Stages of Brain Development

by Gregory J. de Montfort and Dr. Rosemary Boon

From a single fertilized egg of about 0.14 millimeters in diameter, to an adult human being, the neurophysiology of development of the brain and nervous system is nothing short of remarkable. We are born with around 100 billion neurons, and the development of the brain continues long after birth, with dendrites of some neurons in the neocortex continuing to grow well into old age[1].

Pregnancy is a time of great joy and expectation - however, our world and its potential hazards are very different from that of our grandmothers and even our mothers.

Medical science is currently unable to find a definite cause for up to seventy percent of birth abnormalities [2]. In the Western world, at least two percent of babies born alive suffer from major defects while approximately 15% of all pregnancies may miscarry after six weeks [2].

There are many intricate and codependent processes going on during the course of growth and development of a human being. The individual and collective processes can be so easily disrupted and consequently malfunction at any stage that it is truly miraculous that many of us survive to functional adulthood at all. This article is written in simplified form in an attempt to try and illustrate what can go wrong, the most likely stages that it may go wrong and what may be done to potentially prevent it going wrong.

In this regard, it should also be noted that nutritional deficiencies and/or exposure to toxic chemicals on behalf of one or both parents prior to, during pregnancy, as well as *after* birth, have been cited by many studies as being major causes of malformation and/or learning difficulties [2,3,4].

Everything that the mother ingests, inhales or is absorbed through the skin and mucous membranes has the potential to cross the placental barrier to some extent, and/or affect the ovum DNA[1, 2,4,5]. Similarly the same can be said for the father's sperm - if he has been exposed to a hazardous chemical his sperm may be killed, damaged or undergo a mutation which has the potential to be passed to his offspring. Additionally, many toxins can be brought home from the workplace on the clothing or skin to be passed on to the mother and hence the developing fetus. Furthermore, every parent needs to know the hazards of prescribed and recreational drugs during pregnancy. With a little forethought of our rather inconsiderate "modern" world, much can be prevented.

All tissues and organs of the body develop from three germ layers known as the ectoderm, the mesoderm, and the endoderm.

The nervous system and the skin develop from the ectoderm germ layer. This common origin is reflected in a group of disorders, the neurocutaneous syndromes, in which cutaneous (skin) signs co-occur with signs of brain disease.

Examples of neurocutaneous syndromes are: neurofibromatosis, tuberous sclerosis, and the Sturge-Weber syndrome, all of which may be associated with seizures, developmental delay, learning and behavioral problems.

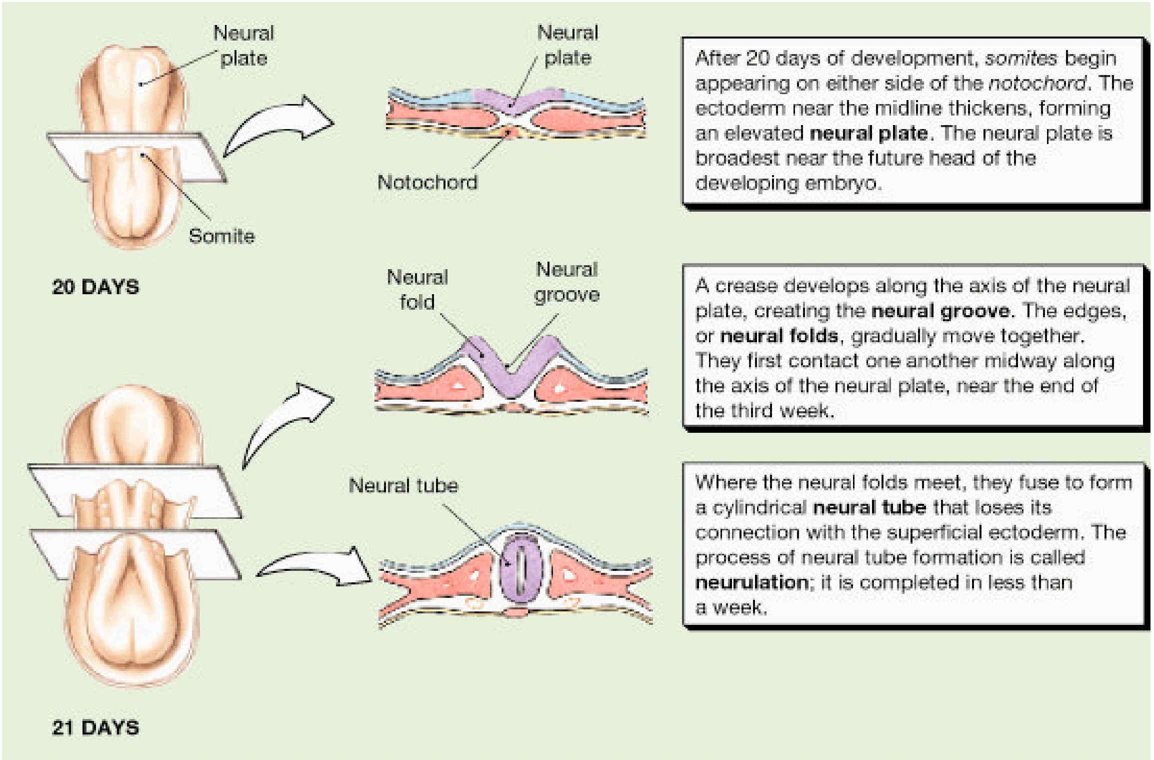
The First Eight Weeks

Through the initial stages of cell development and division, when the zygote (The diploid cell resulting from union of a sperm and an ovum.), duplicates to around 32 cells, and becomes what is known as the blastocyst, implantation in the uterine wall occurs. This establishes the rudimentary placenta as the embryonic disk, which will give rise to the embryo.

