third trimester, the brain development shows important improvement such as functional neural connectivity networks [73]. By GA week 28–30, the fetal brain activity moves from undifferentiated activity to organized sleep states [61,62] indicating that the connection of neurons in the cortical-thalamic area and in the brainstem starts to function in this period. This matches with very important processes consisting of the "firing" of visual sensory cells, without external stimulation, to promote visual development. Those processes, which are essential for the visual system development, take place during REM (rapid eye movement) sleep cycle [61]. In uterus the eyelids are thin and mostly open, the fetus and preterm infant have no pupillary reflex or pupillary constriction before GA week 30 and only variable responses until GA weeks 32 to 34 [81].

Even if visual development is known to be completed after birth, a recent experiment has demonstrated that in the third trimester of pregnancy the human fetus has the capacity to process perceptual information. Examining fetal head turns to visually presented upright and inverted face-like stimuli (projected through the uterine wall) it has been found that the fetus is more likely to engage with upright configural stimuli when contrasted to inverted visual stimuli [82].

The motor development is well established at the third trimester, with the number of spontaneous movements tending to increase until GA week 32, when it then starts to decrease. As fetuses approach term, they appear cramped, movements become smaller, and major joint movements are restricted to rotations and attempts to extend the spine [83]. Simultaneously to the reduction in the number of general movements, an increased number of facial movements may be observed, including opening/closing of jaw, swallowing, and chewing. This pattern is deemed a reflex of the normal development of the fetus' brain. Therefore, the fetal behavior pattern changes as the nervous system matures [46,69,84]. Today it is widely recognised that movement patterns are determined by neurological development [43], so the movement analysis provides an important measure of fetal health [85].

5. Discussion

The reported findings on humans overall confirm that the earliest sensory functions develop concomitantly with the establishment of the anatomical substrate or soon after it. Associated with this neuroanatomical development is a progressive functional maturation, which is reflected in changes in behavior and in the electrical activity of the brain. Recent research highlights that the REM and non-REM sleep in human fetuses starts to appear between weeks 33 and 35 when the neuronal connection in the cortical-thalamic area and in the brainstem starts to function [50]. Therefore, the functional capacity of the brain may have matured sufficiently to support human fetal awareness to external stimuli and to build neural circuits also related to experience [34,86,87]. It is noteworthy that learning in utero has been demonstrated for sound, music, some language features, and odors [74], as well as the possibility to store memories of prenatal experiences [47,55,75,88].

In light of the above-mentioned studies, human fetal neurodevelopment seems to be an early, complex and sophisticated process. Moreover, it seems to be influenced by environmental characteristics and maternal health and behavior [11,89]. Possible epigenetic processes are still being studied [90,91]. Accumulating evidence supports that prenatal maternal stress can affect early brain development in animals [92] and has widespread effect on fetal/birth outcomes via major physiological alterations in the hypothalamic-pituitaryadrenal axis and neurotransmitters [93]. A recent randomized controlled trial demonstrated that maternal regular exercise during pregnancy can affect the development of the human fetal brain, in particular, the children of exercising pregnant women were born with more mature brains [94]. Finally, a recent study [95], assessing human fetuses at GA week 25, showed a congruent mouth motor response to maternal acoustic stimulation, finding that, when mothers sang the syllable "LA" in a nursery rhyme, fetuses significantly increased mouth openings.

Overall, these studies provide evidence of how the sensory and motor systems develop. They function before their neural maturation, but only after the formation of functional circuits they are sufficiently integrated to allow the fetus to learn and respond to external stimuli in a primordial manner. This knowledge can be useful for those who are concerned with childhood development and care.

6. Potential conflict of interest report

The authors indicated no potential conflict of interest.

References

[1] Martín-Ibáñez R, Guardia I, Pardo M, Herranz C, Zietlow R, Vinh N, et al. Insights in spatio-temporal characterization of human fetal neural stem cells. Exp Neurol 2017;291:20–35.

