Overview of the Development of the Human Brain and Spinal Cord

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1.1 Introduction

The development of the human brain and spinal cord may be divided into several phases, each of which is characterized by particular developmental disorders (Volpe 1987; van der Knaap and Valk 1988; Aicardi 1992; Table 1.3). After implantation, formation and separation of the germ layers occur, followed by dorsal and ventral induction phases, and phases of neurogenesis, migration, organization and myelination. With the transvaginal ultrasound technique a detailed description of the living embryo and fetus has become possible (Pooh and Kurjak 2009). With magnetic resonance imaging fetal development of the brain can now be studied in detail from about the beginning of the second half of pregnancy (Garel 2004). In recent years, much progress has been made in elucidating the mechanisms by which the central nervous system (CNS) develops, and also in our understanding of its major developmental disorders, such as neural tube defects, holoprosencephaly, microcephaly and neuronal migration disorders. Molecular genetic data, that explain programming of development aetiologically, can now be incorporated (Sarnat 2000; Flores-Sarnat and Sarnat 2008; Barkovich et al. 2001, 2009, 2012). In this chapter an overview is presented of (1) major stages in the development of the human CNS, (2) the first 3 weeks of development, (3) neurulation, (4) pattern formation, (5) early development of the brain, (6) fetal development of the brain, (7) the development of the blood supply of the brain, and (8) the development of major fibre tracts including the development

H.J. ten Donkelaar et al., *Clinical Neuroembryology*,
DOI 10.1007/978-3-642-54687-7_1, © Springer-Verlag Berlin Heidelberg 2014

of myelination. Mechanisms of development are discussed in Chap. 2, and an overview of the causes of developmental malformations and their molecular genetic basis is presented in Chap. 3. In the second, specialized part of this book the development of the CNS and its disorders are discussed in more detail.

1.2 Major Stages in the Development of the Human Brain and Spinal Cord

The human **embryonic period**, i.e. the first 8 weeks of development, can be divided into 23 stages, the **Carnegie stages** (O'Rahilly and Müller 1987), originally described as developmental horizons (XI-XXIII) by Streeter (1951), and completed by Heuser and Corner (1957; developmental horizon X) and O'Rahilly (1973; developmental stages 1–9). Some of the reconstructed models and drawings of the extensive Carnegie Collection are now archived in the Human Developmental Anatomy Center in Washington, DC (http://nmhm.washingtondc.museum/collections/hdac/index.htm). Important contributions to the description of human embryos were also made by Nishimura et al. (1977) and Jirásek (1983, 2001, 2004). Examples of human embryos, taken from the famous Kyoto Collection, are shown in Figs. 1.1 and 1.2. In the embryonic period, **postfertilization** or **postconceptional age** is estimated by assigning an embryo to a developmental stage using a table of norms, going back to the first *Normentafeln* by Keibel and Elze (1908). The term **gestational age** is commonly used in clinical practice, beginning

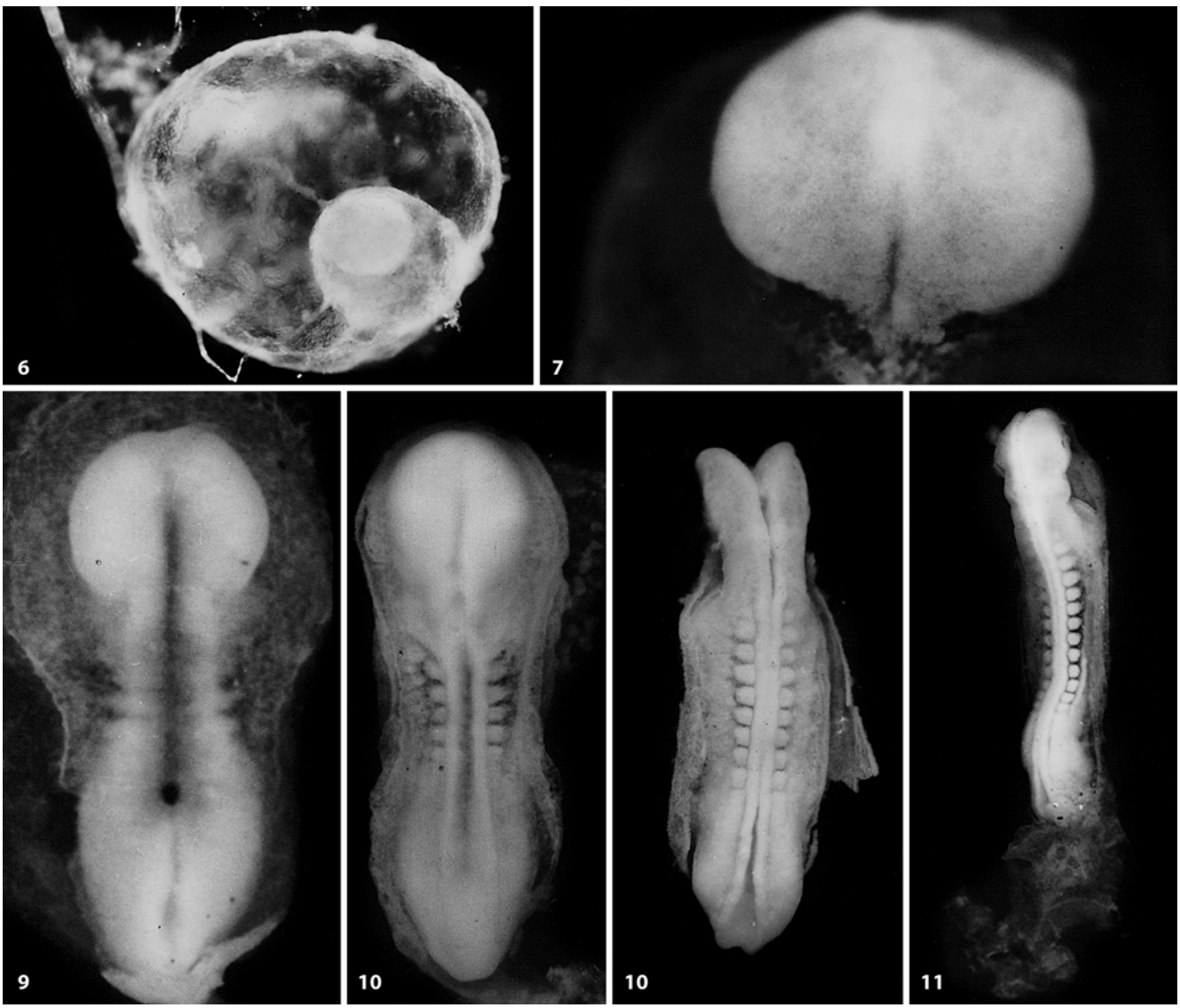

Fig. 1.1 Dorsal views of staged early human embryos (Carnegie stages 6, 7, 9–11; from the Kyoto Collection of Human Embryos; kindly provided by Kohei Shiota)

Table 1.1 Developmental stages and features of human embryos

Carnegie stages	Length (mm)	Age (days)	External features	Internal features (with emphasis on the nervous system)
1		1	Fertilization	
2		2–3	From 2 to about 16 cells	
3		4–5	Free blastocyst	Inner cell mass and trophoblast
4		6	Attaching blastocyst	Cytotrophoblast and syncytiotrophoblast distinguishable
5	0.1–0.2	7–12	Implantation; embryonic disk circular	Amniotic cavity; primary yolk sac; extra-embryonic mesoderm
6	0.2	17	Embryonic disk elongated	Chorionic villi; primitive streak and node; prechordal plate appears; secondary yolk sac
7	0.4	19	Embryonic disk oval	Notochordal process visible; hematopoiesis starts
8	1.0–1.5	23	Primitive pit appears; neural folds may begin to form	Notochordal and neurenteric canals detectable
9	1.5–2.5	25	First somites appear; mesencephalic flexure begins; otic disc forms	Neural groove evident; 3 major subdivisions brain distinguishable; heart begins to develop
10	2–3.5	28	Neural folds begin to fuse; otic pit develops; 4–12 somites; pharyngeal arches 1 and 2 visible	Optic primordium begins to develop; cardiac loop appears; intermediate mesoderm
11	2.5–4.5	29	Rostral neuropore closes; 13–20 somites	Optic vesicles develop
12	3–5	30	Caudal neuropore closes; 21–29 somites; 4 pharyngeal arches visible; upper limb buds appearing	Secondary neurulation starts
13	4–6	32	Otic vesicle closed; lens disc not yet indented; 30 or more somites; 4 limb buds visible	Retinal and lens discs develop; primordium of cerebellum
14	5–7	33	Lens pit appears; upper limb buds elongated	Future cerebral hemispheres; pontine flexure; optic cup develops; adenohypophysial pouch defined
15	7–9	36	Lens pit closed; nasal pit appearing; hand plate forming	Future cerebral hemispheres become defined; retinal pigment visible
16	8–11	38	Retinal pigment visible; nasal sacs face ventrally; auricular hillocks beginning; foot plate appears	Epiphysis cerebri develops; neurohypophysial evagination; olfactory tubercle
17	11–14	41	Head relatively larger; trunk straighter; auricular hillocks distinct; finger rays	Internal and external cerebellar swellings; chondrification begins in humerus, radius and some vertebral centra
18	13–17	44	Body more cuboidal; elbow region and toe rays appearing	Oronasal membrane develops; 1–3 semicircular ducts in internal ear
19	16–18	46	Trunk elongating and straightening	Olfactory bulb develops; cartilaginous otic capsule; choroid plexus of fourth ventricle
20	18–22	49	Upper limbs longer and bent at elbows	Optic fibers reach optic chiasm; choroid plexus of lateral ventricle
21	22–24	51	Fingers longer; hands approach each other, feet likewise	Cortical plate becomes visible; optic tract and lateral geniculate body
22	23–28	53	Eyelids and external ear more developed	Olfactory tract; internal capsule; adenohypophysial stalk incomplete
23	27–31	56	Head more rounded; limbs longer and more developed	Insula indented; caudate nucleus and putamen recognizable; humerus presents all cartilaginous stages

After O'Rahilly and Müller (1987, 2001)

with the first day of the last menstrual period. Usually, the number of **menstrual** or **gestational weeks** exceeds the number of postfertilization weeks by 2. During week 1 (stages 2–4) the blastocyst is formed, during week 2 (stages 5 and 6) implantation occurs and the primitive streak is formed, followed by the formation of the notochordal process and the beginning of neurulation (stages 7–10). Somites first appear at stage 9. The neural folds begin to fuse at stage 10, and the rostral and caudal neuropores close at stages 11 and 12, respectively. Gradually, the pharyngeal bars, the optic and otic vesicles, and the limb buds appear. The main external and internal features of human embryos are summarized in Table 1.1. The first four embryonic weeks are also described as the period of *blastogenesis*, and the fifth to eighth weeks as the period of *organogenesis* (Opitz 1993; Opitz et al. 1997). The **fetal period** cannot be divided into a series of morphologically defined stages. It is the period of *phenogenesis* (Opitz 1993; Opitz et al. 1997). In the clinical literature a subdivision of the prenatal period into three trimesters of 13 weeks each is commonly used. At the junction of the trimesters 1 and 2, the fetus of about 90 days has a greatest length of 90 mm, whereas at the junction of the trimesters 2 and

3, the fetus is about 250 mm in length and weighs approximately 1,000 g (O'Rahilly and Müller 2001; Table 1.2). The newborn brain weighs 300–400 g at full term. Male brains weigh slightly more than those of females but, in either case, the brain constitutes 10 % of the body weight (Crelin 1973).

The brain and spinal cord arise from an area of the ectoderm known as the neural plate. The folding of the neural plate, leading to successively the neural groove and the neural tube, is called primary neurulation. The caudal part of the neural tube does not arise by fusion of the neural folds but develops from the so-called caudal eminence. This process is called secondary neurulation (Chap. 4). Before and after the surface ectoderm of the two sides fuses, the fusing neuroectodermal cells of the neural folds give off the neural crest cells. The neural crest is a transient structure and gives rise to the spinal and cranial ganglia. Moreover, the whole viscerocranium and part of the neurocranium are formed from the neural crest (Le Douarin and Kalcheim 1999; Wilkie and Morriss-Kay 2001; Francis-West et al. 2003; Morriss-Kay and Wilkie 2005; Chap. 5).

Recently, remarkable progress has been made in non-destructive imaging technologies, more in particular magnetic resonance imaging (MRI). By using a super-parallel MR microscope (Matsuda et al. 2007), over 1,400 human embryonic specimens have been imaged in the Kyoto Human Embryo Visualization Project (Yamada et al. 2006, 2010;

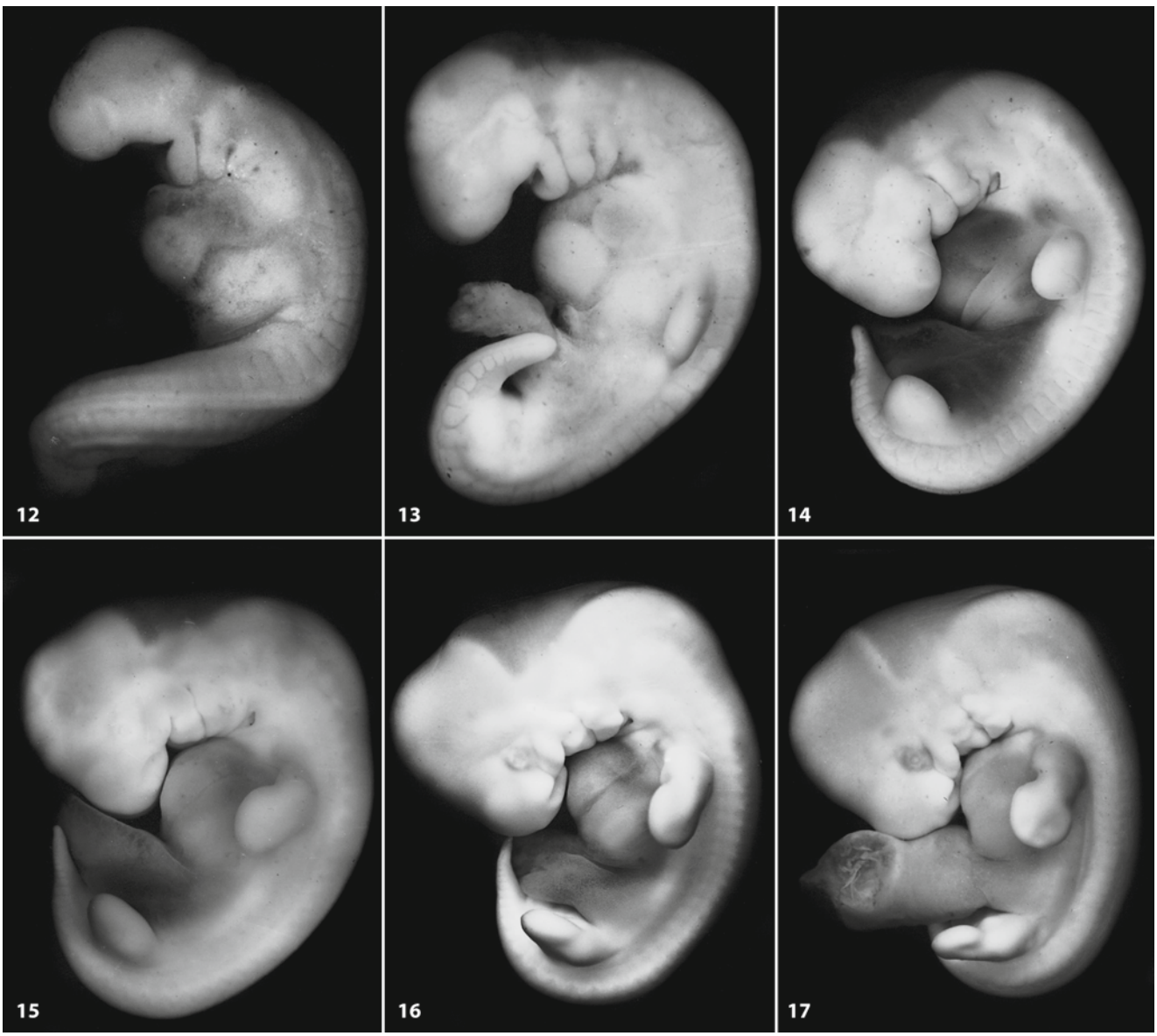

Fig. 1.2 Lateral views of staged human embryos (Carnegie stages 12–23; from the Kyoto Collection of Human Embryos; kindly provided by Kohei Shiota)