The first 8 weeks after implantation are termed the *embryonic period*. It is during this time that the organs, systems and tissues of the future being are induced, differentiated, and put into place. The remaining 30-40 weeks of gestation are devoted to growth, development and refinement of these organs, systems and tissues.

If something goes wrong during the first 8 weeks of this "putting things into place", it may result in a defectively designed structure or system. If the problem occurs after the eighth week, it will more likely result in a failure of growth, development or refinement of the involved structure or system. The latter tends to be more amenable to subsequent intervention.

At about 14 days, the embryo is about 2 millimetres long. By the 17th - 20th day of gestation, the primitive embryo develops what is known as the *neural plate,* which is a sheet of cells that will ultimately develop into the nervous system of the individual.



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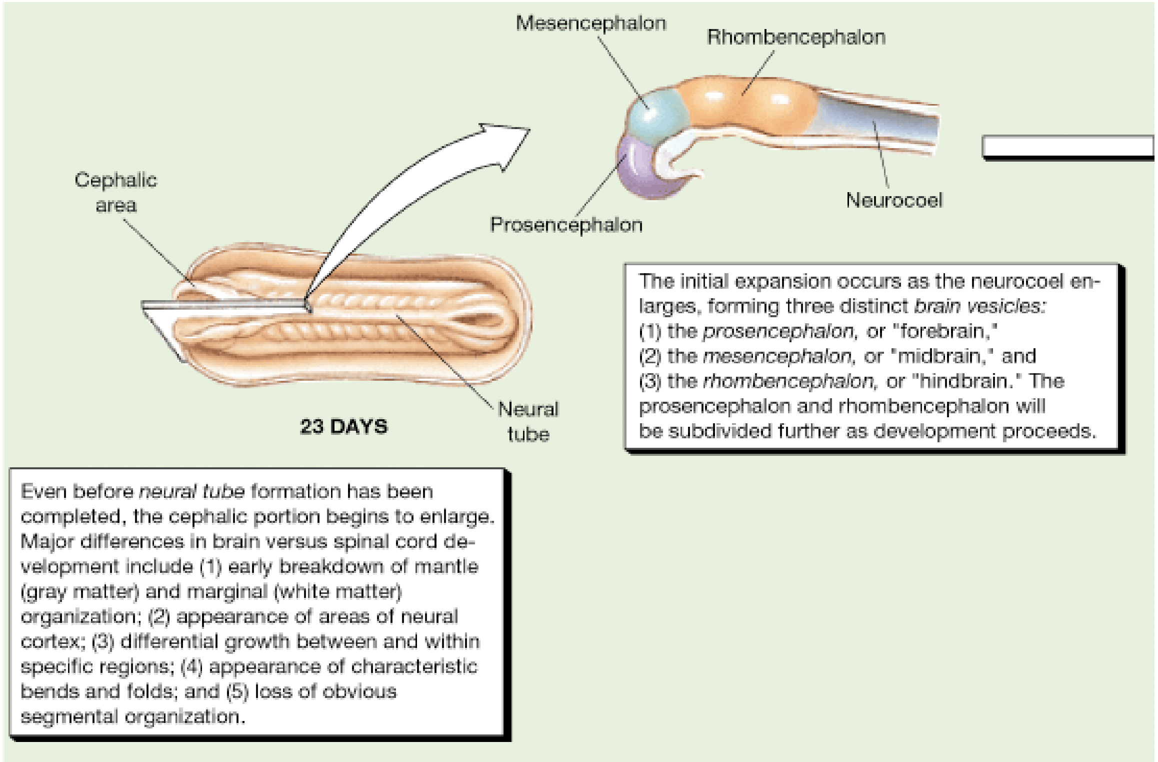
At three weeks of gestation, the embryo has a definite head and tail. As the neural folds within the evolving organism grow, they give rise to paired blocks of mesoderm masses. Mesoderm is one of the three primary germ layers of the embryo (the others being ectoderm and endoderm) which is the origin of connective tissues, myoblasts, blood, the cardiovascular and lymphatic systems, most of the urogenital system, and the lining of the pericardial, pleural, and peritoneal cavities. The mesoderm will ultimately transform into somites which eventually become the vertebral column and its related musculature.