[2] Kostović I, Judas M, Petanjek Z, Simić G. Ontogenesis of goal-directed behavior: anatomo-functional considerations. Int J Psychophysiol 1995;19:85–102.

[3] Humphrey T. Some correlations between the appearance of human fetal reflexes and the development of the nervous system. Progr Brain Res 1964;4:93–135.

[4] Gottlieb G. Conceptions of prenatal development: behavioral embryology. Psychol Rev 1976;83:215.

[5] Graven SN, Browne JV. Sensory development in the fetus, neonate, and infant: introduction and overview. Newborn and Infant Nursing Rev 2008;8:169–72.

[6] Chaudhury S, Sharma V, Kumar V, Nag TC, Wadhwa S. Activity-dependent synaptic plasticity modulates the critical phase of brain development. Brain Dev 2016;38:355–63.

[7] Platt MW. Fetal awareness and fetal pain: the emperor's new clothes. Arch Dis Child Fetal Neonatal Ed 2011;96:F236–7.

[8] Mellor DJ, Diesch TJ, Gunn AJ, Bennet L. The importance of 'awareness' for understanding fetal pain. Brain Res Rev 2005;49:455–71.

[9] Lagercrantz H. Connecting the brain of the child from synapses to screen-based activity. Acta Paediatr 2016;105:352–7.

[10] Della Vedova AM, Imbasciati A. The origins of the mind: the psychic life of the foetus. Giornale di Neuropsichiatria dell'età evolutiva 1998;18:155–68.

[11] Della Vedova AM. The construct of "parental-fetal attachment": A review on the current knowledge. Imago 2005;12:341–59.

[12] Della Vedova AM, Ducceschi B, Cesana BM, Imbasciati A. Maternal bonding and risk of depression in late pregnancy: a survey of Italian nulliparous women. J Reproduct Infant Psychol 2011;29:208–22.

[13] Della Vedova AM, Cristini C, editors. La promozione della salute psichica perinatale. Carocci: Roma; 2011.

[14] Della Vedova AM. Maternal psychological state and infant's temperament at three months. J Reproduct Infant Psychol 2014;32:520–34.

[15] Borsani E, Buffoli B, Bonazza V, Reiter RJ, Rezzani R, Rodella LF. Single administration of melatonin modulates the nitroxidergic system at the peripheral level and reduces thermal nociceptive hypersensitivity in neuropathic rats. Int J Mol Sci 2017;18(10).;pii: E2143.

[16] Borsani E. Aquaporins in sensory and pain transmission. Curr Neuropharmacol 2010;8:122–7.

[17] Borsani E, Giovannozzi S, Boninsegna R, Rezzani R, Labanca M, Tschabitscher M, et al. Nitroxidergic system in human trigeminal ganglia neurons: a quantitative evaluation. Acta Histochem 2010;11:444–51.

[18] Jessell TM, Development Sanes JR. The decade of the developing brain. Curr Opin Neurobiol 2000;10:599–611.

[19] Bystron I, Blakemore C, Rakic P. Development of the human cerebral cortex: boulder committee revisited. Nat Rev Neurosci 2008;9:110–22.

[20] Budday S, Steinmann P, Kuhl E. Physical biology of human brain development. Front Cell Neurosci 2015;9:257.

[21] de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? Early Hum Dev 2006;82(4):257–66.

[22] Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci 1995;18:383–8.

[23] Kostović I. Structural and histochemical reorganization of the human prefrontal cortex during perinatal and postnatal life. Prog Brain Res 1990;85:223–39 discussion 239-40.

[24] Fietz SA, Kelava I, Vogt J, Wilsch-Bräuninger M, Stenzel D, Fish JL, et al. OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. Nat Neurosci 2010;13:690–9.

[25] Sidman RL, Rakic P. Neuronal migration, with special reference to developing human brain: a review. Brain Res 1973;62:1–35.