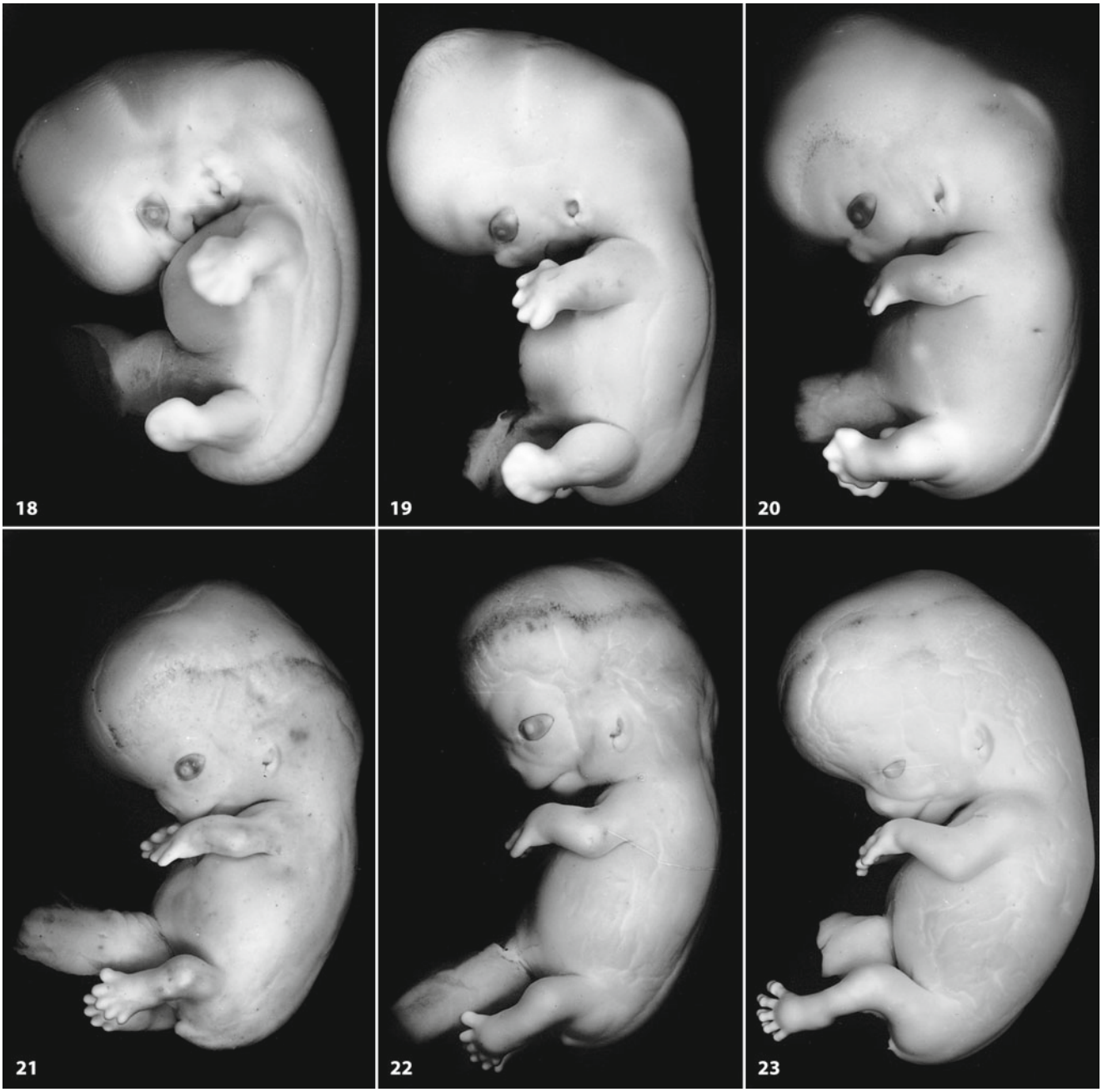

Fig. 1.2 (continued)

Shiota et al. 2007; Fig. 1.3). Selective images from the database can be viewed on the web (http://bird.cac.med.kyoto-u.ac.jp/index_e.html). Episcopic fluorescence image capture is another novel method that can provide registered 2D image stacks suitable for rapid 3D rendering (Weninger and Mohun 2002). More recently, this technique has been used in a developmental atlas of the early first trimester embryo from Carnegie stages 13 to 23 (Yamada et al. 2010).

The embryonic period includes three in time overlapping phases: formation and separation of the germ layers, dorsal and ventral induction phases (Table 1.3). During the first phase, the neural plate is formed. In the **dorsal induction phase**, the neural tube is formed and closed, and the three primary divisions or neuromeres of the brain (the prosencephalon, mesencephalon and rhombencephalon) appear. In the **ventral induction phase** (*telencephalization*), the cerebral hemispheres, the eye vesicles, the olfactory bulbs and tracts, the pituitary gland and part of the face are formed. In the sixth week of development strong proliferation of the ventral walls of the telencephalic vesicles gives rise to

Table 1.2 Criteria for estimating age during the fetal period

Age (postconceptional weeks)	Average crown-rump length (mm)	Average foot length (mm)	Average weight (g)	Main external characteristics
Previable fetuses				
9	50	7	8	Eyes closing or closed; head large and more rounded; external genital not distinguishable as male or female; intestines in proximal part of umbilical cord; low-set ears
10	61	9	14	Intestines returned to abdomen; early fingernail development
12	87	14	45	Sex distinguishable externally; well-defined neck
14	120	20	110	Head erect; eyes face anteriorly; ears close to their definitive position; lower limbs well-developed; early toenail development
16	140	27	200	External ears stand out from head
18	160	33	320	Vernix caseosa covers skin; quickening felt by mother
20	190	39	460	Head and body hair (lanugo) visible
Viable fetuses				
22	210	45	630	Skin wrinkled, translucent, pink to red colour
24	230	50	820	Fingernails present; lean body
26	250	55	1,000	Eyes partially open; eyelashes present
28	270	59	1,300	Eyes wide open; good head of hair may be present; skin slightly wrinkled
30	280	63	1,700	Toenails present; body filling out; testes descending
32	300	68	2,100	Fingernails reach finger tips; skin pink and smooth
36	340	79	2,900	Body usually plump; lanugo hairs almost absent; toenails reach toe tips; flexed limbs; firm grasp
38	360	83	3,400	Prominent chest; breasts protrude; testes in scrotum or palpable in inguinal canals; fingernails extend beyond finger tips

After Moore et al. (2000)

the ganglionic or ventricular eminences. These elevations do not only form the basal ganglia but, in addition, give rise to many neurons that migrate tangentially to the cerebral cortex. **Neurogenesis** starts in the spinal cord and the brain stem. Neurogenesis in the cerebellum and the cerebral cortex occurs largely in the fetal period. The human **fetal period** extends from the ninth week of development to the time of birth. With regard to the prenatal ontogenesis of the cerebral cortex, Marín-Padilla (1990) suggested to divide this long developmental period into two separate ones: (1) the **fetal period proper** (9–24 gestational weeks), characterized by the formation of the cortical plate; and (2) the **perinatal period**, extending from the 24th week of gestation to the time of birth. This period is characterized by neuronal maturation. The separation between these two periods at the 24th week of gestation is somewhat arbitrary but may be clinically relevant. The 24th week of gestation approximates roughly the lower limit for possible survival of the prematurely born infant. Disorders of migration are more likely to occur in the fetal period, whereas abnormalities affecting the architectonic organization of the cerebral cortex are more likely to occur in the perinatal period (Chap. 10). Kostović suggested a further subdivision of the fetal period into four developmental phases and correlated histogenetic events with structural MRI (Kostović and Jovanov-Milošević 2006; Kostović and Vasung 2009; Chap. 10): (1) an **early fetal phase** (9–13 postconceptional weeks) with prominent proliferative zones and a trilaminar cerebral wall; (2) a **fetal phase** (15–23 postconceptional weeks) with transient fetal cellular zones fully developed, a synapse-rich subplate dominating on MRI and thalamocortical axons accumulating below the cortical plate; (3) a **preterm phase** (24–36 postconceptional weeks), characterized by the development of gyri and sulci, thalamocortical fibres penetrating the cortical plate, persistence of the subplate, vulnerable periventricular axonal crossroads and poorly myelinated fibre systems; and (4) a **near-term phase** (36–41 postconceptional weeks) with gradual disappearance of transient fetal zones.

Each of the developmental phases of the brain is characterized by particular **developmental disorders** (Table 1.3). During the separation of the germ layers, enterogenous cysts and fistulae may occur. In the dorsal induction phase, neural tube defects (Chap. 4) occur. Developmental disorders in the ventral induction phase, in which the prosencephalon is normally divided into the diencephalon and the two cerebral hemispheres, are characterized by a single, incompletely divided forebrain (holoprosencephaly; Chap. 9). This very heterogeneous disorder may be due to disorders of ventralization of the neural tube (Sarnat 2000; Flores-Sarnet and Sarnat 2008) such as underexpression of the strong ventralizing gene *Sonic hedgehog* (*SHH*). During neurogenesis of the forebrain, malformations due to abnormal neuronal proliferation or apoptosis may occur, leading to microcephaly or megalocephaly. During the migration of the cortical neurons, malformations due to abnormal neuronal migration may

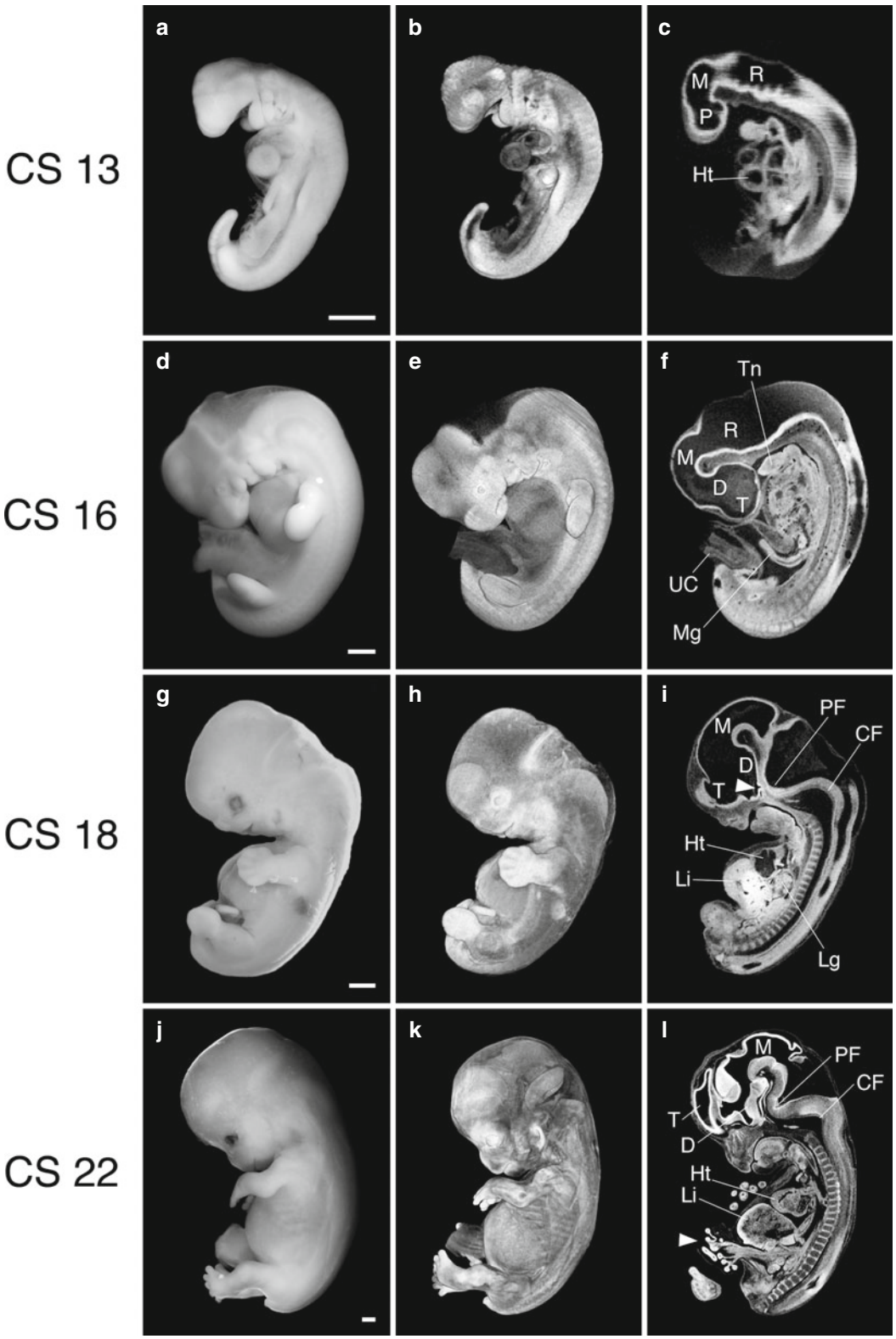

Fig. 1.3 MR microscopy of human embryos at different developmental stages. Human embryos at Carnegie stages (CS) 13, 16, 18 and 22 were imaged by MR microscopy. (**a**, **d**, **g**, **j**) Photographs of the embryos; (**b**, **e**, **h**, **k**) 3D reconstructions of the same embryos using MR images; (**c**, **f**, **i**, **l**) 2D MR images in the sagittal plane. At CS 13 (**a**–**c**), limb buds are present and the prosencephalon (*P*), mesencephalon (*M*) and rhombencephalon (*R*) with rhombomeres can be seen. Also notable is the looped heart tube (*C*). At CS 16 (**d**–**f**), the eye primordia and upper and lower limb buds with limb paddles are observed (*E*). In the abdominal cavity, the midgut (*Mg*) is invested in the umbilical cord (*UC*). At CS 18 (**g**–**i**), anlagen for the digits are evident in the forelimb (**g**, **h**). In the thoracic cavity, the heart (*Ht*) and the lung are clearly seen (**i**). At CS 22 (**j**–**l**), craniofacial and eye development have advanced considerably and the digits in the fore- and hindlimbs are well developed (**l**). At this stage of development, most of the abdominal cavity is occupied by the liver (*Li*) and physiological midgut herniation is present (*arrowhead* in **l**). *CF* cervical flexure, *D* diencephalon, *PF* pontine flexure, *T* telencephalon, *Tn* tongue; bars: 1 mm (From Yamada et al. 2010; courtesy Shigehito Yamada)

Table 1.3 Major stages of human CNS development

Stage	Time of occurrence (weeks)	Major morphological events in brain	Main corresponding disorders
Embryonic period			
Formation and separation of germ layers	2	Neural plate	Enterogenous cysts and fistulas; split notochord syndrome
Dorsal induction: primary neurulation	3–4	Neural tube, neural crest and derivatives; closure of rostral and caudal neuropores; paired alar plates	Anencephaly, encephalocele, myeloschisis; myelomeningocele, Chiari malformations
Ventral induction: telencephalization	4–6	Development of forebrain and face; formation of cerebral vesicles; optic and olfactory placodes; rhombic lips appear; 'fusion' of cerebellar plates	Holoprosencephaly; Dandy-Walker malformation; craniosynostosis
Fetal period			
Neuronal and glial proliferation	6–16	Cellular proliferation in ventricular and subventricular zones; early differentiation of neuroblasts and glioblasts; cellular death (apoptosis); migration of Purkinje cells and external granular layer in cerebellum	Microcephaly, megalencephaly
Migration	12–24	Migration of cortical neurons; formation of corpus callosum	Neuronal migration disorders (lissencephalies, polymicrogyria, schizencephaly, heterotopia)
Perinatal period			
Organization	24 to postnatal	Late migration; organization and maturation of cerebral cortex; synaptogenesis; formation of internal granular layer in cerebellum	Minor cortical dysplasias
Myelination	24 to 2 years postnatally		Myelination disorders, destructive lesions (secondarily acquired injury of normally formed structures)

Based on Aicardi (1992)

appear, varying from classic lissencephaly ('smooth brain'), several types of neuronal heterotopia, polymicrogyria till minor cortical dysplasias. For many of these malformations, disorders of secretory molecules and genes that mediate migration have been found (Chap. 10). Many of these malformations are characterized by the presence of intellectual disability and epilepsy. Cerebellar disorders are more difficult to fit into this scheme. The Dandy-Walker malformation is thought to arise late in the embryonic period, whereas cerebellar hypoplasia presumably occurs in the fetal period. These malformations are discussed in Chap. 8.

1.3 The First 3 Weeks of Development

During the first 3 weeks of development, the three germ layers (ectoderm, mesoderm and endoderm), the basis of the various organs and systems of the body, are established. During the first week of development (stages 2–4), the embryo develops from a solid mass of totipotent cells or blastomeres (the **morula**) into the blastocyst. This occurs when 16–32 cells are present. The **blastocyst** is composed of an inner cell mass or **embryoblast**, giving rise to the embryo, and the **trophoblast**, the peripherally situated cells, surrounding the blastocystic cavity and forming the developmental adnexa (Fig. 1.4). Embryoblast cells adjacent to this cavity form a new layer of flat cells, the **hypoblast**. This cell layer covers the blastocystic cavity from inside that is now called the **primitive umbilical vesicle** or **yolk sac**. The rest of the inner cell mass remains relatively undifferentiated and is known as the **epiblast**. Duplication of the inner cell mass is probably the basis for most cases of monozygotic twinning. Possibly, such divisions arise during 'hatching', the emergence of the blastocyst from the zona pellucida (O'Rahilly and Müller 2001). At approximately 6 days (stage 4b), the blastocyst becomes attached to the endometrium of the uterus.