By the 23rd day, or the third week of development of the new entity, the *neural groove* (which is the embryonic brain structure) is visible. Two days later, the edges of this groove, which have continued to 'curl up' until now, start to join together to form the *neural tube*, which forms the basis of the entire nervous system. The closure of the neural tube is dependent upon protein bridges bound together by calcium.



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It is interesting to note that the neural tube, at this stage of development, contains around 125,000 cells. At birth, the human brain contains around 100 billion neurons - we can infer from this information that new neurons are being generated at the rate of about 250,000 ***per minute*** during the nine months of gestation. (Cowan, 1979).

By the 27th day, the ends of the tube - the pores, close.

Once closure is effected, the neural crest also begins to form. The crest is the source of neurons for the peripheral nervous system as well as for chromoform cells in the inner part of the adrenal gland. Chromoform cells are responsible for synthesizing and secreting two important hormones instrumental in emotional arousal - epinepherine and norepinepherine. The neural crest is derived from neuroectodermal cells that originate in the dorsal aspect of the neural folds or neural tube; these cells leave the neural tube or folds and differentiate into various cell types including dorsal-root ganglion cells, autonomic ganglion cells, the chromaffin cells of the adrenal medulla, Schwann cells, sensory ganglia cells of cranial nerves, 5, 9, and 10, part of the meninges, or integumentary pigment cells.

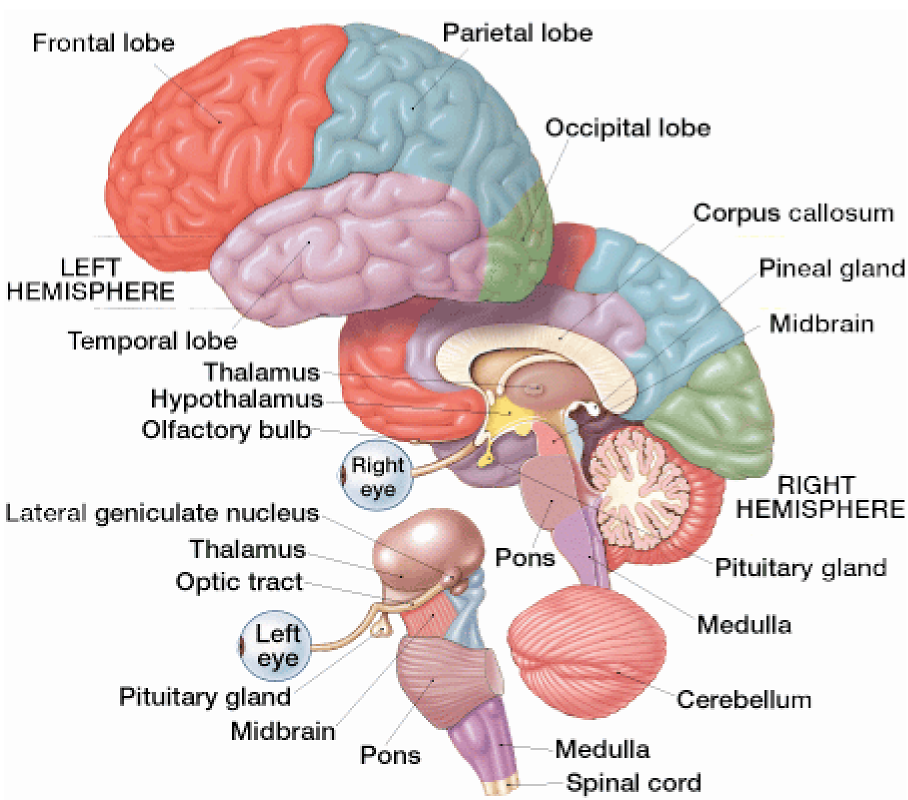
The neural tube is of course the precursor of the spinal canal.

Failure or ineffective closure of the neural tube, is the cause of *spina bifida* (embryologic failure of fusion of one or more vertebral arches; subtypes of spina bifida are based on degree and pattern of malformation associated with neuroectoderm involvement); *meningocele* (Protrusion of the membranes of the brain or spinal cord through a defect in the skull or spinal column); *myelocele* (Protrusion of the spinal cord in spina bifida.), *anencephaly* (Congenital defective development of the brain, with absence of the bones of the cranial vault and absent or rudimentary cerebral and cerebellar hemispheres, brainstem, and basal ganglia); and *pilonidal cyst* (a fistula or pit in the sacral region, communicating with the exterior, containing hair which may act as a foreign body producing chronic inflammation).

It is thought that inadequate dietary intake, or malabsorption of certain essential nutrients on behalf of the mother during this period of embryonic development may be at root of a failure of the neural tube to effectively close.

By the end of the third week of embryonic development, the precursors of the eyes and ears (the occular and auditory vesicles) are evident. A primary system for blood circulation is formed, and a rudimentary heart begins to beat. The alimentary canal, from mouth to anus is formed, and connects to the yolk sac for nourishment. The ends of the arms and legs are present. The tonic labrinthine reflex is thought to develop during this stage of growth.