[26] Molliver ME, Kostović I, van der Loos H. The development of synapses in cerebral cortex of the human fetus. Brain Res 1973;50:403–7.

[27] Kostović I, Judas M. The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatr. 2010;99:1119–27.

[28] Feller MB. Spontaneous correlated activity in developing neural circuits. Neuron 1999;22:653–6.

[29] Olson L, Boréus LO, Seiger A. Histochemical demonstration and mapping of 5-hydroxytryptamine- and catecholamine-containing neuron systems in the human fetal brain. Z Anat Entwicklungsgesch 1973;139:259–82.

[30] Kostović I. Prenatal development of nucleus basalis complex and related fiber systems in man: a histochemical study. Neuroscience 1986;17:1047–77.

[31] Humphrey T. The development of the pyramidal tracts in human fetuses, correlated with cortical differentiation. In: Tower DB, Schadé JP, editors. Structure and Function of the Cerebral Cortex. Amsterdam: Elsevier; 1960. p. 93–103.
[32] Müller F, O'Rahilly R. The human brain at stages 21–23, with particular reference to the cerebral cortical plate and to the development of the cerebellum. Anat Embryol (Berl) 1990;182:375–400.
[33] Müller F, O'Rahilly R. The human rhombencephalon at the end of the embryonic period proper. Am J Anat 1990;189:127–45.
[34] Lee SJ, Ralston HJ, Drey EA, Partridge JC, Rosen MA. Fetal pain: a systematic multidisciplinary review of the evidence. JAMA 2005;294:947–54.
[35] Sarnat HB, Yu W. Maturation and dysgenesis of the human olfactory bulb. Brain Pathol 2015;26:301–18.
[36] Humphrey T. The development of the olfactory and the accessory olfactory formations in human embryos and fetuses. J Comp Neurol 1940;73:431–68.
[37] Witt M, Reutter K. Embryonic and early fetal development of human taste buds: a transmission electron microscopical study. Anat Rec 1996;246:507–23.
[38] Lim R, Brichta AM. Anatomical and physiological development of the human inner ear. Hear Res 2016;338:9–21.
[39] Lecanuet JP, Graniere-Deferre C, Jacquet AY, DeCasper AJ. Fetal discrimination of low-pitched musical notes. Dev Psychobiol 2000;36:29–39.
[40] Wulle KG. Electron microscopy of the fetal development of the corneal endothelium and Descemet's membrane of the human eye. Invest Ophthalmol 1972;11:897–904.
[41] Preyer W. Spezielle Physiologie des Embryo. Leipzig: Grieben; 1885.
[42] Ianniruberto A, Tajani E. Ultrasonographic study of fetal movements. Semin Perinatol 1981;5:175–81.
[43] De Vries JIP, Fong BF. Normal fetal motility: an overview. Ultrasound Obstet Gynecol 2006;276:701–11.
[44] Guimarães Filho HA, Araujo Júnior E, Mello Júnior CF, Nardozza LM, Moron AF. Assessment of fetal behavior using four-dimensional ultrasonography: current knowledge and perspectives. Rev Assoc Med Bras 1992;2013(59):507–13.
[45] Kurjak A, Stanojevic M, Andonotopo W, Scazzocchio-Duenas E, Azumendi G, Carrera JM. Fetal behavior assessed in all three trimesters of normal pregnancy by four-dimensional ultrasonography. Croat Med J 2005;46:772–80.
[46] Kurjak A, Stanojević M, Predojević M, Laušin I, Salihagić-Kadić A. Neurobehavior in fetal life. Semin Fetal Neonatal Med 2012;17:319–23.
[47] Hepper PG, Wells DL, Dornan JC, Lynch C. Long-term flavor recognition in humans with prenatal garlic experience. Dev Psychobiol 2013;55:568–74.
[48] Parma V, Brasselet R, Zoia S, Bulgheroni M, Castiello U. The origin of human handedness and its role in pre-birth motor control. Sci Rep 2017;7:16804.
[49] Kostović I, Lukinović N, Judas M, Bogdanović N, Mrzljak L, Zecević N, et al. Structural basis of the developmental plasticity in the human cerebral cortex: the role of the transient subplate zone. Metab Brain Dis 1989;4:17–23.