1.3.1 Implantation

The second week is characterized by **implantation** (stage 5) and the formation of the primitive streak (stage 6). The trophoblast differentiates into the **cytotrophoblast** and the more peripherally situated **syncytiotrophoblast** that invades the endometrium. Blood-filled spaces, the **lacunae**, soon develop within the syncytiotrophoblast and communicate with endometrial vessels, laying the basis for the placental circulation. Between the epiblast and the cytotrophoblast, the **amniotic cavity** appears. The embryonic disc is now known as the **bilaminar embryo**. Only the cylindric epiblast cells adjacent to the hypoblast form the embryo. The remaining flattened

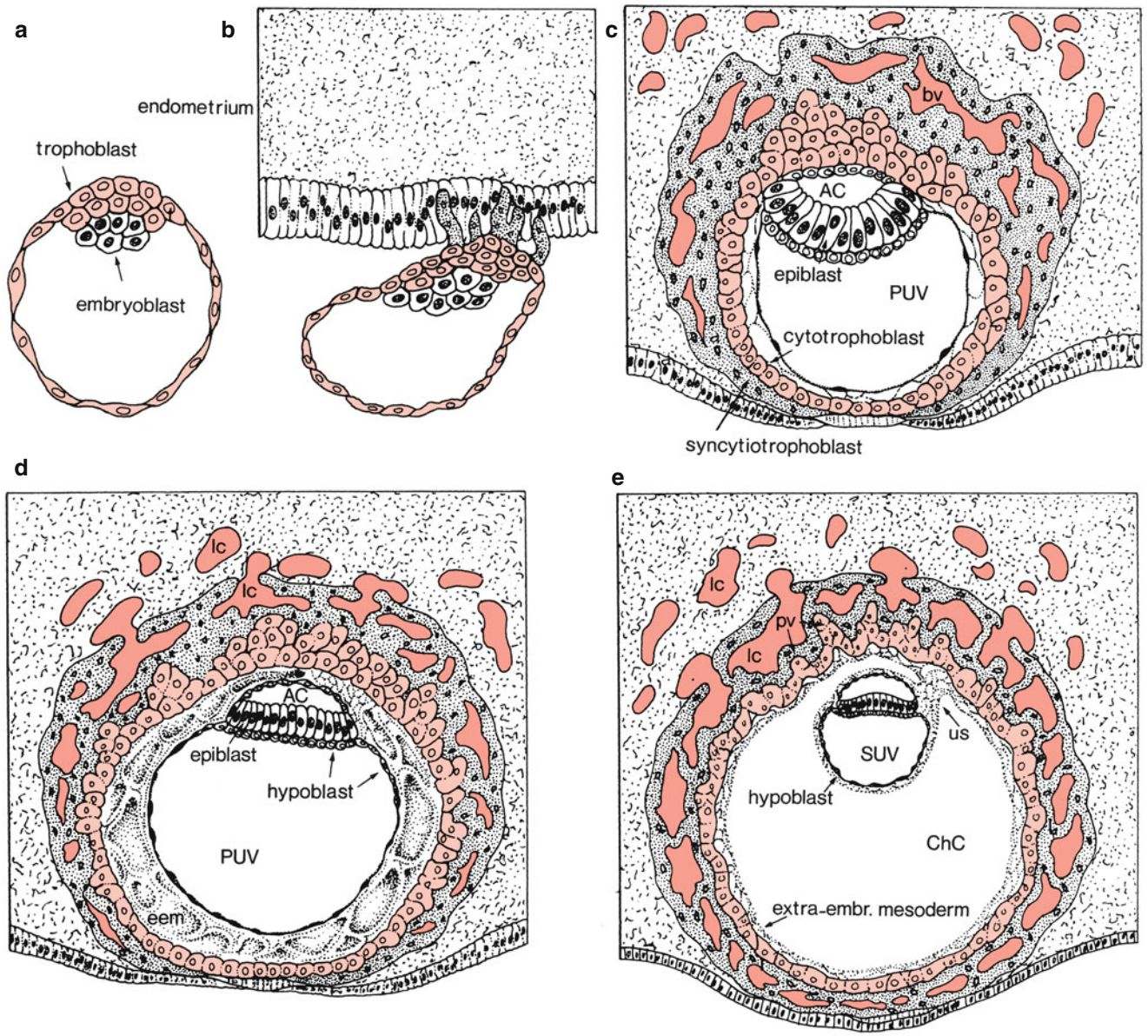

Fig. 1.4 Implantation and the formation of the bilaminar embryo: (**a**) 107-cell blastocyst; (**b**–**e**) blastocysts of approximately 4.5, 9, 12 and 13 days, respectively. The trophoblast and the cytotrophoblast are indicated in *light red*, the syncytiotrophoblast is *stippled* and maternal blood in lacunae is shown in *red*. *AC* amniotic cavity, *ChC* chorionic cavity, *eem* extra-embryonic mesoderm, *lc* lacuna, *pv* primary villi, *PUV* primary umbilical vesicle, *SUV* secondary umbilical vesicle (yolk sac), *us* umbilical stalk (After Langman 1963)

epithelial cells participate in the formation of the amnion (Fig. 1.4). The amniotic cavity is bounded ventrally by the epiblast and dorsally by a layer of amniotic ectoderm.

1.3.2 Gastrulation

During stage 6, in the slightly elongated embryonic disc caudally situated cells of the epiblast migrate ventralwards along the median plane, and form the **primitive streak** (Fig. 1.5). It probably appears between days 12 and 17 (Jirásek 1983, 2001; Moore et al. 2000; O'Rahilly and Müller 2001). The rostral, usually distinct part of the primitive streak is known as the **primitive node** of Hensen. The primitive streak is a way of entrance whereby cells invaginate, proliferate and migrate to subsequently form the extra-embryonic mesoderm, the endoderm and the intra-embryonic mesoderm. Remnants of the primitive streak may give rise to ***sacrococcygeal teratomas*** (Chap. 6). The **endoderm** replaces the hypoblast. The remaining part of the epiblast is the **ectoderm**. For this process the term **gastrulation** is frequently used. Originally, the term referred to the invagination of a monolayered blastula to form a bilayered gastrula, containing an endoderm-lined archenteron as found in amphibians

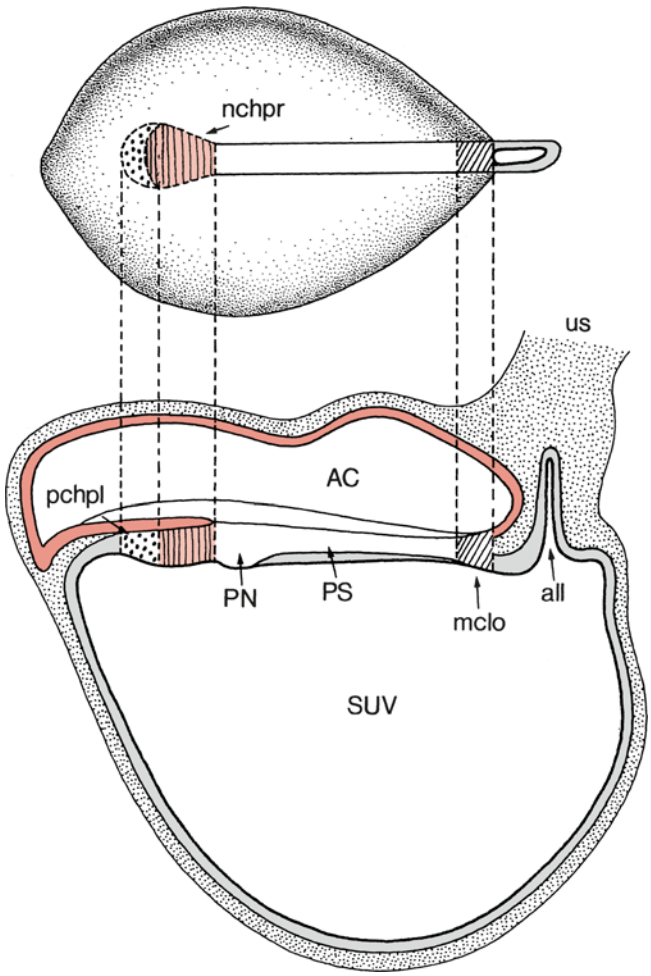

Fig. 1.5 Dorsal (*top*) and medial (*bottom*) views of a stage 7 embryo. The ectoderm is indicated in *red*, the notochordal process in *light red* and the endoderm in *grey*. *AC* amniotic cavity, *all* allantois, *mclo* membrana cloacalis, *nchpr* notochordal process, *pchpl* prechordal plate, *PN* primitive node, *PS* primitive streak, *SUV* secondary umbilical vesicle (yolk sac), *us* umbilical stalk (After O'Rahilly 1973)

(Chap. 2). Nowadays, the term gastrulation is more generally used to delimit the phase of development from the end of cleavage until the formation of an embryo possessing a defined axial structure (Collins and Billett 1995). Rostral to the primitive node, the endoderm appears thicker and is called the **prechordal plate**. Caudally, the epiblast is closely related to the endoderm, giving rise to the **cloacal membrane** (Fig. 1.5). The primitive streak is the first clear-cut indication of bilaterality, so the embryo now, apart from rostral and caudal ends, also has right and left sides. Genetic mutations expressed in the primitive streak may lead to duplication of the neural tube (Chap. 6) or its partial or complete agenesis (Sarnat 2000; Flores-Sarnat and Sarnat 2008).

The **extra-embryonic mesoderm** soon covers the trophoblast, the amniotic ectoderm and the yolk sac (Fig. 1.4). Extra-embryonic mesoderm at the caudal part of the embryo forms the **connecting** or **umbilical stalk** that anchors the embryo to the chorion. The **chorion** is composed of the trophoblast and the covering extra-embryonic mesoderm. Hypoblast cells and the covering extra-embryonic mesoderm form the wall of the yolk sac, whereas the amniotic epithelium and its mesodermal layer form the **amnion**. The **secondary umbilical vesicle** or **yolk sac** develops from the primary one, probably by collapse and disintegration of the latter (Luckett 1978). The yolk sac is involved in active and passive transport to the embryo, and is possibly associated with the relationship between metabolic disorders such as diabetes mellitus and congenital malformations (O'Rahilly and Müller 2001). The chorion encloses the **chorionic cavity**, in which the embryonic disk, now a **trilaminar embryo**, is located.

During the third and the fourth weeks, the somites, the heart, the neural folds, the three major divisions of the brain, the neural crest and the beginnings of the internal ear and the eye develop. At approximately 19 days (stage 7), rostral to the primitive streak, a prolongation below the ectoderm, the **notochordal process**, arises from the primitive node, and extends rostrally as far as the prechordal plate (Fig. 1.5). The floor of the notochordal process breaks down at stage 8, giving rise to the notochordal plate. The embryonic disc is now broader rostrally, and a shallow neural groove appears, which is the first morphological indication of the nervous system (O'Rahilly 1973; O'Rahilly and Gardner 1979; O'Rahilly and Müller 1981; Jirásek 2001, 2004). The primitive node may be hollowed by a **primitive pit**, which extends into the notochordal process as the **notochordal canal** (O'Rahilly 1973). The channel becomes intercalated in the endoderm, and its floor begins to disintegrate at once, allowing temporary communication between the amniotic cavity and the umbilical vesicle. The remnant of the notochordal canal at the level of the primitive pit is known as the **neurenteric canal** (Fig. 1.6a). It may be involved in the pathogenesis of ***enterogenous cysts*** (Chap. 6). The **prechordal plate** is wider than the notochordal process, and is in close contact with the floor of the future forebrain. The prechordal plate is derived from the prechordal mesendoderm (de Souza and Niehrs 2000) and it is essential for the induction of the forebrain. The prechordal plate is usually defined as mesendodermal tissue underlying the medial aspect of the anterior neural plate just anterior to the rostral end of the notochord.

1.3.3 Folding of the Embryo

At approximately 25 days (stage 9), **folding** of the **embryo** becomes evident. Rostral or cephalic and caudal folds overlie the beginning foregut and hindgut, respectively (Fig. 1.6). Caudal to the cloacal membrane, the allantois arises as a dorsal diverticle of the umbilical vesicle. On each side the mesoderm is arranged into three components (Fig. 1.6e): (1) a longitudinal, **paraxial** band adjacent to the notochord, form-

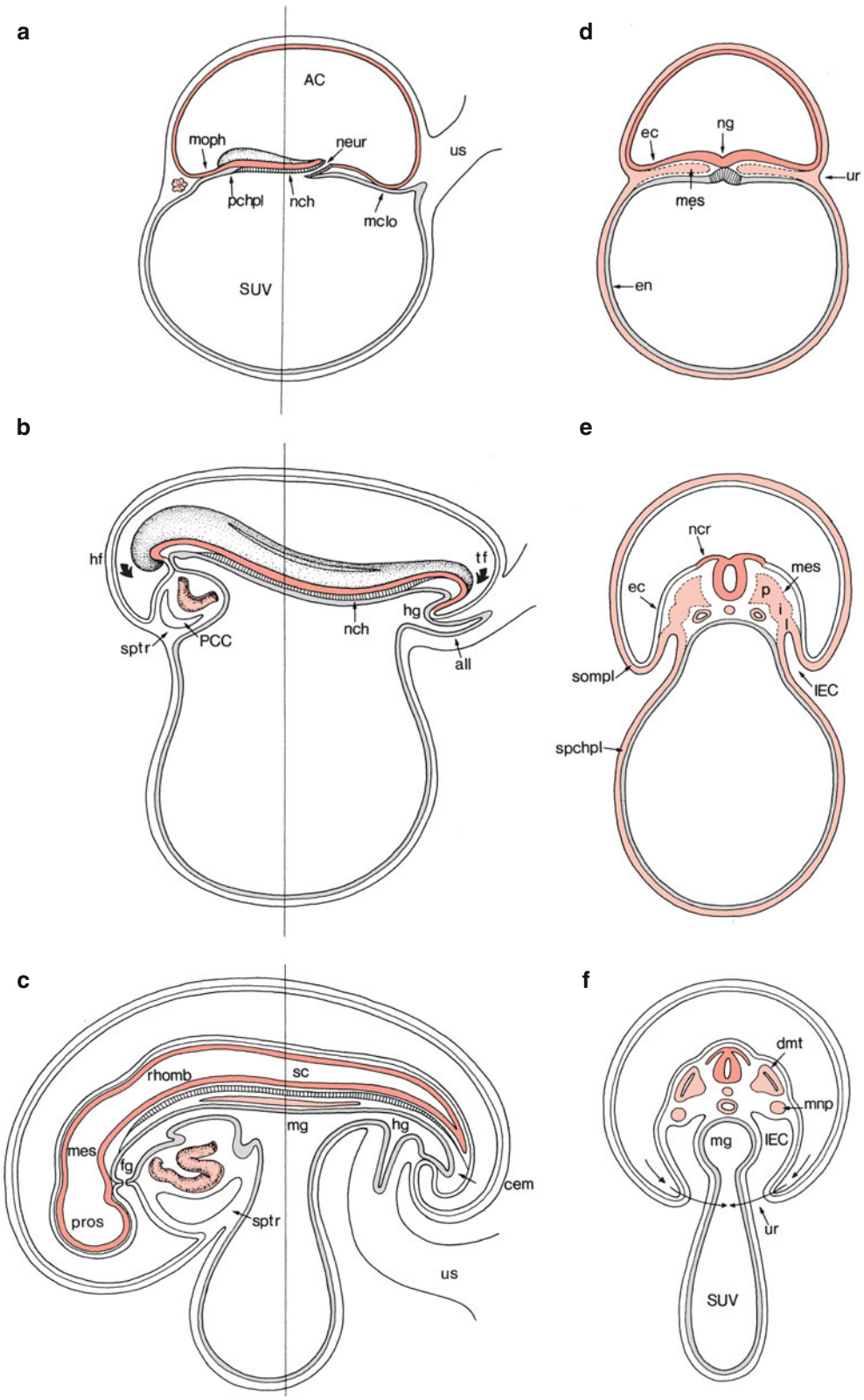

Fig. 1.6 The folding of the embryo: (**a**, **d**) Carnegie stage 8; (**b**, **e**) Carnegie stage 10; (**c**, **f**) Carnegie stage 11/12. The ectoderm (*ec*) and its derivates are indicated in *red*, derivates of the mesoderm (*mes*) in *light red* and the endoderm (*en*) in *grey*. *AC* amniotic cavity, *all* allantois, *cem* caudal eminence, *dmt* dermamyotome, *fg* foregut, *hf* head fold, *hg* hindgut, *i* intermediate mesoderm, *IEC* intra-embryonic coelom, *l* lateral plate of mesoderm, *mclo* membrana cloacalis, *mes* mesencephalon, *mg* midgut, *mnp* mesonephros, *moph* membrana oropharyngealis, *nch* notochord, *ncr* neural crest, *neur* neurenteric canal, *ng* neural groove, *p* paraxial mesoderm, *PCC* pericardiac cavity, *pchpl* prechordal plate, *pros* prosencephalon, *rhomb* rhombencephalon, *sc* spinal cord, *sompl* somatopleure, *spchpl* splanchnopleure, *sptr* septum transversum, *SUV* secondary umbilical vesicle (yolk sac), *tf* tail fold, *ur* umbilical ring, *us* umbilical stalk (After Streeter 1951; Hamilton and Mossman 1972)

ing the somites; (2) **intermediate** mesoderm, giving rise to the urogenital system; and (3) a **lateral plate**, giving rise to two layers covering the body wall and the viscera, respectively. The first layer is known as the **somatopleure**, the other as the **splanchnopleure**. In the Anglo-Saxon literature, however, the terms somatopleure and splanchnopleure include the covering ectoderm and endoderm, respectively (O'Rahilly and Müller 2001). The space between the

somatopleure and the splanchnopleure is the **coelom**. At first it is found outside the embryo (the *extra-embryonic coelom*), later also within the embryo. This is the *intra-embryonic coelom* or body cavity, which develops in the lateral plate mesoderm (Fig. 1.6e, f). For a discussion of body wall closure and its relevance to ***gastroschisis*** and other ventral body wall defects, see Sadler and Feldkamp (2008) and Hunter and Stevenson (2008).

Somites arise at stage 9 in longitudinal rows on each side of the neural groove. The first four pairs of somites belong to the occipital region. Within the next 10 days subsequently 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and some 3–6 coccygeal somites are formed, but they are never visible together at one stage of development. Each somite divides into a ventromedial **sclerotome**, participating in the formation of the vertebral column (Chap. 6), and a dorsolateral **dermamyotome** that forms a myotome and the overlying dermis (**dermatome**). Each **myotome** divides into two parts: (1) a dorsal *epimere*, giving rise to the erector spinae, and (2) a ventral *hypomere*, from which the ventral vertebral muscles (*epaxial* muscles), the muscles of the lateral and ventral body wall (*hypaxial* muscles) and the muscles of the extremities arise. The derivatives of the epimeres become innervated by the dorsal rami of the spinal nerves, those of the hypomeres by the ventral rami (Chap. 6).