Also during this third busy week of embryonic development (or proliferation of cells), three vesicles develop at the 'head end' of the neural tube, which will develop into:- 1). The forebrain or proencephalon, 20. The midbrain or mesencephalon, and 30. The hindbrain or rhombencephalon. These rudimentary 'parts' will further differentiate in due course through proliferation and migration.



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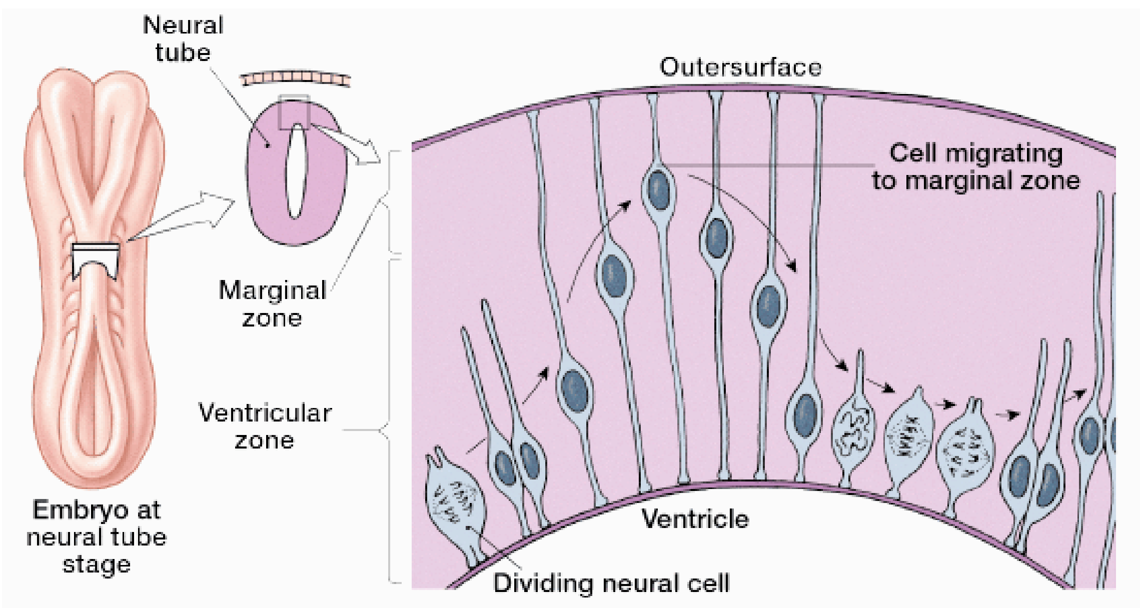
Summary Of The Developmental Sequence of Brain Regions

Three-vesicle stage	Five-vesicle stage	Brain region
Prosencephalon	Telencephalon	Cerebral hemisphere
	Diencephalon	Diencephalon
		Optic nerve and retina
Mesencephalon	Mesencephalon	Mesencephalon
Rhombencephalon	Metencephalon	Pons
		Cerebellum
	Myelencephalon	Medulla oblongata

Currently, it is not known what initiates migration, and many theories have been proposed. New molecular imaging techniques are being utilised in research establishments and may reveal the triggers and antecedants.

Many neuroblasts migrate (travel) in a fashion we can consider as similar to an amoeba, that is, by extending a part of itself, grabbing something to hang onto and then pulling the rest of the cell along. In the neocortex and cerebellum, neuroblasts must travel to their final destinations, locating themselves in the correct cell layer, orient themselves, and initiate dendritic growth to make the appropriate synaptic connections.



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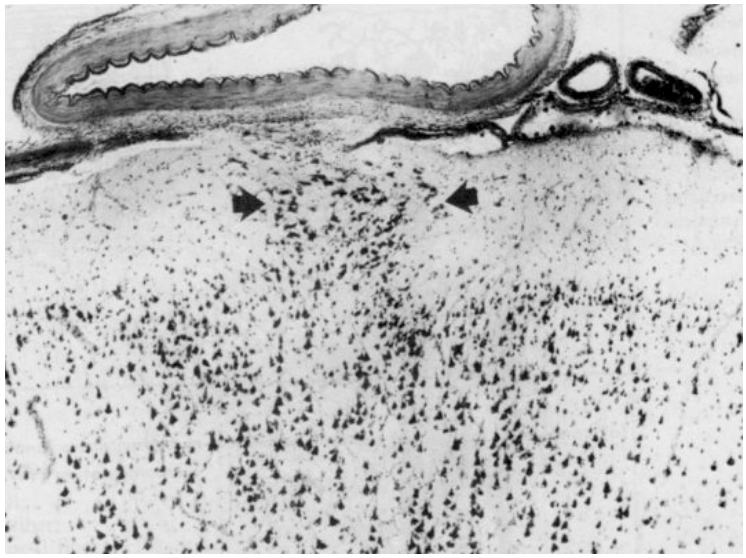
Deviations from the 'appropriate' locations can lead to abnormalities in brain structure and behaviour. An example of this was noted by Geshwind and Galaburda in 1985, in a few dyslexic individuals. Failure in the proper migration during fetal development was found in abnormal arrangement of neurons in a region of the left hemisphere important for language comprehension.