[50] Andonotopo W, Kurjak A, Kosuta MI. Behavior of an anencephalic fetus studied by 4D sonography. J Matern Fetal Neonatal Med 2005;17:165–8.
[51] Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology 2010;35:147–68.
[52] Huisman TA, Martin E, Kubik-Huch R, Marincek B. Fetal magnetic resonance imaging of the brain: technical considerations and normal brain development. Eur Radiol 2002;12:1941–51.
[53] Kostović I, Judas M, Rados M, Hrabac P. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. Cereb Cortex 2002;12:536–44.
[54] Browne JV. Chemosensory development in the fetus and newborn. Newborn Infant Nurs Rev 2008;8:180–6.
[55] Schaal B, Marlier L, Soussignan R. Olfactory function in the human fetus: evidence from selective neonatal responsiveness to the odor of amniotic fluid. Behav Neurosci 1998;112:1438–49.
[56] Sites BD. Fetal pain. JAMA 2006;295:159–61.
[57] Lee SJ, Ralston HJP, Drey EA, Partridge JC, Rosen MA. Fetal pain - reply. JAMA 2006;295:159–61.
[58] Pujol R, Lavigne-Rebillard M. Development of neurosensory structures in the human cochlea. Acta Otolaryngol 1992;112:259–64.
[59] Kisilevsky BS, Low JA. Human fetal behavior: 100 years of study. Dev Rev 1998;18:1–29.
[60] Lecanuet JP, Fifer WP, Krasnegor NA, Smotherman WP. Fetal development: A psychobiological perspective. Hillsdale: Lawrence Erlbaum Associated; 1995.
[61] Graven SN, Browne JV. Sleep and brain development: the critical role of sleep in fetal and early neonatal brain development. Newborn Infant Nurs Rev 2008;8:173–9.
[62] Graven SN, Browne JV. Visual development in the human fetus, infant, and young child. Newborn Infant Nurs Rev 2008;8:194–201.
[63] Vanhatalo S, Lauronen L. Neonatal SEP - back to bedside with basic science. Semin Fetal Neonatal Med 2006;11:464–70.
[64] Brody BA, Kinney HC, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropathol Exp Neurol 1987;46:283–301.
[65] Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. J Neuropathol Exp Neurol 1988;47:217–34.
[66] Wózniak W, O'Rahilly R. An electron microscopic study of myelination of pyramidal fibres at the level of the pyramidal decussation in the human fetus. J Hirnforsch 1982;23:331–42.
[67] Gupta RK, Hasan KM, Trivedi R, Pradhan M, Das V, Parikh NA, et al. Diffusion tensor imaging of the developing human cerebrum. J Neurosci Res 2005;81:172–8.
[68] Kostović I, Judas M. Transient patterns of cortical lamination during prenatal life: do they have implications for treatment? Neurosci Biobehav Rev 2007;31:1157–68.
[69] Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, et al. Cortical pain responses in human infants. J Neurosci 2006;26:3662–6.
[70] Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJ. Pain activates cortical areas in the preterm newborn brain. Pain 2006;122:109–17.
[71] Levitt P. Structural and functional maturation of the developing primate brain. J Pediatr 2003;143:S35–45.
[72] Hüppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GP, Jolesz FA, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol 1998;43:224–35.
[73] Thomason ME, Grove LE, Lozon TA, Vila AM, Ye Y, Nye MJ, et al. Age-related increases in long-range connectivity in fetal functional neural connectivity networks in utero. Dev Cog Neurosci 2015;11:96–104.
[74] James DK. Fetal learning: a critical review. Infant Child Dev 2010;19:45–54.
[75] Krueger C, Garvan C. Emergence and retention of learning in early fetal development. Infant Behav Dev 2014;37:162–73.
[76] Reissland N, Kisilevsky BS. Fetal development: research on brain and behavior, environmental influences, and emerging technologies. New York: Springer; 2016.
[77] Mistretta CM, Bradley RM. Taste and swallowing in utero: A discussion of fetal sensory function. British Med Bull 1975;31:80–4.