The primitive streak becomes confined to a region known as the **caudal eminence**, or end-bud, which gives rise to the hindgut, adjacent notochord and somites, and the most caudal part of the spinal cord (O'Rahilly and Müller 2001). Malformations in this region may lead to the still poorly understood ***caudal regression syndrome*** that is discussed in Chap. 4. Rostrally, the ectoderm and the endoderm come together as the **oropharyngeal membrane**, which temporarily separates the gut from the amniotic cavity. Pharyngeal arches, clefts and pouches become visible. The **pharyngeal arches** are separated by the **pharyngeal clefts**, and appear ventrolaterally on the head and neck between 4 and 5 weeks. Four pairs are visible at stage 13 (Fig. 1.2). More caudally, no clear-cut arrangement is found, but it is customary to distinguish a fifth and a sixth arch. The externally situated clefts have internal counterparts, the **pharyngeal pouches**. The development of the pharyngeal arches is closely related to that of the rhombomeres and the neural crest, and is controlled by *Hox* genes (Favier and Dollé 1997; Rijli et al. 1998). Each pharyngeal arch is characterized by a unique combination of *Hox* genes. Rostral to the somites, the paraxial mesoderm forms the **somitomeres** from which the external eye musculature and the muscles of the pharyngeal bars arise (Noden 1991; Noden and Trainor 2005). These aspects and developmental disorders of the pharyngeal arches are discussed in Chap. 5. The major sensory organs of the head develop from the interactions of the neural tube with a series of epidermal thickenings called the **cranial ectodermal placodes**. The olfactory placode forms the olfactory epithelium, the trigeminal placode the trigeminal ganglion, the otic placode or disc forms the inner ear, and the epibranchial placodes the distal ganglia of the VIIth, IXth and Xth nerves. The lens placode forms the lens and induces the overlying ectoderm to form the transparent cornea.

1.4 Neurulation

The first indication of the neural plate in human embryos is a median sulcus around 23 days of development. At approximately 25 days (stage 9), this **neural groove** is deeper and longer. Its rostral half represents the forebrain, its caudal half mainly the hindbrain (Fig. 1.7). The **neural folds** of the forebrain are conspicuous. The **mesencephalic flexure** appears, and allows a first subdivision of the brain into three major divisions in the still unfused neural folds (O'Rahilly 1973; O'Rahilly and Gardner 1979; Müller and O'Rahilly 1983, 1997; Jirásek 2001, 2004): the forebrain or **prosencephalon**, the midbrain or **mesencephalon**, and the hindbrain or **rhombencephalon** (Fig. 1.8). The otic discs, the first indication of the internal ears, can also be recognized. At stage 10, the two subdivisions of the forebrain, the **telencephalon** and the **diencephalon**, become evident (Müller and O'Rahilly 1985). An **optic sulcus** is the first indication of the developing eye. Closure of the neural groove begins near the junction between the future brain and the spinal cord. Rostrally and caudally, the cavity of the developing neural tube communicates via the **rostral** and **caudal neuropores** with the amniotic cavity. The rostral neuropore closes at about 30 days (stage 11), and the caudal neuropore about 1 day later (stage 12). The site of final closure of the rostral neuropore is at the site of the embryonic lamina terminalis (O'Rahilly and Müller 1999). The closure of the neural tube in human embryos is generally described as a continuous process that begins at the level of the future cervical region, and proceeds both rostrally and caudally (O'Rahilly and Müller 1999, 2001). Nakatsu et al. (2000), however, provided evidence that neural tube closure in humans may initiate at multiple sites as in mice and other animals. ***Neural tube defects*** are among the most common of human malformations (Chap. 4).

When the surface ectodermal cells of both sides fuse, the similarly fusing neuro-ectodermal cells of the neural folds give off neural crest cells (Fig. 1.7). These cells arise at the neurosomatic junction. The **neural crest** cells migrate extensively to generate a large diversity of differentiated cell types (Le Douarin and Kalcheim 1999; Chap. 5), including (1) the spinal cranial and autonomic ganglia, (2) the enteric nervous system, (3) the medulla of the adrenal gland, (4) the melanocytes, the pigment-containing cells of the epidermis, and (5) many of the skeletal and connective tissue of the head. The final phase of primary neurulation is the separation of neural

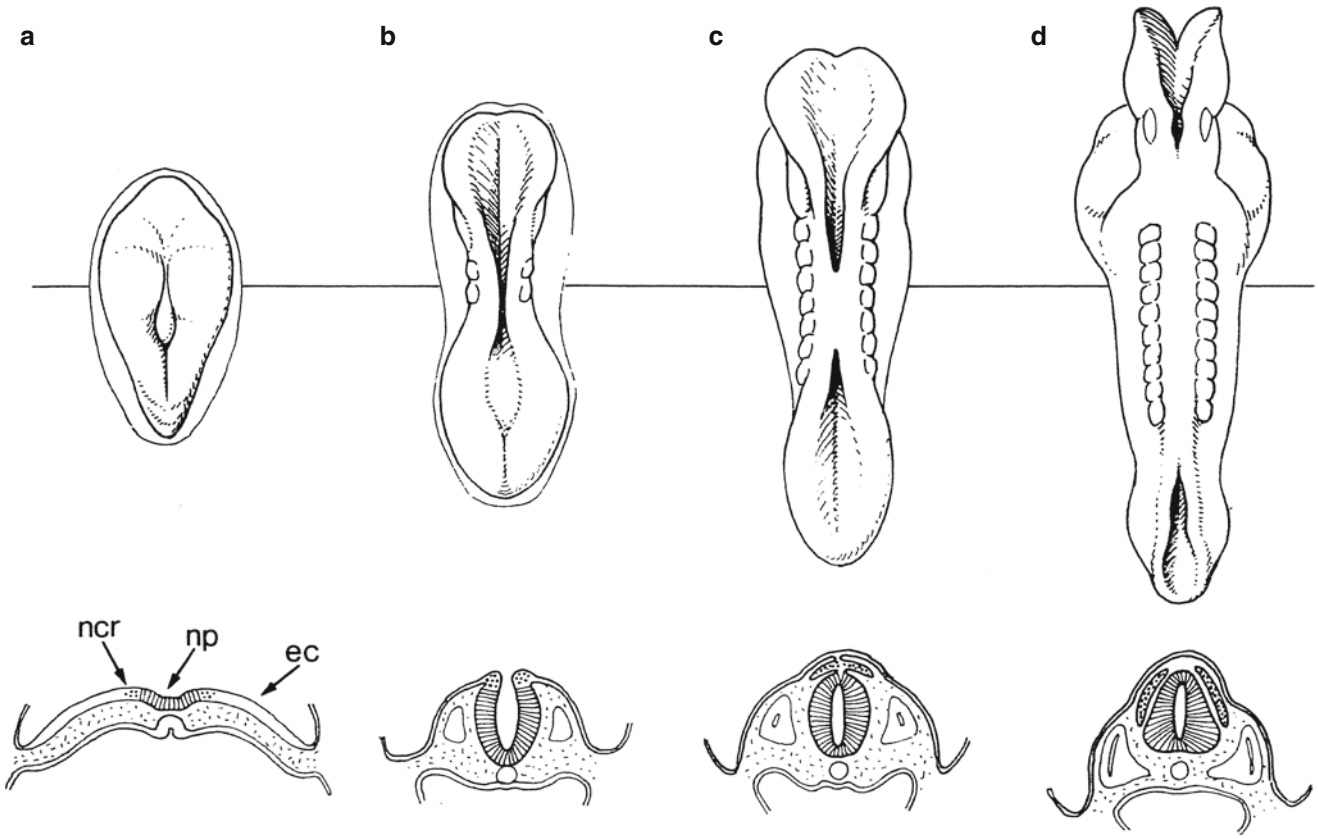

Fig. 1.7 The formation of the neural tube and neural crest. Dorsal views and transverse sections are shown for human embryos of stages 8 (**a**), 9 (**b**), 10 (**c**, seven somites) and 10 (**d**, ten somites). *ec* ectoderm, *ncr* neural crest, *np* neural plate

and surface ectoderm by mesenchyme. Failure to do so may lead to an encephalocele, at least in rats (O'Rahilly and Müller 2001). Malformations of the neural crest (***neurocristopathies***) may be accompanied by developmental disorders of the CNS (Chap. 5).

Detailed **fate map** studies are available for amphibians and birds (Chap. 2). The organization of vertebrate neural plates appears to be highly conserved. This conservation probably extends to mammals, for which detailed fate maps are more difficult to obtain. Nevertheless, available data (Rubinstein and Beachy 1998; Rubinstein et al. 1998; Inoue et al. 2000; Puelles et al. 2012) show that in mice ventral parts of the forebrain such as the hypothalamus and the eye vesicles arise from the medial part of the rostral or prosencephalic part of the neural plate (Fig. 1.10c). Pallial as well as subpallial parts of the telencephalon arise from the lateral parts of the prosencephalic neural plate. The lateral border of this part of the neural plate forms the dorsal, septal roof of the telencephalon. The most rostral, median part of the neural plate gives rise to the commissural plate from which the anterior commissure and the corpus callosum arise.

Initially, the wall of the neural tube consists of a single layer of neuroepithelial cells, the **germinal neuroepithelium** or **matrix layer**. As this layer thickens, it gradually acquires the configuration of a pseudostratified epithelium. Its nuclei become arranged in more and more layers, but all elements remain in contact with the external and internal surface. Mitosis occurs on the internal, ventricular side of the cell layer only (Chap. 2), and migrating cells form a second layer around the original neural tube. This layer, the **mantle layer** or **intermediate zone**, becomes progressively thicker as more cells are added to it from the germinal neuroepithelium that is now called the **ventricular zone**. The cells of the intermediate zone differentiate into neurons and glial cells. Radial glial cells are present during early stages of neurogenesis. Most radial glial cells transform into astrocytes (Chap. 2). The neurons send axons into an outer layer, the **marginal zone**. The mantle layer, containing the cell bodies, becomes the **grey matter**, and the axonal, marginal layer forms the **white matter**. In the spinal cord, this three-zone pattern is retained throughout development.

Secondary proliferative compartments are found elsewhere in the brain. The **external germinal** or **granular layer** is confined to the cerebellum. It develops from the ventricular zone of the rhombic lip, a thickened germinal zone in the rhombencephalic alar plate, and gives rise to the granule cells of the cerebellum. The **subventricular zone** is found in the lateral and basal walls of the telencephalon. This zone

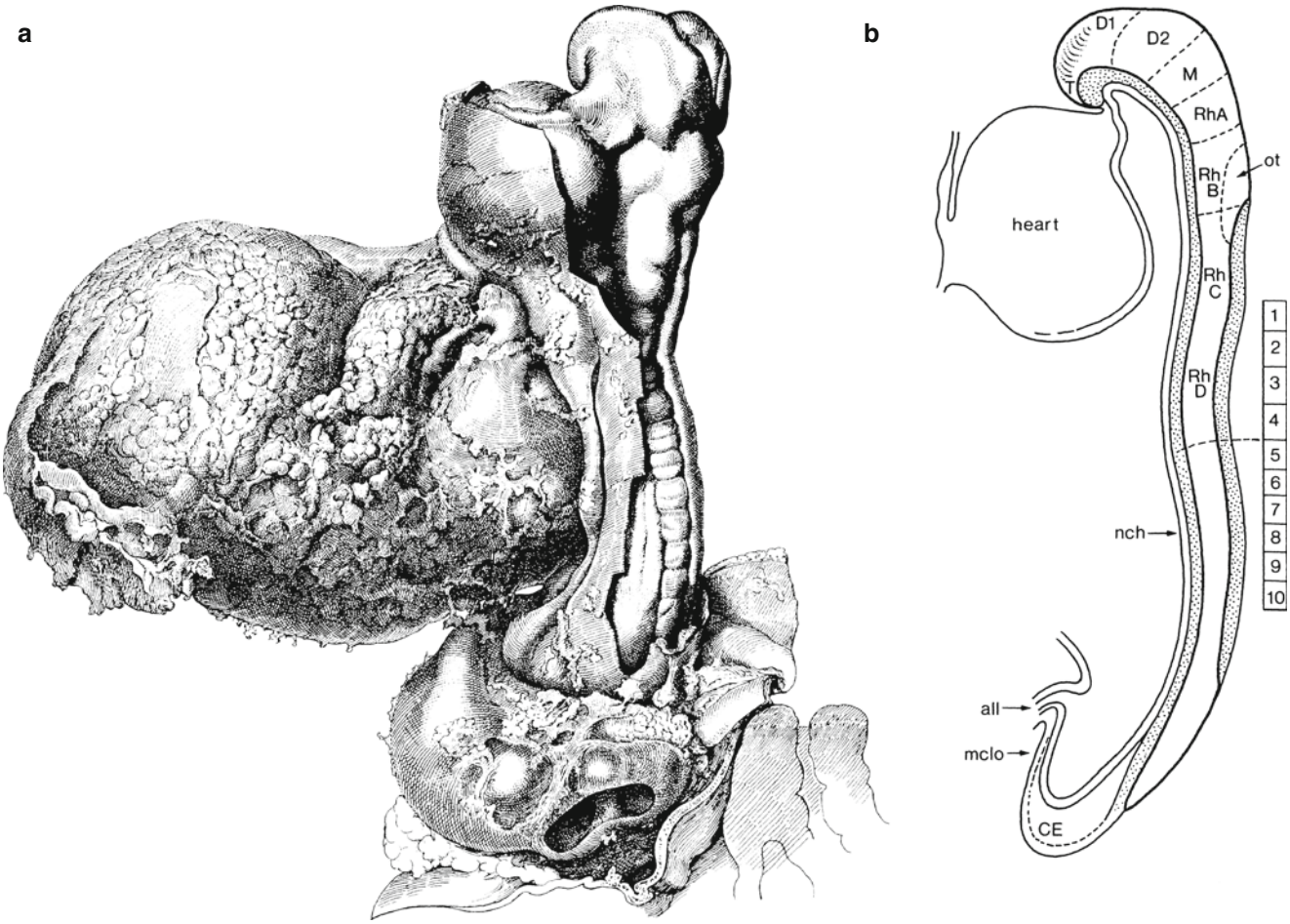

Fig. 1.8 Corner's ten-somite embryo (**a**). (**b**) A median section, showing the subdivision of the brain into the primary neuromeres. *all* allantois, *CE* caudal eminence, *D1*, *D2* diencephalic neuromeres, *M* mesomere, *mclo* membrana cloacalis, *nch* notochord, *ot* otocyst, *RhA-RhD* primary rhombomeres, *T* telencephalic neuromere, *1–10* first ten somites (**a** Illustrated by James Didusch, from Corner 1929, with permission; **b** after O'Rahilly and Müller 1987)

gives rise to a large population of glial cells and to the granule cells of the olfactory bulb. Recently, a special role for the outer subventricular zone as a proliferative compartment for neurons has been demonstrated (Kriegstein and Alvarez-Buylla 2009; Lui et al. 2011; Chaps. 2 and 10).