Abnormal cell aggregation in the brain of a person with dyslexia.
(From *Biological Psychology* by D.P. Kimble)

Brain malformations may result from exogenous and endogenous causes. Exogenous causes are nutritional, radiologic, viral, chemical, medications, or ischemic. Endogenous causes are genetic.

This migration which results in cells being arranged in a particular alignment with other cells by layer and direction is called aggregation. Theoretically, each cell in the human body carries with it the entire DNA coding of the individual and can therefore differentiate into *any* cell type required at a particular location.

Growth cones, at the end of 'buds' on the cell body are responsible for the growth of axons and dendrites which 'close' the synaptic connections. The growth cones appear to 'recognize' target cells, and as Santiago Ramon Cajal, their discoverer, described over 100 years ago - "pushes aside mechanically all obstacles to reach its destination".

The third and fourth week sees the development of the spinal cord, and by the end of the fourth week of gestation, the marginal layer nerve fibres appear and begins to accept fibres of ganglion nerves that are sent in to them from the peripheral ganglia. Once connected, they begin to function.

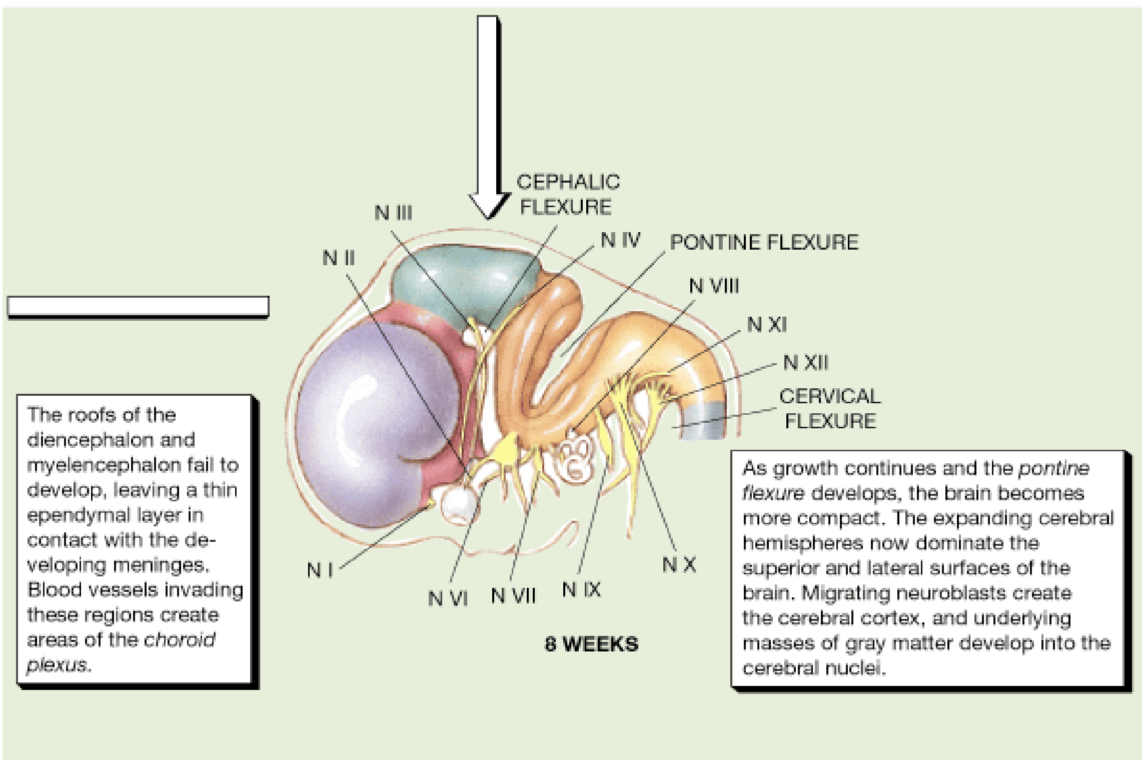
The cerebral hemispheres differentiate around the fifth week.

By the end of the sixth week the rudimentary development of the five brain vesicles is complete. The cerebral hemispheres have grown and now cover the diencephalon, the mesencephalon and the cerebellum, which has only just begun development. As these two hemishpheres grow toward each other, they meet in the middle and continue their growth downwards. The membrane that separates them is the falx cerebri - a part of the dural membrane system of the meninges, of which it is the outer layer - the dura mater. The fissure thus created is known as the longitudinal fissure.

By the seventh week of life, the embryo will achieve a crown to rump length of around 20-25 millimetres. It is at this stage of development that differentiation of the genitals - male or female - takes place. Ossification of cartilage into bone occurs - at this stage most visible in the skull, ribs, scapulae, arms and legs, as well as the hard palate.