[78] Kisilevsky BS, Pang LH, Hains SMJ. Maturation of human fetal responses to airborne sound in low-and high-risk fetuses. Early Hum Dev 2000;58:179–95.

[79] Kisilevsky BS, Davies GA. Auditory processing deficits in growth restricted fetuses affect later language development. Med Hypotheses 2007;68:620–8.

[80] Dunn K, Reissland N, Reid VM. The functional foetal brain: A systematic preview of methodological factors in reporting foetal visual and auditory capacity. Dev Cog Neurosci 2015;13:43–52.

[81] Graven SN. Early neurosensory visual development of the fetus and newborn. Clin Perinatol 2004;31:199–216.

[82] Reid VM, Dunn K, Young RJ, Amu J, Donovan T, Reissland N. The human fetus preferentially engages with face-like visual stimuli. Curr Biol 2017;27:1825–8.

[83] Hayat TT, Nihat A, Martinez-Biarge M, McGuinness A, Allsop JM, Hajnal JV, et al. Optimization and initial experience of a multisection balanced steady-state free precession cine sequence for the assessment of fetal behaviour in utero. AJNR Am J Neuroradiol 2011;32:331–8.

[84] Sparling JW, Wilhelm IJ. Quantitative measurement of fetal movement: fetal-posture and movement assessment (F-PAM). Phys Occup Ther Pediatr 1993;12:97.

[85] Lai J, Nowlan NC, Vaidyanathan R, Shaw CJ, Lees CC. Fetal movements as a predictor of health. Acta Obstet Gynecol Scand 2016;95:968–75.

[86] Mellor DJ, Diesch TJ, Gunn AJ, Bennet L. The importance of 'awareness' for understanding fetal pain. Brain Res Brain Res Rev 2005;49:455–71.

[87] Mellor DJ, Diesch TJ. Onset of sentience: the potential for suffering in fetal and newborn farm animals. Appl Animal Behav Sci 2006;100:48–57.

[88] De Casper AJ, Spence MJ. Prenatal maternal speech influences newborns perception of speech sound. Infant Behav Dev 1986;9:133–50.

[89] Glover V, Capron L. Prenatal parenting. Curr Opin Psychol 2017;21:66–70.

[90] Zannas AS, Chrousos GP. Epigenetic programming by stress and glucocorticoids along the human lifespan. Mol Psychiatry 2017;22:640–6.

[91] Vaiserman AM, Koliada AK. Early-life adversity and long-term neurobehavioral outcomes: epigenome as a bridge? Human Genomics 2017;11:34.

[92] Huizink AC, Mulder EJ, Buitelaar JK. Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility? Psychol Bull 2004;130:115.

[93] Fatima M, Srivastav S, Mondal AC. Prenatal stress and depression associated neuronal development in neonates. Int J Dev Neurosci 2017;60:1–7.

[94] Labonte-Lemoyne E, Curnier D, Ellemberg D. Exercise during pregnancy enhances cerebral maturation in the newborn: A randomized controlled trial. J Clin Exp Neuropsychol 2017;39:347–54.

[95] Ferrari GA, Nicolini Y, Demuru E, Tosato C, Hussain M, Scesa E, et al. Ultrasonographic investigation of human fetus responses to maternal communicative and non-communicative stimuli. Front Psychol 2016;7:354.