1.5 Development of the Spinal Cord

After neurulation, the **spinal cord** can be divided into dorsal **alar plates** derived from lateral parts of the neural plate, and ventral **basal plates** derived from its medial parts (Fig. 1.9). The alar and basal plates are separated by the **sulcus limitans** of His (1880). The alar plates are united by a small roof plate, and the basal plates by a thin floor plate. The alar plates and incoming dorsal roots form the afferent or sensory part of the spinal cord, whereas the basal plate and its exiting ventral root form the efferent or motor part. The spinal ganglia arise from the neural crest. The development of the alar and basal plates is induced by **extracellular signalling molecules**, secreted by the notochord and the adjacent ectoderm (Fig. 1.9). The protein SHH of the *SHH* gene in the notochord induces the formation of the floor plate. In its turn, the floor plate induces the formation of motoneurons in the basal plate. Bone morphogenetic proteins (BMPs) from the ectoderm induce the formation of the alar and roof plates and of the neural crest. BMP4 and BMP7 induce the expression of the transcription factor 'Slug' in the neural crest and the expression of certain *Pax* transcription factors in the alar plates. SHH suppresses these dorsal *Pax* genes in the ventral half of the spinal cord. Many other genes are involved in the specification of the various types of neurons in the spinal cord (Chap. 6). Motoneurons are the first neurons to develop (Windle and Fitzgerald 1937; Bayer and Altman 2002). They appear in the uppermost spinal segments at approximately embryonic day 27 (about Carnegie stage 13/14). At this time of development also dorsal root ganglion cells are present. Dorsal root fibres enter the spinal grey matter very

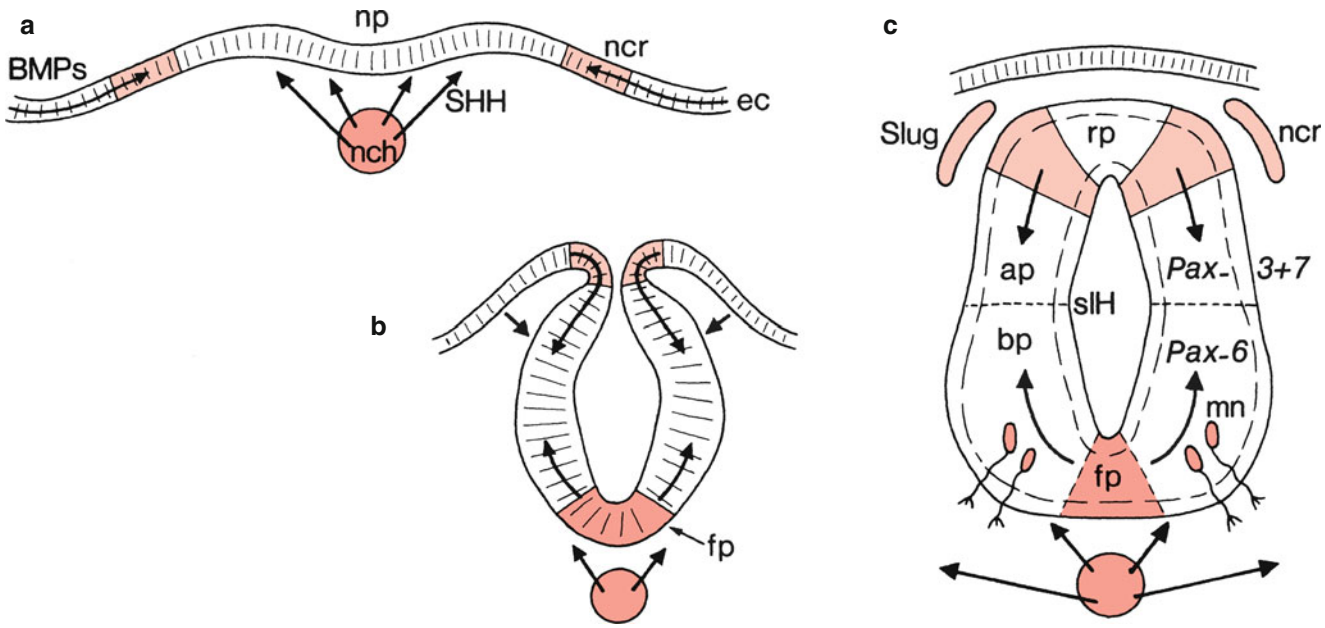

Fig. 1.9 The development of the spinal cord and the dorsalizing (bone morphogenetic proteins, *BMPs*) and ventralizing (Sonic hedgehog, *SHH*) factors involved. (**a**) SHH in the notochord (*nch*, *red*) induces the formation of the floor plate (*fp*), after which SHH in the floor plate induces the formation of motoneurons (**b**, **c**). BMP4 and BMP7 (*light red*) from the ectoderm (*ec*) induce Slug in the neural crest (*ncr*) and support the expression of *Pax3* and *Pax7* in the dorsal part of the spinal cord. SHH suppresses the expression of these transcription factors. *ap* alar plate, *bp* basal plate, *mn* motoneurons, *np* neural plate, *rp* roof plate, *slH* sulcus limitans of His (After Carlson 1999)

early in development (Windle and Fitzgerald 1937; Konstantinidou et al. 1995; Chap. 6). The first synapses between primary afferent fibres and spinal motoneurons were found in a stage 17 embryo (Okado et al. 1979; Okado 1981). Ascending fibres in the dorsal funiculus have reached the brain stem at stage 16, i.e. at about 37 postovulatory days (Müller and O'Rahilly 1989). The first descending supraspinal fibres from the brain stem have extended into the spinal cord at stage 14 (Müller and O'Rahilly 1988b). Even the late developing pyramidal tract extends as far caudally as the spinomedullary junction at the end of the embryonic period (Müller and O'Rahilly 1990c; ten Donkelaar 2000). The spinal cord then still reaches the end of the vertebral canal. During the fetal period, it 'ascends' to lumbar levels (Chap. 6).

1.6 Pattern Formation of the Brain

Prospective subdivisions of the brain are specified through **pattern formation** which takes place in two directions: from medial to lateral, and from rostral to caudal (Lumsden and Krumlauf 1996; Rubinstein and Beachy 1998; Fig. 1.10). Mediolateral or ventrodorsal pattern formation generates longitudinal areas such as the alar and basal plates, and rostrocaudal pattern formation generates transverse zones (one or more neuromeres). Most likely, the rostrocaudal regionalization of the neural plate is induced already during gastrulation (Nieuwkoop and Albers 1990). In amphibians, the first mesoderm to ingress gives rise to the anterior head mesoderm. The mesoderm that follows will form the chordamesoderm and more lateral mesodermal structures. The anterior mesoderm differs from the chordamesoderm also in the genes that it expresses. Signals from both the anterior mesoderm and the chordamesoderm initiate neural development by inducing neural tissue of an anterior type, i.e. forebrain and midbrain, in the overlying ectoderm along its entire anteroposterior length. A second signal from chordamesoderm alone converts the overlying neuroectoderm induced by the first signal into a posterior type of neural tissue, i.e. hindbrain and spinal cord (Chap. 2). Endodermal signalling molecules also play an important role in the induction of the rostral part of the CNS (de Souza and Niehrs 2000).

Developmental gene expression studies show that the vertebrate CNS can be divided into three regions. The anterior region comprises the forebrain and most of the midbrain, and is characterized by expression of the **homeobox genes** *Emx* and *Otx*. The middle division comprises the posterior part of the midbrain and most of the first rhombomere. It is known as the **midbrain-hindbrain boundary** (**MHB**) or isthmocerebellar region. The third region comprises the rhombencephalon and spinal cord, and is characterized by *Hox* gene expression. **Longitudinal patterning centres** are present along the ventral (notochord and prechordal plate, and later the floor plate) and dorsal (epidermal-neuroectodermal

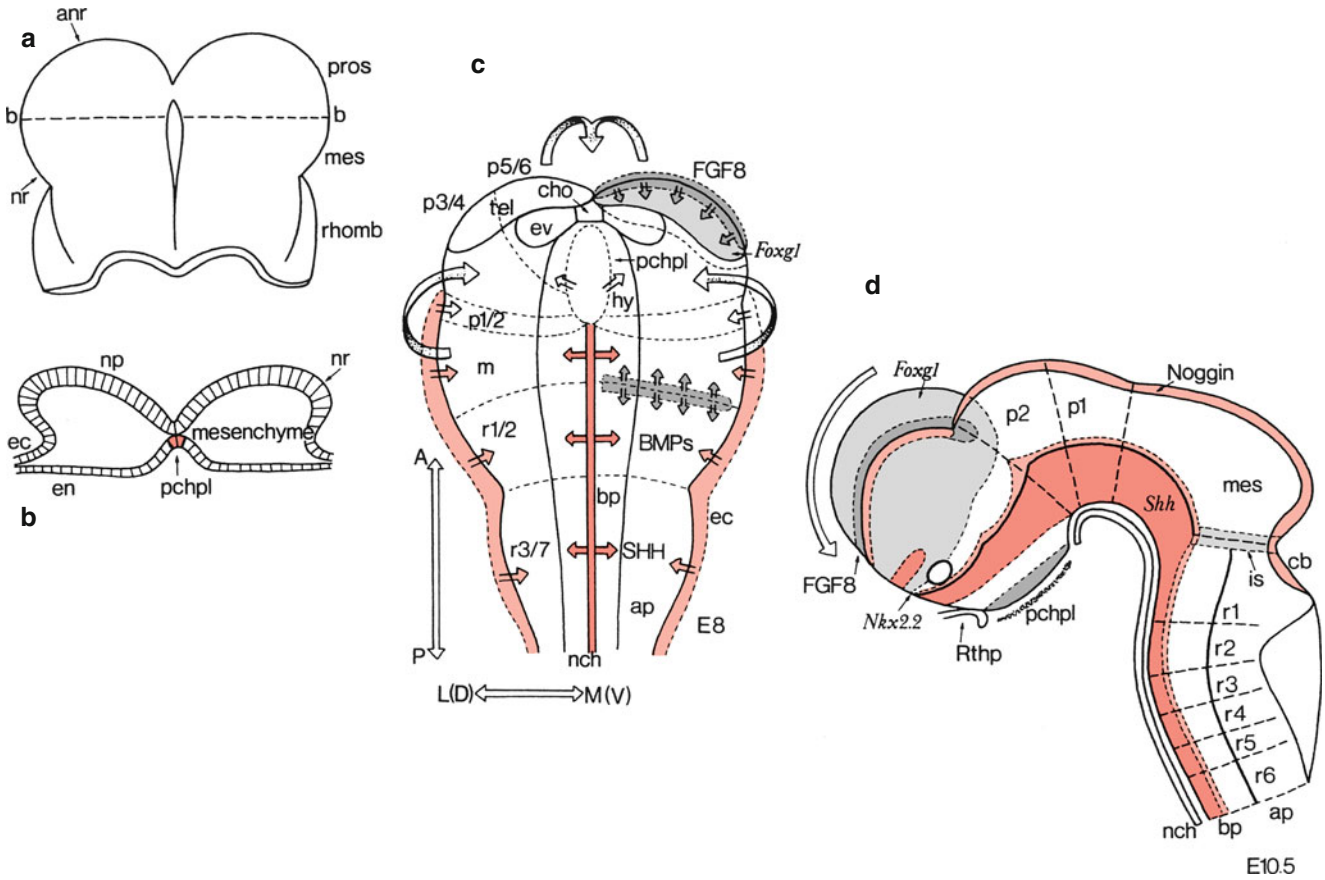

Fig. 1.10 Bauplan and pattern formation of the mouse brain. (**a**) The dorsal view of the rostral part of the neural plate (*np*) shows the approximate locations of the prosencephalon (*pros*), mesencephalon (*mes*) and rhombencephalon (*rhomb*), and (**b**) the transverse section shows the structures involved. The expression of some genes involved in the patterning of the brain is shown in a dorsal view of the neural plate of an E8 mouse (**c**) and in a median section through the neural tube at E10.5 (**d**). The *arrows* indicate the morphogenetic processes involved in the closure of the neural tube. The expression of lateralizing (*L*) or dorsalizing (*D*) signalling molecules such as BMPs is indicated in *light red*, the medializing (*M*) or ventralizing (*V*) factor SHH in *red*, the fibroblast growth factor 8 (*FGF8*) in *dark grey* and brain factor 1 (*Foxg1*) in *grey*. Medial signals induce the basal plate (*bp*), whereas lateral signals induce the alar plate (*ap*). *anr* anterior neural ridge, *cb* cerebellum, *cho* chiasma opticum, *ec* ectoderm, *en* endoderm, *ev* eye vesicle, *hy* hypothalamus, *is* isthmus, *m* mesencephalon, *nch* notochord, *nr* neural ridge, *pchpl* prechordal plate, *p1*, *p6* prosomeres, *Rthp* Rathke's pouch, *r1–r7* rhombomeres, *tel* telencephalon (After Rubinstein and Beachy 1998; Rubinstein et al. 1998)

junction, and later the roof plate) aspects of the neural plate and early neural tube. Medial, i.e. **ventralizing**, signals such as SHH play an important role during the formation of the primordia of the basal plate. SHH induces the formation of motoneurons in the spinal cord and brain stem (Chap. 6). Lateral, i.e. **dorsalizing**, signals such as BMPs from the adjacent ectoderm induce the formation of the alar plate and the dorsal part of the forebrain. SHH is not only responsible for dorsoventral patterning in the CNS, but also plays a role during the specification of oligodendrocytes, the proliferation of neural precursors and the control of axon growth (Marti and Bovolenta 2002). The BMPs also have a variety of functions (Mehler et al. 1997). ***Holoprosencephaly***, a defect in brain patterning, is the most common structural anomaly of the developing forebrain (Golden 1998; Muenke and Beachy 2000; Sarnat and Flores-Sarnat 2001; Chap. 9).

Specialized, **transverse patterning centres** are present at specific anteroposterior locations of the neural plate such as the anterior neural ridge, the zona limitans intrathalamica and the already mentioned MHB (Fig. 1.10). They provide a source of secreted factors that establish the regional identity in adjacent domains of the neural tube. The posterior limit of *Otx2* expression marks the anterior limit of the MHB, whereas the anterior limit of *Gbx2* expression marks its posterior limit. In *Otx2* knockout mice, the rostral neuroectoderm is not formed, leading to the absence of the prosencephalon and the rostral part of the brain stem (Acampora et al. 2001; Wurst and Bally-Cuif 2001). In *Gbx2* knockouts, all structures arising from the first three rhombomeres such as the cerebellum, are absent. Cells in the MHB (the **isthmic organizer**) secrete fibroblast growth factors (FGFs) and *Wnt* proteins which are required for the differentiation

and patterning of the midbrain and hindbrain (Rhinn and Brand 2001). The **zona limitans intrathalamica** is important for the establishment of regional identity in the diencephalon (Kiecker and Lumsden 2012). It separates the (dorsal) thalamus from the ventral thalamus or prethalamus (Chaps. 2 and 9). Signals from the **anterior neural ridge** including FGF8 regulate the expression of *Foxg1* (earlier known as *brain factor 1*, *BF1*), a transcription factor that is required for normal telencephalic and cortical morphogenesis (Rubinstein and Beachy 1998; Monuki and Walsh 2001). Although much of our insight into these patterning mechanisms relies on studies in mice, humans are subject to a wide variety of naturally occurring mutations (Chap. 9).

1.7 Early Development of the Brain

Lateral and medial views of the developing brain are shown in Figs. 1.11 and 1.12. The neural tube becomes bent by three flexures: (1) the **mesencephalic flexure** at the midbrain level, already evident before fusion of the neural folds; (2) the **cervical flexure**, situated at the junction between the rhombencephalon and the spinal cord, and (3) the **pontine flexure** in the hindbrain. The three main divisions of the brain (prosencephalon, mesencephalon and rhombencephalon) can already be recognized when the neural tube is not yet closed. The forebrain soon divides into an end portion, the **telencephalon**, and the **diencephalon**, and the optic vesicles can be identified (Fig. 1.12). With the development of the **cerebellum**, the pons and the trigeminal nerve, the division of the hindbrain into a rostral part, the **metencephalon**, and a caudal part, the **medulla oblongata** or **myelencephalon**, becomes evident. The junction between the hindbrain and midbrain is relatively narrow and is known as the **isthmus rhombencephali**. The first part of the telencephalon that can be recognized is the **telencephalon medium** or **impar**. By stage 15, the future cerebral hemispheres can be recognized. The **cerebral hemispheres** enlarge rapidly so that by the end of the embryonic period they completely cover the diencephalon. Frontal, temporal and occipital poles and

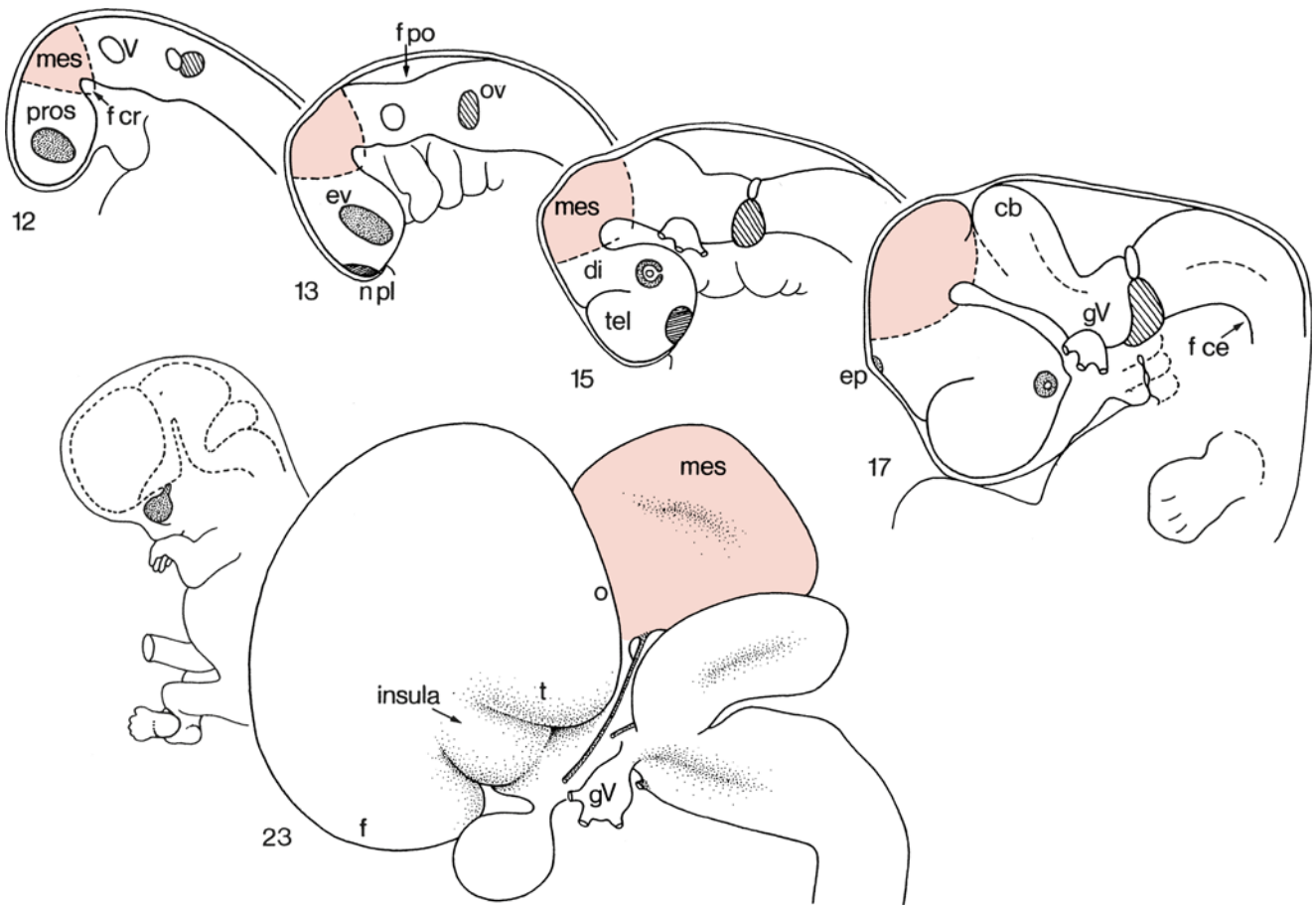

Fig. 1.11 Lateral views of the developing brain in Carnegie stages 12, 13, 15, 17 and 23. The mesencephalon is indicated in *light red*. *cb* cerebellum, *di* diencephalon, *ep* epiphysis, *ev* eye vesicle, *f* frontal lobe, *f ce* flexura cervicalis, *f cr* flexura cranialis, *f po* flexura pontina, *gV*, *V* trigeminal ganglion, *mes* mesencephalon, *n pl* nasal placode, *o* occipital lobe, *pros* prosencephalon, *t* temporal lobe, *tel* telencephalon (After O'Rahilly and Müller 1999)