In the seventh week also, the pineal gland forms, as does the choroid plexus, that place in the roof of the diencephalon whose specialized cells secrete cerebrospinal fluid. If there is a malformation in the arrangement of the roof of the diencephalon, it can potentially obstruct the flow of cerebrospinal fluid resulting in *hydrocephalus*. (A condition marked by an excessive accumulation of cerebrospinal fluid resulting in dilation of the cerebral ventricles and raised intracranial pressure; may also result in enlargement of the cranium and atrophy of the brain).

By the eighth week, which is the end of the embryonic period, all of the organ systems are established - the blue prints have been laid out - and from this time forward the organ systems will continue to develop and refine. Well defined finger and toe joints are present, and there is visible ossification of the ulna, and radius, the illium, and of the fibula and tibia. The two halves of the hard palate have been growing toward each other and begin to unite in this week, and any failure to do so correctly by the tenth week may result in a cleft palate. (A congenital fissure in the median line of the palate, often associated with cleft lip. Often occurs as a feature of a syndrome or generalized condition, e.g., diastrophic dwarfism or spondyloepiphyseal dysplasia congenita; its general genetic behavior resembles that of cleft lip).



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The cerebral cortex has undergone remarkable growth and development during this first eight weeks. By its growth and folding, it now caps two thirds of the sub-cortical brain. First the frontal lobes form, then the parietal and concurrently, the temporal and occipital lobes. The limbic system is well developed by this time and all will continue to grow and develop during the next stages.

The Fetal Stage of Development

The third through ninth month is known as the fetal stage of human development.

Brain functions are expressed through activity of neural circuits. These circuits are formed throughout the fetal period and throughout the life by the formation of synapses in a process which has been called synaptogenesis. Not all synapses formed in the fetal period will survive, and new synapses are formed shortly after birth.

During the third month the fetus will have grown to around 75mm and a growth rate of about 12 mm each week. The face now looks much more human, with the eyes having moved from the sides to a more frontal position. The ears are visible and some of the inner structures of the ears, the tympani (ear drums), and vestibular apparatus are now recognizable. At 9 weeks the spinal galant reflex emerges.

Ossification of cartilage continues throughout this stage of development, as does refinement of the organs and systems of the body. At 11 weeks, the palmar reflex emerges.

The communication lines between the brain and the periphery of the body (cortico-spinal tracts) develop very rapidly and are largely complete by the seventh month of gestation. The olfactory bulbs grow forward, and begin forming connections with smell receptors in the lining of the nose. The cerebral cortex continues to grow and fold in an effort to develop more surface area.

The commissures of the brain develop during this stage as well. Commissures are the nerve fibre tracts that cross over the midline to connect different parts of the brain. They are largely involved in integrating right and left side brain activities.

Myelination of the nerve fibres begins in the third month, with the first myelination occurring in the cranial nerves that arise from the midbrain and medulla oblongata. The ventricular system (which allows the flow of cerebrospinal fluid throughout the brain and spinal cord) is now largely complete.

The Second Trimester

In the fourth month of gestation, the fetus is about 12-13 centimetres in length from crown to rump. This is the beginning of motor function for the new entity, as evidenced in the first bringing of its hands together and turning bodily within the uterus.

During this month, all the spinal arches will close with cartilage which will later undergo ossification into bone. The first sacral vertebra and the pubis show signs of ossification. Ossification of the malleus and the incus takes place, and the cartilage of the eustachian tubes and the ring around the tympani forms. The commissure known as the corpus collosum is evident and undergoes further growth and refinement. Tonsils are present, and the formation of the genitals takes place.

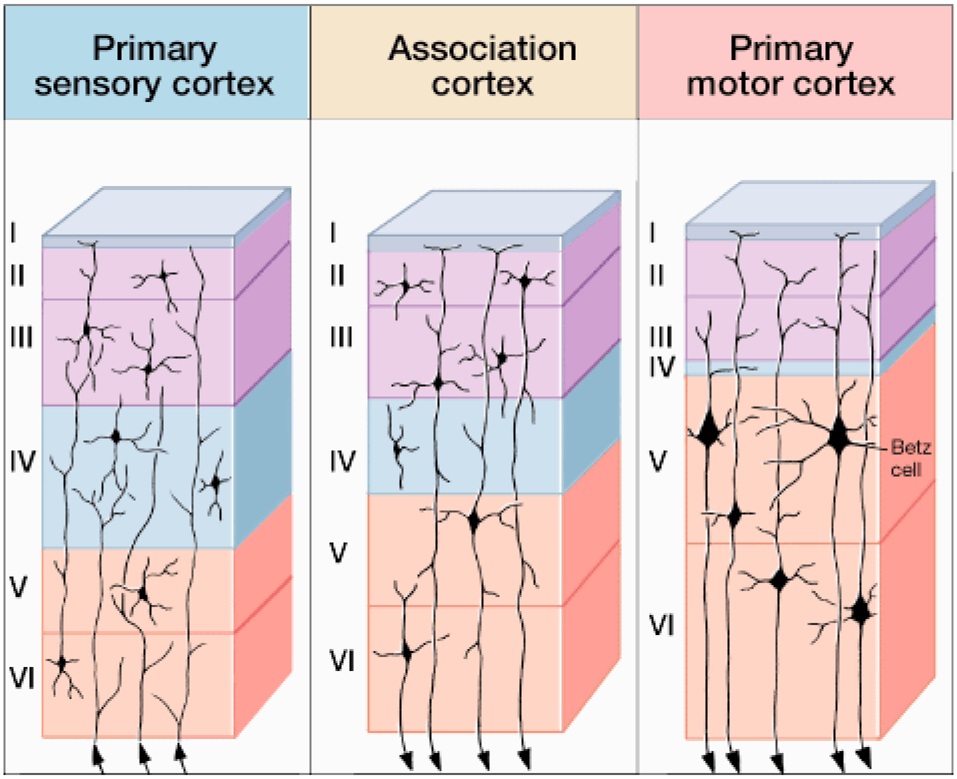
By this stage the fetus is now inhaling and exhaling amniotic fluid. All the raw materials are in place and the brain and spinal cord are growing at a rapid rate. At around 18 weeks, the asymmetrical tonic neck reflex emerges.