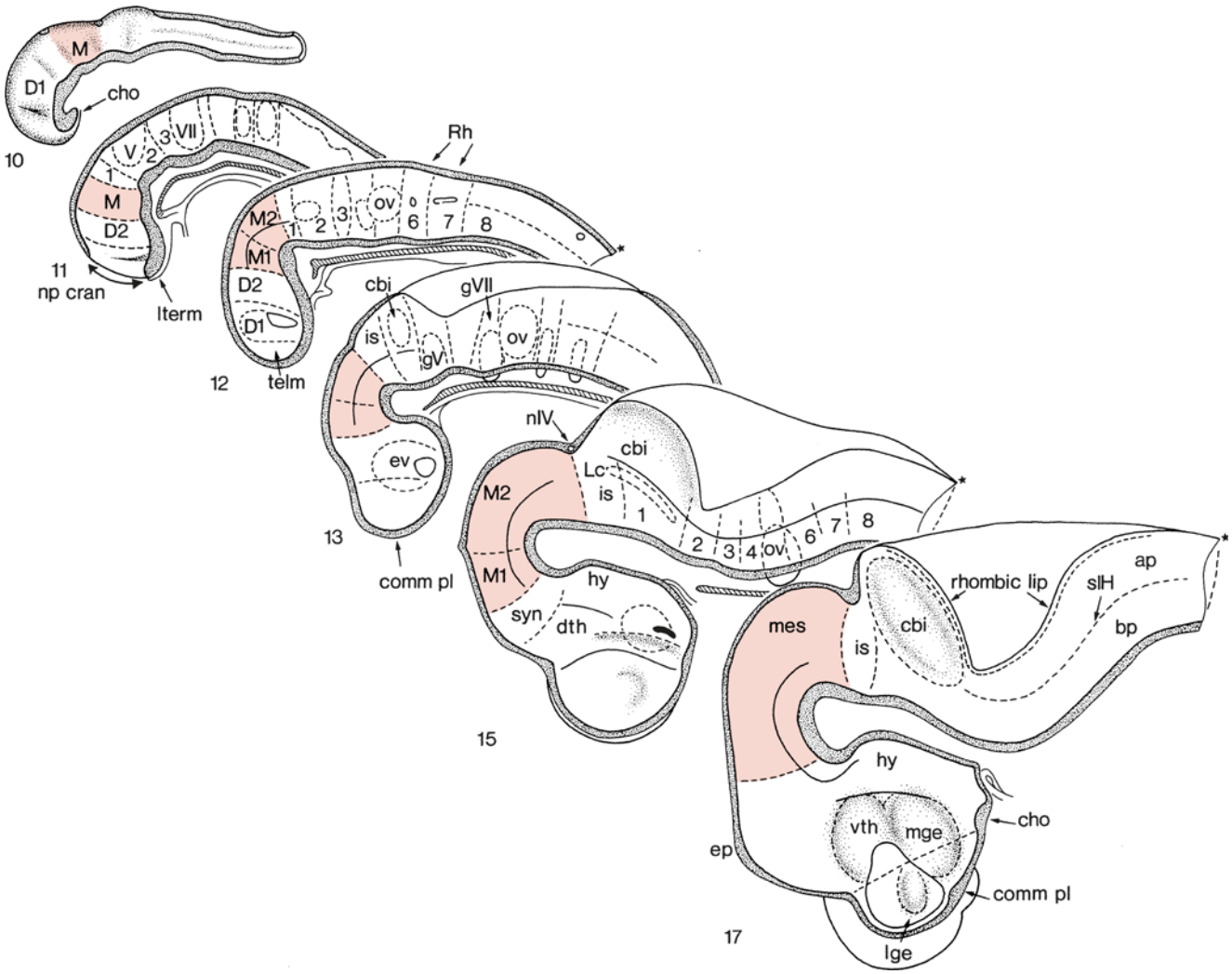

Fig. 1.12 Medial views of the developing brain in Carnegie stages 10–13, 15 and 17. The mesomeres (*M*, *M1*, *M2*) and the mesencephalon (*mes*) are indicated in *light red*. *Asterisks* indicate the spinomedullary junction. *ap* alar plate, *bp* basal plate, *cbi* internal cerebellar bulge, *cho* chiasma opticum, *comm pl* commissural plate, *D1*, *D2* diencephalic neuromeres, *dth* dorsal thalamus, *ep* epiphysis, *ev* eye vesicle, *gV* trigeminal ganglion, *gVII* facial ganglion, *hy* hypothalamus, *is* isthmus, *Lc* locus coeruleus, *lge* lateral ganglionic eminence, *lterm* lamina terminalis, *mge* medial ganglionic eminence, *np* cran cranial neuropore, *nIV* nervus trochlearis, *ov* otic vesicle, *1–8* rhombomeres, *slH* sulcus limitans of His, *syn* synencephalon, *telm* telencephalon medium, *vth* ventral thalamus (After O'Rahilly and Müller 1999)

the insula become recognizable (Fig. 1.11), whereas an olfactory bulb becomes visible on the ventral surface. Recently, Nakashima et al. (2011) used MR microscopic imaging for a morphometric analysis of the brain vesicles during the embryonic period.

1.7.1 Imaging of the Embryonic Brain

The introduction of the ultrasound method has opened new possibilities for studying the human embryonic brain. The use of the transvaginal route has so greatly improved the image quality that a detailed description of the living embryo and early fetus has become possible (Fig. 1.13). Ultrasound data show agreement with the developmental time schedule described in the Carnegie staging system (Blaas et al. 1994, 1995a, b; Blaas and Eik-Nes 1996, 2009; van Zalen-Sprock et al. 1996; Blaas 1999; Pooh 2009; Pooh et al. 2003, 2011). Human development and possible maldevelopment can be followed in time. Three-dimensional ultrasound techniques have made it possible to reconstruct the shape of the brain ventricles and to measure their volumes (Blaas et al. 1995a, b; Blaas 1999; Blaas and Eik-Nes 2002). Anomalies of the ventricular system such as diverticula are rare (Hori et al. 1983, 1984a). Accessory ventricles of the posterior horn are relatively common and develop postnatally (Hori et al. 1984b; Tsuboi et al. 1984).

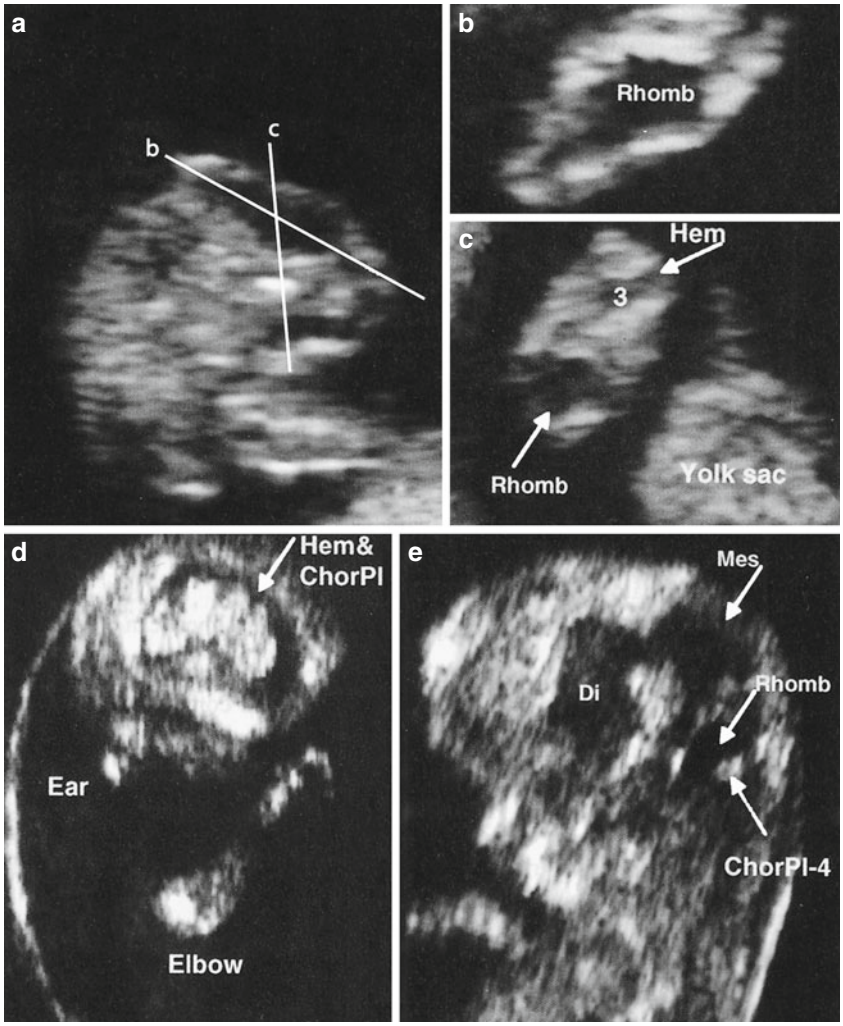

Fig. 1.13 Ultrasound images in human embryos of 7.5 (**a**–**c**), 9.5 (**d**) and 10 (**e**) weeks of gestation with crown-rump lengths of 11, 29 and 33 mm, respectively. *ChorP1-4* choroid plexuses of lateral and fourth ventricles, *Di* diencephalon, *Hem* cerebral hemisphere, *Mes* mesencephalon, *Rhomb* rhombencephalon, *3* third ventricle (Kindly provided by Harm-Gerd K. Blaas, Trondheim)

1.7.2 Neuromeres

Morphological segments or neuromeres of the brain were already known to von Baer (1828), and described for the human brain by Bartelmez (1923) and Bergquist (1952), and for many other vertebrates (Nieuwenhuys 1998). **Neuromeres** are segmentally arranged transverse bulges along the neural tube, particularly evident in the hindbrain (Fig. 1.14). Only recently, interest in neuromeres was greatly renewed owing to the advent of gene-expression studies on development, starting with the homeobox genes. The expression of *HOX* genes in the developing human brain stem is directly comparable to that of *Hox* genes in mice (Vieille-Grosjean et al. 1997). Each rhombomere is characterized by a unique combination of *Hox* genes, its *Hox* code. The timing and sequence of appearance of neuromeres and their derivatives were studied in staged human embryos (Müller and O'Rahilly 1997; Fig. 1.15). The neuromeres of the forebrain, midbrain and hindbrain were determined morphologically on the basis of sulci, mitotic activity in the walls and fibre tracts. Six **primary neuromeres** appear already at stage 9 when the neural folds are not fused (Fig. 1.7b): prosencephalon, mesencephalon and four rhombomeres (A-D). Sixteen **secondary neuromeres** can be recognized from about stage 11. They gradually fade after stage 15 (Fig. 1.12). Eight **rhombomeres** (**Rh1**-**8**), an **isthmic neuromere** (**I**), two **mesomeres** (**M1**, **M2**) of the midbrain, two **diencephalic neuromeres** (**D1**, **D2**) and one **telencephalic neuromere** (**T**) have been distinguished. The diencephalic neuromere D2 can be further subdivided into the **synencephalon**, the **parencephalon caudalis** and the **parencephalon rostralis**. Neuromere D1 was suggested to give rise to the eye vesicles and the medial ganglionic eminences (Müller and O'Rahilly 1997; O'Rahilly and Müller 2008). It should be emphasized that Müller and O'Rahilly's subdivision of the prosencephalon is rather arbitrary. The prosomere D1 is defined as a far too large neuromere extending to the rostral border of the chiasmatic plate. It seems more likely that the prosomeric model developed by Puelles and Rubinstein can also be applied to human embryos. In this model the

Fig. 1.14 Dorsal view of a malformed embryo (Carnegie stage 14) showing the bulging of several rhombomeres (Kindly provided by Kohei Shiota, Kyoto)

primary prosencephalon becomes divided into the **caudal prosencephalon**, giving rise to the prosomeres P1-P3 (the **caudal diencephalon**), and the **secondary prosencephalon**, giving rise to the hypothalamus (the **rostral diencephalon**), the eye vesicles, the neurohypophysis and the entire telencephalon including the medial and lateral ganglionic eminences (Fig. 1.16). In fact, the human prosomeres D1 and T together form the secondary prosencephalon. Consequently, the medial ganglionic eminence and the hypothalamus arise from the secondary prosencephalon.

In mice (Chap. 2), the prosencephalon has been divided into six **prosomeres**, numbered P1-P6 from caudal to rostral. Prosomeres P1-P3 form the diencephalon: P1 is the synencephalon, P2 the parencephalon caudalis and P3 the parencephalon rostralis. The alar component of the synencephalon forms the pretectum, that of the caudal parencephalon the thalamus and epithalamus and that of the rostral parencephalon the prethalamus. The basal components jointly form the diencephalic or prerubral tegmentum. The prosomeres P4-P6, together known as a protosegment, form the **secondary prosencephalon** (Rubinstein et al. 1998; Puelles et al. 2000, 2012, 2013; Puelles and Rubinstein 2003; Martínez et al. 2012), from which the hypothalamus, both optic vesicles, the neurohypophysis and the telencephalon arise. The basal parts of the secondary prosencephalon give rise to the basal parts of the hypothalamus, whereas from the alar parts alar parts of the hypothalamus and the entire telencephalon, i.e. the cerebral cortex and the subcortical centers such as the basal ganglia, arise. The optic vesicles and the neurohypophysis arise from the most rostral part of the secondary prosencephalon, i.e. the acroterminal region. Recently, Puelles et al. (2012) subdivided the secondary prosencephalon into two hypotha-

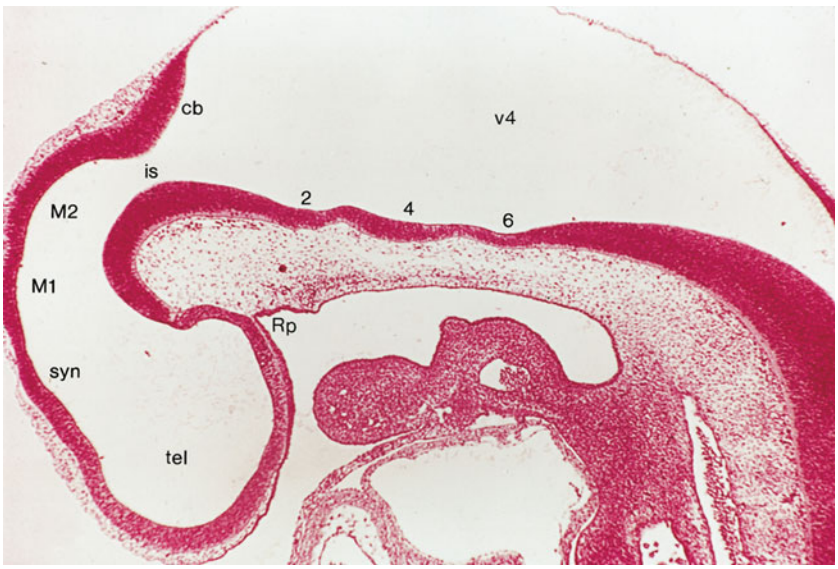

Fig. 1.15 Median section of a stage 13 embryo. Rhombomeres *2*, *4* and *6* can be recognized by ventral bulges. *cb* cerebellum, *is* isthmus, *M1*, *M2* mesomeres, *Rp* Rathke's pouch, *syn* synencephalon, *tel* telencephalon, *v4* fourth ventricle (From O'Rahilly 1975, with permission)

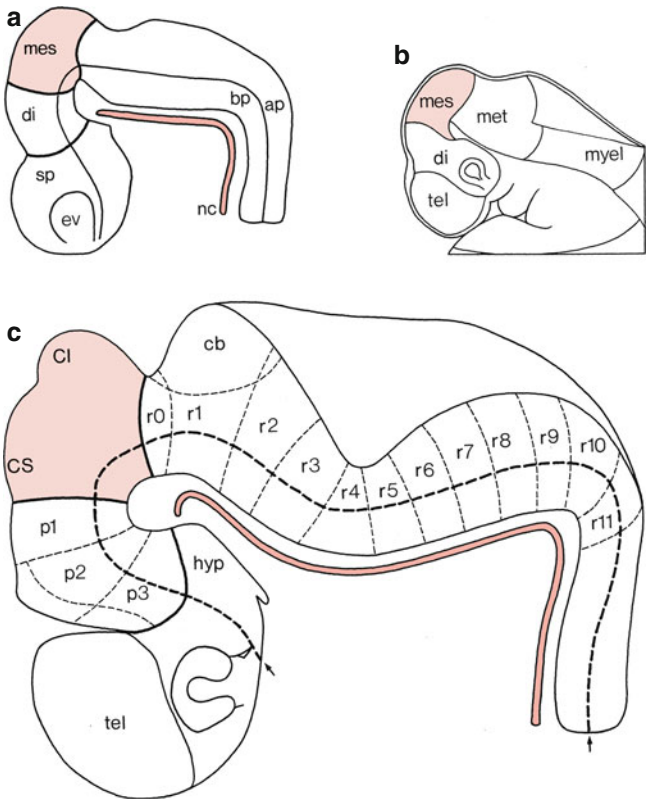

Fig. 1.16 (**a**, **c**) Segmentation of the human brain; (**b**) shows the classic O'Rahilly and Müller subdivision. *ap* alar plate, *bp* basal plate, *cb* cerebellum, *CI* colliculus inferior, *CS* colliculus superior, *di* diencephalon, *ev* eye vesicle, *hyp* hypothalamus, *mes* mesencephalon (in *light red*), *met* metencephalon, *myel* myelencephalon, *nc* notochord (in *medium red*), *p1–p3* prosomeres, *r0–r11* rhombomeres, *sp* secondary prosencephalon, *tel* telencephalon (See text for further explanation; after Puelles et al. 2008)

lamic 'prosomeres' (hp2 and hp1) and the acroterminal region (Fig. 1.16; Chaps. 2 and 9). Puelles and Verney (1998) applied the prosomeric subdivision to the human forebrain. The prosomeric model of the vertebrate forebrain was implemented in the HUDSEN Atlas (http://www.hudsen.org), a three-dimensional spatial framework for studying gene expression in the developing human brain (Kerwin et al. 2010).

The subdivision of the **mesencephalon** into two, almost even large, **mesomeres** has also been questioned. Fate mapping and gene expression data showed that only a very small caudal mesomere 2 can be distinguished, the large remainder of the mesencephalon arising from the rostral mesomere 1 (Martínez et al. 2012; Chap. 7). Currently, the **hindbrain** is subdivided into 11 **rhombomeres** (r1-r11), counting the isthmus as r0 (Martínez et al. 2012; Watson 2012; Fig. 1.16). The rostral hindbrain corresponds to the part influenced by the isthmic organizer and can be divided into the isthmus or r0 and rhomobomere 1. The large remainder of the hindbrain is marked by the expression of *Hox* genes and can be divided into 10 segments (r2-r11). Rhombomeres r2 to r6 can be recognized as overt bulges separated by constrictions in the embryonic hindbrain. The caudal hindbrain was first subdivided into two rhombomeres, r7 and r8. Fate mapping and differential *Hox* gene expression in the avian medulla oblongata suggested a further subdivision into rhombomeres r7 to r11. Rodent data also suggest such a subdivision (Watson 2012; Puelles et al. 2013).

Each neuromere has **alar** (dorsal) and **basal** (ventral) components. In the developing spinal cord and brain stem, the **sulcus limitans** divides the proliferative compartments into alar and basal plates. The mesencephalic part of the sulcus is not continuous with a more rostral, diencephalic sulcus (Keyser 1972; Gribnau and Geijsberts 1985; Müller and O'Rahilly 1997; Fig. 1.12). Studies in mice (Bulfone et al. 1993; Puelles and Rubinstein 1993; Shimamura et al. 1995; Rubinstein et al. 1998; Martínez et al. 2012; Medina and Abellán 2012; Puelles et al. 2012) show that some genes are expressed in the alar plate only, others only in the basal plate (Fig. 1.10). One gene, *Nkx2.2*, is expressed along the longitudinal axis of the brain, ending in the chiasmatic region. Based on these findings, in all murine prosomeres alar and basal parts are distinguished (Rubinstein et al. 1998; Puelles et al. 2000; Puelles and Rubinstein 2003; Martínez et al. 2012).

1.7.3 The Ganglionic Eminences

At first, each cerebral hemisphere consists of a thick basal part, the **subpallium**, giving rise to the basal ganglia, and a thin part, the **pallium**, that becomes the future cerebral cortex. The subpallium appears as medial and lateral elevations, known as the **ganglionic** (*Ganglionhügel* of His 1889) or **ventricular eminences** (Fig. 1.17). The caudal part of the ventricular eminences is also known as the **caudal ganglionic eminence**, and primarily gives rise to parts of the amygdala. The **medial ganglionic eminence** is involved in the formation of the globus pallidus, whereas the larger **lateral ganglionic eminence** gives rise to the caudate nucleus and the putamen (Chap. 9). As the internal capsule develops, its fibres separate the caudate nucleus from the putamen, and the thalamus and the subthalamus from the globus pallidus. Both the lateral and the medial ventricular eminences are also involved in the formation of the cerebral cortex. The pyramidal cells of the cerebral cortex arise from the ventricular zone of the pallium, but the cortical GABAergic interneurons arise from both ganglionic eminences, the medial eminence in particular (Parnavelas 2000; Anderson et al. 2001; Marín and Rubinstein 2001; Chap. 9). In the human forebrain, cortical

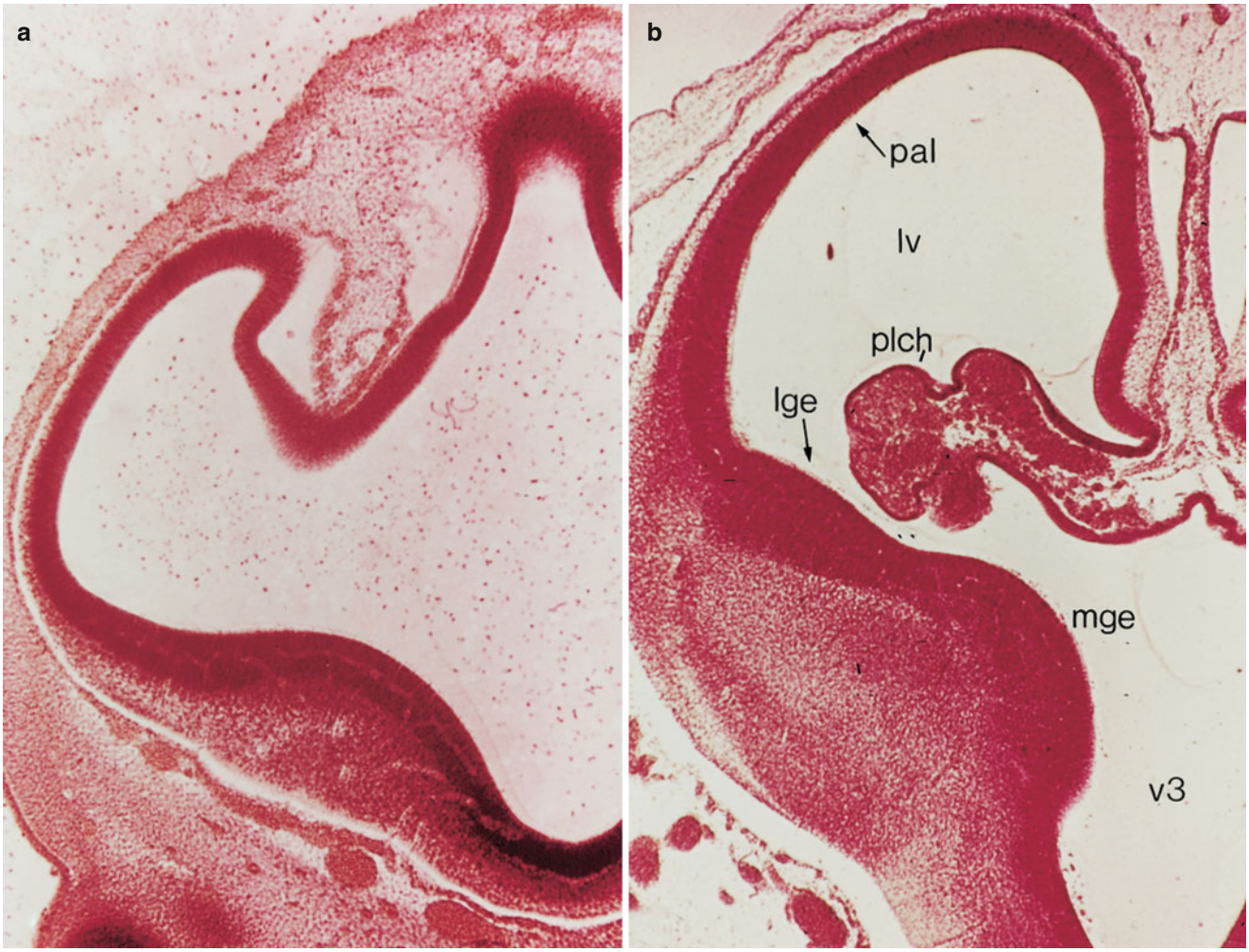

Fig. 1.17 Transverse sections through the human forebrain, showing the developing ganglionic or ventricular eminences at stages 17 (**a**) and 20 (**b**), respectively. *lge* lateral ganglionic eminence, *lv* lateral ventricle, *mge* medial ganglionic eminence, *pal* pallium, *plch* plexus choroideus, *v3* third ventricle (From O'Rahilly 1975, with permission)

interneurons arise both in the ganglionic eminences as well as locally in the ventricular and subventricular zones of the dorsal telencephalon (Rakic 2009). The caudal part of the ganglionic eminence also gives rise to a contingent of GABAergic neurons for thalamic association nuclei such as the pulvinar through a transient fetal structure, the **gangliothalamic body** (Rakić and Sidman 1969; Letinić and Kostović 1997; Letinić and Rakic 2001).

1.8 Fetal Development of the Brain

The most obvious changes in the fetal period are (1) the outgrowth of the cerebellar hemispheres and the formation of its median part, the vermis, (2) the continuous expansion of the cerebral hemispheres, the formation of the temporal lobe and the formation of sulci and gyri and (3) the formation of commissural connections, the corpus callosum in particular. The fetal period has been extensively illustrated in Bayer and Altman's 'Atlas of Human Central Nervous System Development' (Bayer and Altman 2003, 2005, 2006, 2007). For a quantitative approach to brain growth, gyrus formation and myelination, see Gilles and Nelson (2012).

1.8.1 The Cerebellum

The development of the **cerebellum** takes largely place in the fetal period (Fig. 1.18). The cerebellum arises bilaterally from the alar layers of the first rhombomere (Fig. 1.12). Early in the fetal period, the two cerebellar primordia are said to unite dorsally to form the vermis. Sidman and Rakic (1982), however, advocated Hochstetter's (1929) view that such a fusion does not take place, and suggested one cerebellar primordium (the **tuberculum cerebelli**). The tuberculum cerebelli consists of a band of tissue in the dorsolateral part

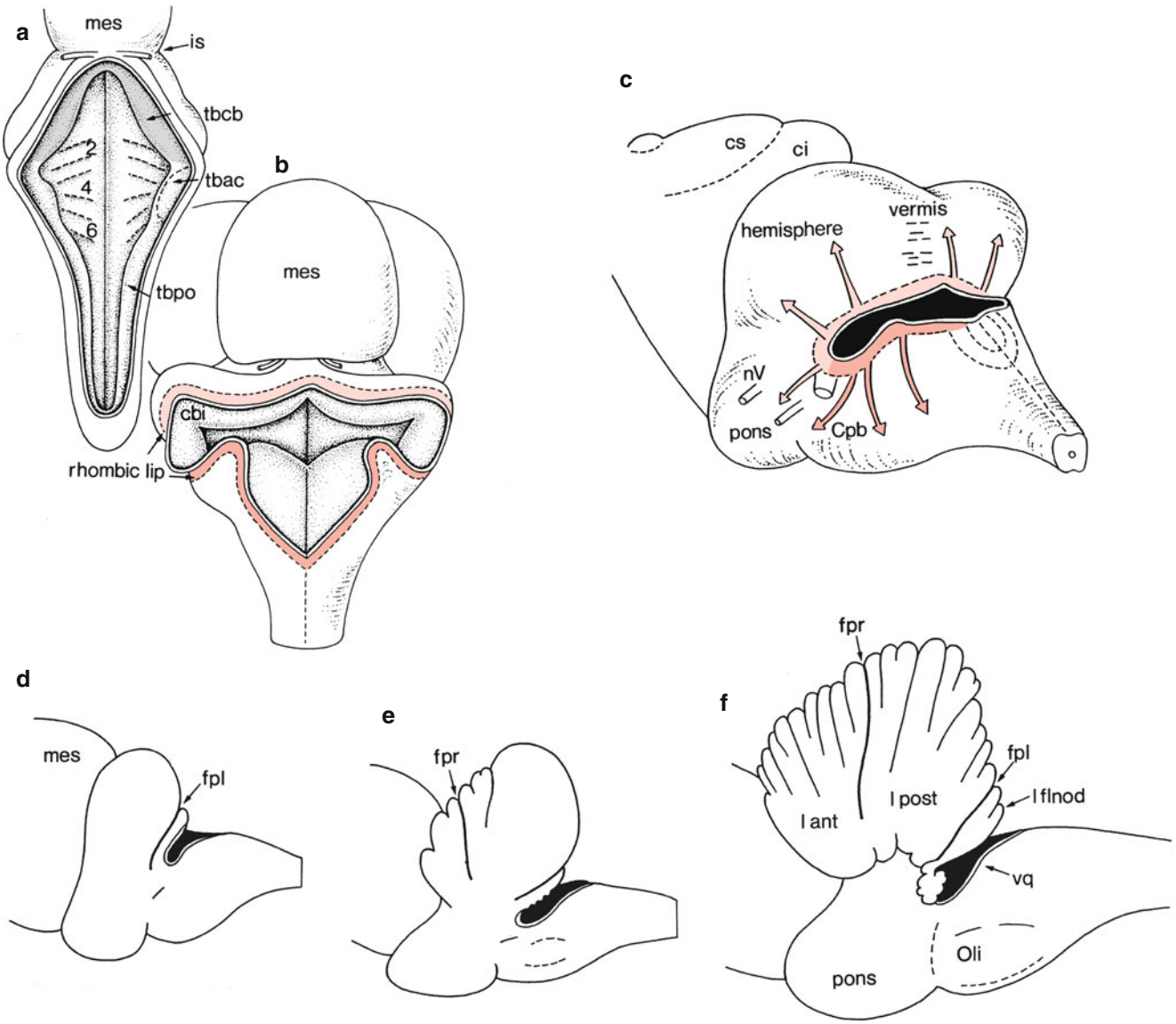

Fig. 1.18 Embryonic (**a**, **b**) and fetal (**c**–**f**) development of the human cerebellum: **a** approximately 4 weeks; (**b**) at the end of the embryonic period; **c**–**f** at 13 weeks (**c**, **d**), and 4 (**e**) and 5 (**f**) months of development. The V-shaped tuberculum cerebelli (*tbcb*) is indicated in *grey*, and the upper and lower rhombic lips in *light red* and *red*, respectively. *cbi* internal cerebellar bulge, *ci* colliculus inferior, *Cpb* corpus pontobulbare, *cs* colliculus superior, *fpl* fissura posterolateralis, *fpr* fissura prima, *is* isthmus, *l ant* lobus anterior, *l flnod* lobus flocculonodularis, *l post* lobus posterior, *mes* mesencephalon, *nV* trigeminal nerve, *Oli* oliva inferior, *tbac* tuberculum acusticum, *tbpo* tuberculum pontoolivare, *vq* ventriculus quartus, *2*, *4*, *6* rhombomeres (**a** After Streeter 1911, 1912; Jakob 1928; **b** after Hochstetter 1929; **c**–**f** after Streeter 1911, 1912)

of the alar plate that straddles the midline in the shape of an inverted V. The arms of the V are directed caudally as well as laterally, and thicken enormously, accounting for most of the early growth of the cerebellum. The rostral, midline part of the V, however, remains small and relatively inconspicuous. The further morphogenesis of the cerebellum can be summarized as follows: (1) the caudally and laterally directed limbs of the tuberculum cerebelli thicken rapidly during the sixth postovulatory week and bulge downwards into the fourth ventricle (on each side the internal cerebellar bulge or *innerer Kleinhirnwulst* of Hochstetter which together form the **corpus cerebelli**); (2) during the seventh week, the rapidly growing cerebellum bulges outwards as the external cerebellar bulges (*äusserer Kleinhirnwulst* of Hochstetter) which represent the **flocculi**, which are delineated by the posterolateral fissures; (3) during the third month of development, i.e. early in the fetal period, growth of the midline component accelerates and begins to fill the gap between the limbs of the V, thereby forming the **vermis**; and (4) by the 12th to 13th weeks of development, outward, lateral and rostral growth processes have reshaped the cerebellum to a transversely oriented bar of tissue overriding the fourth