The fifth month sees the fetus growing to around 165 millimetres, and motor development rate increases, as felt by the interuterine movements of the fetus. The development of the vernix caseosa (the fatty substance, consisting of desquamated epithelial cells, lanugo hairs, and sebaceous matter, which covers the skin of the fetus) takes place.

The germs of teeth both first and permanent are seen, and the organs of the inner ear form - particularly those of pitch discrimination - the organs of corte. Myelin formation in the spinal cord and dorsal root nerves begins, and further development and refinement of the motor tracts takes place. The spinal galant reflex emerges during the fifth month and will be needed to assist the fetus in it's exit down the birth canal in 4 months time.

By the sixth month of pregnancy the fetus will have reached a length of about 255 millimetres (10 inches). Sebaceous glands are evident and lymph glands which will help to protect the fetus from noxious substances from this moment to the end of its days. Up until now the fetus has relied exclusively on mother's anti-bodies for protection from toxins including environmental ones. It is here that the rooting reflex emerges, this reflex will be required for early feeding after birth.

The cerebral hemispheres now cover the whole top and sides of the brain including the cerebellum. Cerebellar development begins from this moment, but will not be complete until two years after birth. Six distinct layers are now differentiated within the cerebral cortex, and almost all of the neurons within the central nervous system are present by the end of this sixth month of life and neural 'circuitry' continues to develop.



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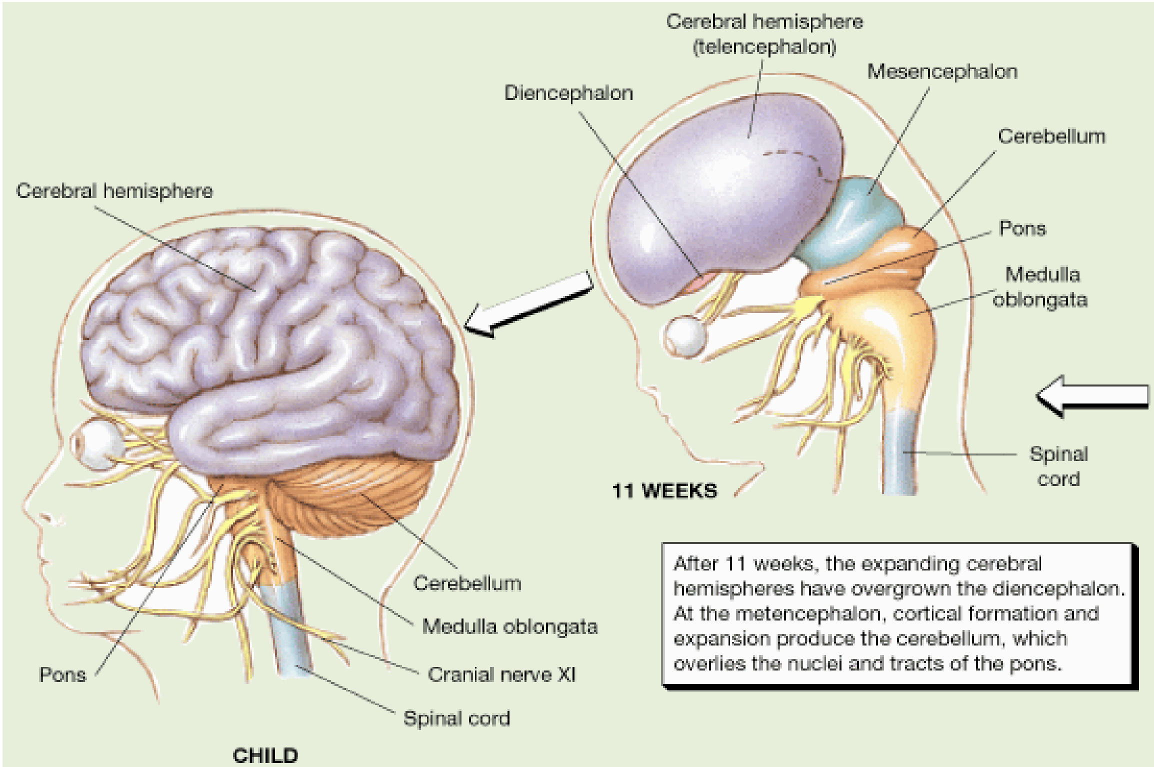
The Third Trimester

The seventh month of gestation witnesses the appearance of many new osseous (bone) formations. The developing fetus is now 305 millimetres long. Sulci and gyri (the convolutions) of the brain are much more in evidence, membranes over the pupils disappears and the eyes open. The insula (An oval region of the cerebral cortex overlying the extreme capsule, lateral to the lenticular nucleus, buried in the depth of the fissura lateralis cerebri (sylvian fissure), separated from the adjacent opercula by the circular sulcus of insula.) and the tubercula quadrigemina develop.

The seventh month is essentially characterised by rapid growth, development and organisational refinement.

By the eighth month, the fetus will be 405+ millimetres (16+ inches), from crown to heel. During this month of development the fetus will strengthen its body and the nervous system will increase its connections and receive more sensory input, and gain more motor control.

During the ninth month the fetus will reach 510 millimetres (20 inches) or more. All ossification points are in place, and further refinement of motor and other neuronal connections takes place for the ninth month fetus is usually very active.



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Summary Table of the Stages of Brain Development

Developmental Stage	***Main Feature of Developmental Stage***
Induction	Production of cells that will become nervous tissue
Proliferation	Cell reproduction (mitosis)
Migration	Location of cells in appropriate brain areas
Differentiation	Development of neurons into particular type
Synaptogenesis	Formation of appropriate synaptic connections
Selective cell death	Elimination of mislocated cells and cells that failed to form the proper synaptic connections
Functional validation	Strengthening of synapses in use, weakening of unused synapses

The Labor Process and Delivery

The labor and birthing process are part of the fetus' continuing education in sensory motor perception and integration.

During uterine contractions the pressure of the amniotic fluid is increased, and as the process continues, it forces part of the fluid filled membraneous sac containing the fetus into the birth canal. At this point the fetus' head enters the canal (engages) with a volume of fluid preceding it. Soon the membranes will rupture under the continued pressure of the contractions, and still further contractions will force the fetus down the birth canal. The head is subjected to pressure from all sides and the still forming skull accommodates this by allowing the head to shape somewhat to the opening. Once free of the birth canal, the body still has a twisting wringing sort of exit to make, comparable to a whole friction body massage during which the spinal galant reflex is instrumental in the fetus making it's way down the birth canals.

At birth, all reflexes are of brain stem origin with minimal cortical control.

Many children who are caesarian births, and/or have missed out on some part of the natural development or birth process, viz. trauma, toxicity exposure, anesthetics etc., are more at risk of having retained reflexes that will require specialist intervention for either transformation or inhibition. These retained reflexes are of themselves evidence of delayed motor development that if left unattended, can further inhibit normal sensory-motor development, impacting upon subsequent learning capability.

Postnatal Brain Development

The weight of the brain of the newborn is approximately 300 grams (or around 10% of body weight) in contrast to the adult brain - which weighs approximately 1400 grams (only 2% of body weight). Brain weight increases with age and achieves 'adult' weight between six and fourteen years of life. (Each of us is unique and therefore possesses differing patterns of growth of development). We are born with our full compliment of neurons.

Postnatal growth of the brain is due to an increase in the size of neurons, and subsequent increase in number of supporting cells (glia), development of neural processes and synapses (The contacts with other neurons which provide for the 'circuitry' of the brain), and the laying down of the insulation of nerve processes (myelin sheaths). Synapses are formed at a very rapid rate during the early months of life, usually achieving maximum density between six and twelve months after birth. There is a decrease after this due to disuse or natural attrition. The brain is a judicious budgeter of energy. The infant's brain forms and retains only those synapses that it frequently uses. Early sensory experiences are thus vital to the formation and *retention* of synapses.

In the neonate, metabolic activity is most noticeable in the sensory-motor cortex and brain stem, areas necessary for reflex functions. At two to three months, metabolic activity is prominent in the visual and the adjacent parietal cortex which corresponds with the development of visual-spatial integrative function. Between six months and a year, metabolic activity is notably in the frontal cortex which corresponds to the development of higher cortical functions such as interactions with the immediate environment, stranger anxiety, etc.

Functional imaging studies have demonstrated that early stimulation will enhance brain function, whereas a lack of early stimulation correspondingly leads to loss of brain function.

Developmental research has determined that there are "developmental windows of opportunity" for different brain functions. As a guide, the windows of opportunity for emotional development is 0-2 years, mathematics and logic is around 0-4 years, language is 0-10 years, and music from about 3-10 years.

If these "windows of opportunity" are not appropriately capitalized upon by parents, care-givers and educators, then impedance of the potential of the child, and/or a loss of the appropriate function will result.

NOTE: This article is for your information only. Please do not email for advice. If you have any concerns in this area please see your doctor or health care professional for advice.

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