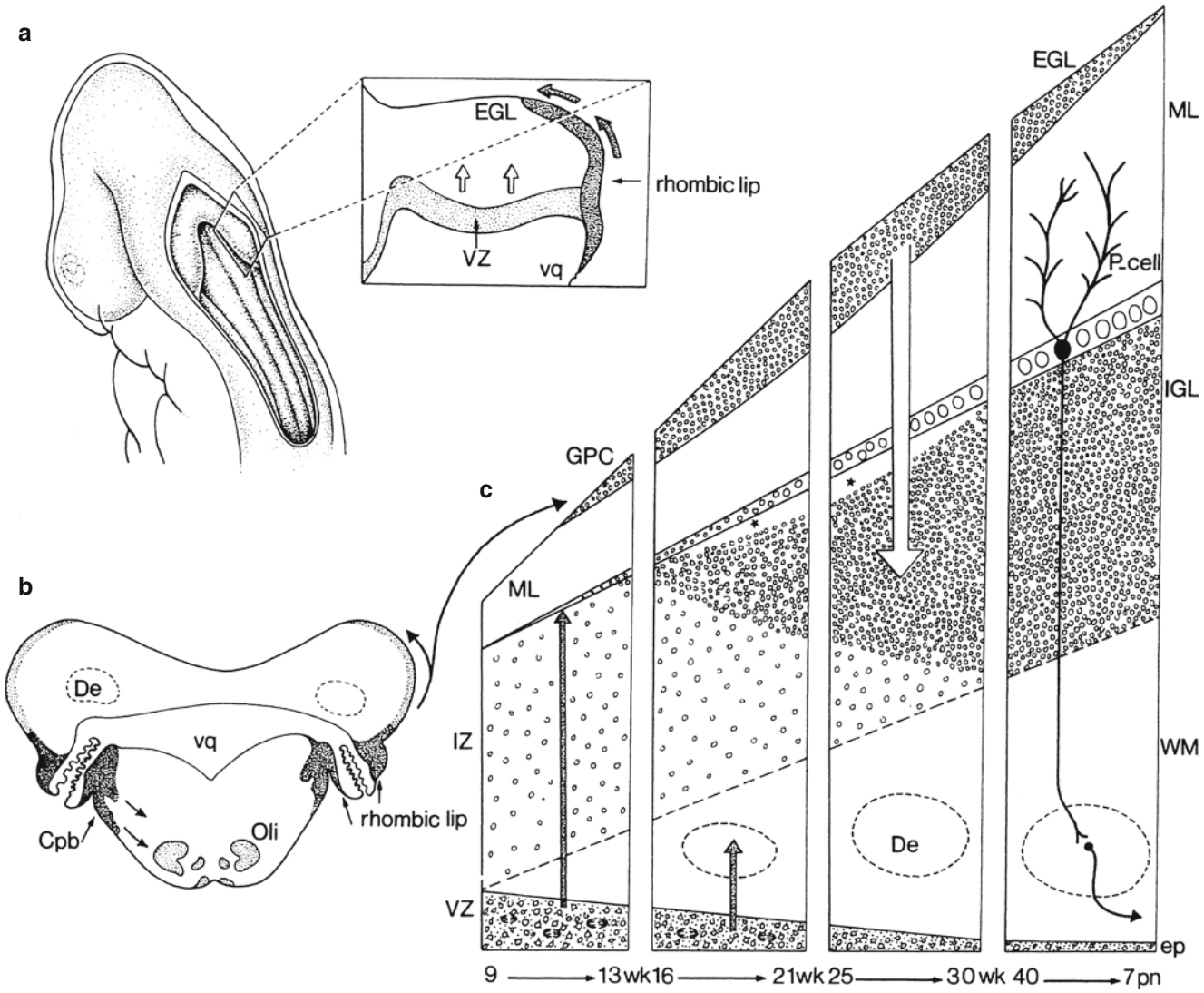

Fig. 1.19 Overview of the histogenesis of the cerebellum. (**a**) A dorsolateral view of a human embryo and part of the tuberculum cerebelli enlarged, showing the two proliferative compartments: the ventricular zone (*VZ*), giving rise to Purkinje cells and the deep cerebellar nuclei, and the external germinal or granular layer (*EGL*), giving rise to the granule cells. (**b**) The position of the rhombic lip in a transverse section at the level of the lateral recess of the fourth ventricle. The upper rhombic lip is found lateral to the lateral recess, and the lower rhombic lip medial to the recess. (**c**) The formation of the layers of the cerebellum in four periods from the early fetal period until 7 weeks postnatally. The lamina dissecans is indicated with *asterisks*. The *arrows* in **a**–**c** show the migration paths. *Cpb* corpus pontobulbare, *De* dentate nucleus, *ep* ependyma, *GPC* granule precursor cells, *IGL* internal granular layer, *IZ* intermediate zone, *Ml* molecular layer, *Oli* oliva inferior, *P-cell* Purkinje cell, *vq* ventriculus quartus, *WM* white matter (After Sidman and Rakic 1982, Hatten et al. 1997, and O'Rahilly and Müller 2001; from ten Donkelaar et al. 2003, with permission)

ventricle. At the 12th week, fissures begin to form transverse to the longitudinal axis of the brain, first on the vermis and then spreading laterally into the hemispheres. By stage 18 (about 44 days), the internal cerebellar swellings contain the dentate nuclei, the first sign of the superior cerebellar peduncles can be seen around stage 19 (about 48 days) and the cerebellar commissures appear at the end of the embryonic period (Müller and O'Rahilly 1990b).

The **histogenesis** of the cerebellum is summarized in Fig. 1.19. The main cell types of the cerebellum arise at different times of development and at different locations. The Purkinje cells and the cerebellar nuclei arise from the ventricular zone of the metencephalic alar plates. Bayer et al. (1995) estimated that in man the cerebellar nuclei as well as the Purkinje cells are generated from the early fifth to sixth weeks of development. Towards the end of the embryonic period, granule cells are added from the rhombic lip. The **rhombic lip** (*Rautenleiste* of His 1890) is the dorsolateral part of the alar plate, and it forms a proliferative zone along the length of the hindbrain. Cells from its rostral part, the **upper rhombic lip**, reach the superficial part of the cerebellum, and form the **external germinal** or **granular**

layer at the end of the embryonic period. Granule cells are formed in the external germinal layer. The granule cells that arise from it migrate along the processes of Bergmann glia cells to their deeper, definitive site. Adhesion molecules such as TAG1, L1 and astrotactin play a role in this migration (Hatten et al. 1997). In the fetal period, the **internal granular layer** is formed by further proliferation and migration of the external germinal cells. This layer, situated below the layer of Purkinje cells, is the definitive granular layer of the cerebellar cortex. A transient layer, the **lamina dissecans**, separates the internal granular layer from the Purkinje cells. It is filled by migrating granule cells and disappears (Rakic and Sidman 1970). At the same time as the postmitotic granule cells migrate inwards (16–25 weeks), the Purkinje cells enlarge and develop dendritic trees. In man, the external germinal layer appears at the end of the embryonic period and persists for several months to 1–2 years after birth (Lemire et al. 1975). The caudal part of the rhombic lip, the **lower rhombic lip**, gives rise to the pontine nuclei and the inferior olivary nucleus (Essick 1912; Wingate 2001; Fig. 1.18c). Neurons of these precerebellar nuclei migrate along various pathways, the **corpus pontobulbare** in particular, to their ultimate position in the brain stem (Altman and Bayer 1997).

Several genes have marked impact upon cerebellar development. In mice, knockouts of the *Wnt1* and *En1* genes largely or totally eliminate the cerebellum, whereas in *En2* knockouts the lobular pattern of the posterior vermis is disrupted (Hatten et al. 1997; Millen et al. 1999; Wang and Zoghbi 2001). The *Math1* (mouse atonal homologue) gene is expressed in the rhombic lip (Ben-Arie et al. 1997). In *Math1* knockout mice, no granular layer is formed. SHH is expressed in migrating and settled Purkinje cells, and acts as a potent mitogenic signal to expand the granule cell progenitor population (Wechsler-Reya and Scott 1999). ***Medulloblastoma***, a brain stem tumour of childhood, is thought to originate in malignant external granule cells. **Developmental malformations** of the cerebellum are mostly bilateral and may be divided into (1) malformations of the vermis and (2) malformations of the vermis as well as of the hemispheres (Norman et al. 1995; Kollias and Ball 1997; Ramaekers et al. 1997; Barkovich 2000; ten Donkelaar et al. 2003; ten Donkelaar and Lammens 2009; Boltshauser and Schmahmann 2012). ***Agenesis*** or ***hypoplasia*** of the ***vermis*** may occur in a great variety of disorders, most frequently in the ***Dandy-Walker malformation*** (Chap. 8). ***Pontocerebellar hypoplasia*** forms a large group of disorders, characterized by a small pons and a varying degree of hypoplasia of the cerebellum (Barth 1993; Ramaekers et al. 1997; Boltshauser and Schmahmann 2012), up to its near-total absence (Gardner et al. 2001).

1.8.2 The Cerebral Cortex

The outgrowth of the **cerebral cortex** and the proliferation and migration of cortical neurons largely takes place in the fetal period. Each hemisphere first grows caudalwards, and then bends to grow into ventral and rostral directions (Figs. 1.20 and 1.21). In this way the temporal lobe arises.

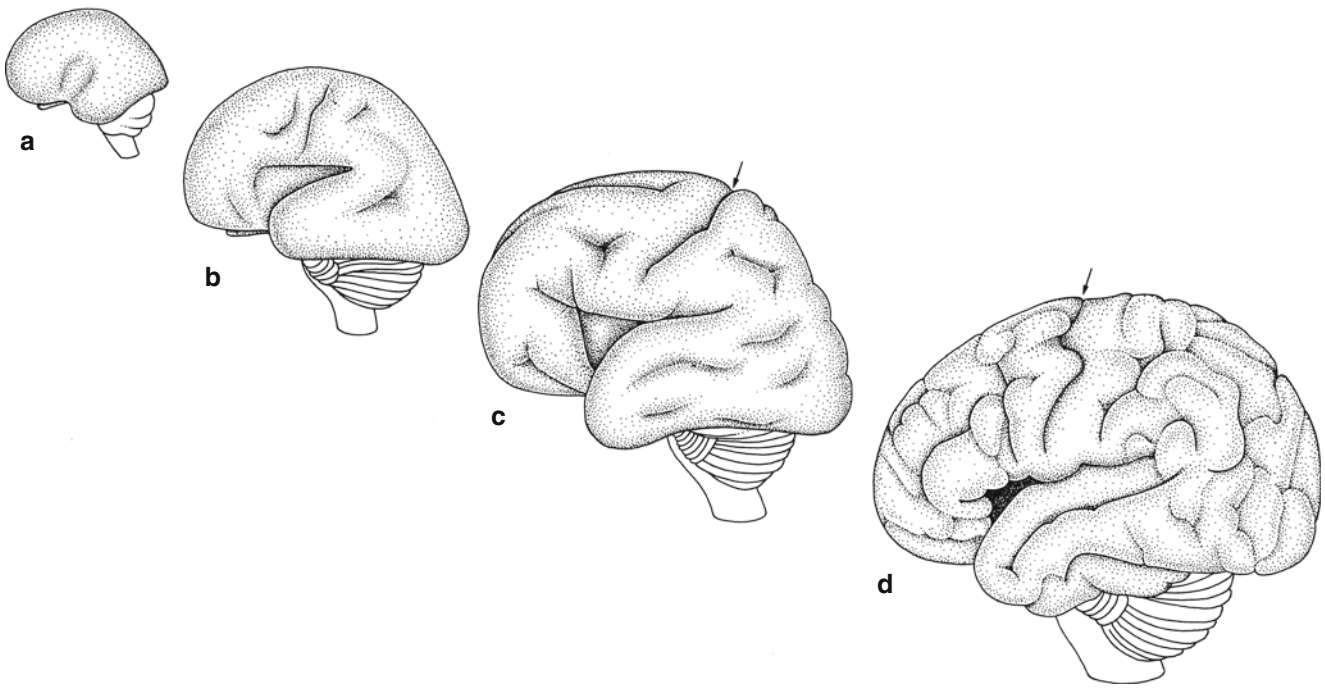

Fig. 1.20 Lateral views of the developing human brain in the fourth (**a**), sixth (**b**) and eighth (**c**) gestational months, and in a neonate (**d**). The *arrows* indicate the central sulcus (After Kahle 1969; O'Rahilly and Müller 1999)

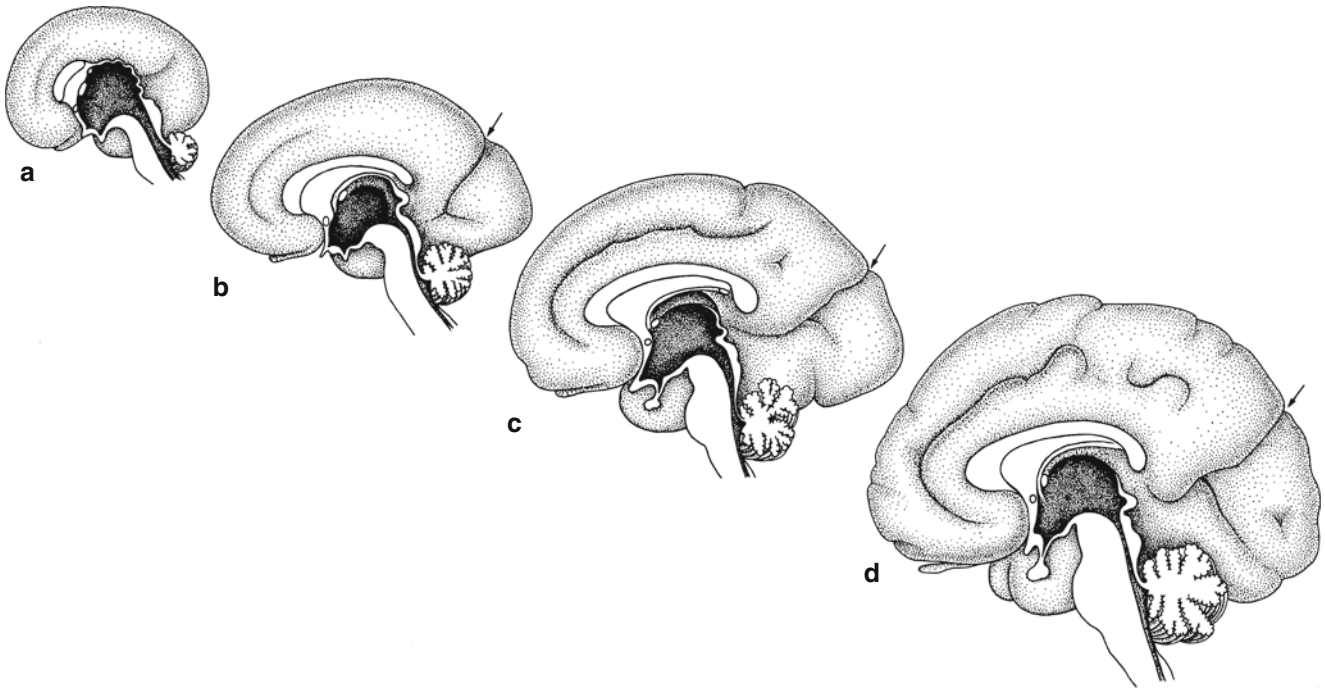

Fig. 1.21 Medial views of the developing human brain in the fourth (**a**), sixth (**b**) and eighth (**c**) gestational months, and in a neonate (**d**). The *arrows* indicate the sulcus parieto-occipitalis (After Macchi 1951, Kahle 1969 and Feess-Higgins and Larroche 1987)

The outgrowth of the caudate nucleus, the amygdala, the hippocampus and the lateral ventricle occurs in a similar, C-shaped way. During the fetal period, the complex pattern of sulci and gyri arises. On the lateral surface of the brain the **sulcus lateralis** and the **sulcus centralis** can be recognized from 4 months onwards. Owing to the development of the prefrontal cortex, the sulcus centralis gradually moves caudalwards. On its medial surface first the parieto-occipital and cingulate sulci appear, followed by the calcarine and central sulci. The formation of sulci and gyri in the right hemisphere usually preceeds that in the left one. It should be noted that the morphology of cortical gyri and sulci is complex and variable among individuals with an established asymmetry appearing very early on (Dubois et al. 2008a, b, 2010; Habas et al. 2012). The **plexus choroideus** of the lateral ventricle arises in the lower part of the medial wall of the telencephalic vesicle (Fig. 1.17).

Usually, the **pallium** is divided into a **medial pallium** or **archipallium**, a **dorsal pallium** or **neopallium** and a **lateral pallium** or **paleopallium** (Fig. 1.22). More recently, an additional **ventral pallium** was added (Puelles et al. 2000; Marín and Rubinstein 2002; Schuurmans and Guillemot 2002). The medial pallium forms the hippocampal cortex, the three-layered allocortex. Parts of the surrounding transitional cingulate and entorhinal cortex, the four-to-five-layered mesocortex, may have the same origin. The dorsal pallium forms the six-layered isocortex. The lateral pallium forms the olfactory cortex and the ventral pallium the claustroamygdaloid complex. The **subpallium** consists of two progenitor domains,

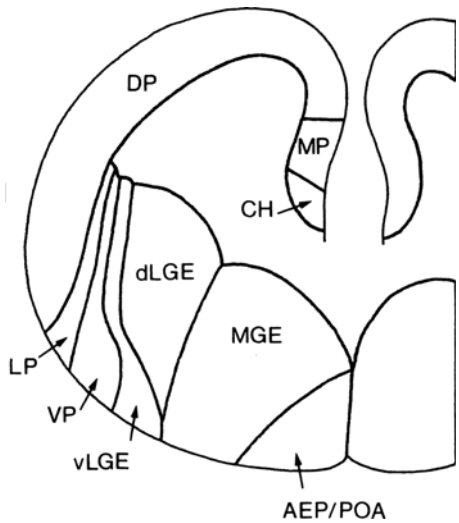

Fig. 1.22 Subdivision of the forebrain into the medial pallium (*MP*), dorsal pallium (*DP*), lateral pallium (*LP*) and ventral pallium (*VP*) and subpallium. *AEP/POA* anterior entopeduncular/preoptic area, *CH* cortical hem, *dLGE* dorsal part of lateral ganglionic eminence, *MGE* medial ganglionic eminence, *vLGE* ventral part of lateral ganglionic eminence (After Puelles et al. 2000; Schuurmans and Guillemot 2002)

the lateral and medial ganglionic eminences, generating the striatum and the pallidum, respectively. Dorsal and ventral domains of the developing telencephalon are distinguished by distinct patterns of gene expression, reflecting the initial acquisition of regional identity by progenitor populations (Puelles et al. 2000; Schuurmans and Guillemot 2002; Chap. 9).

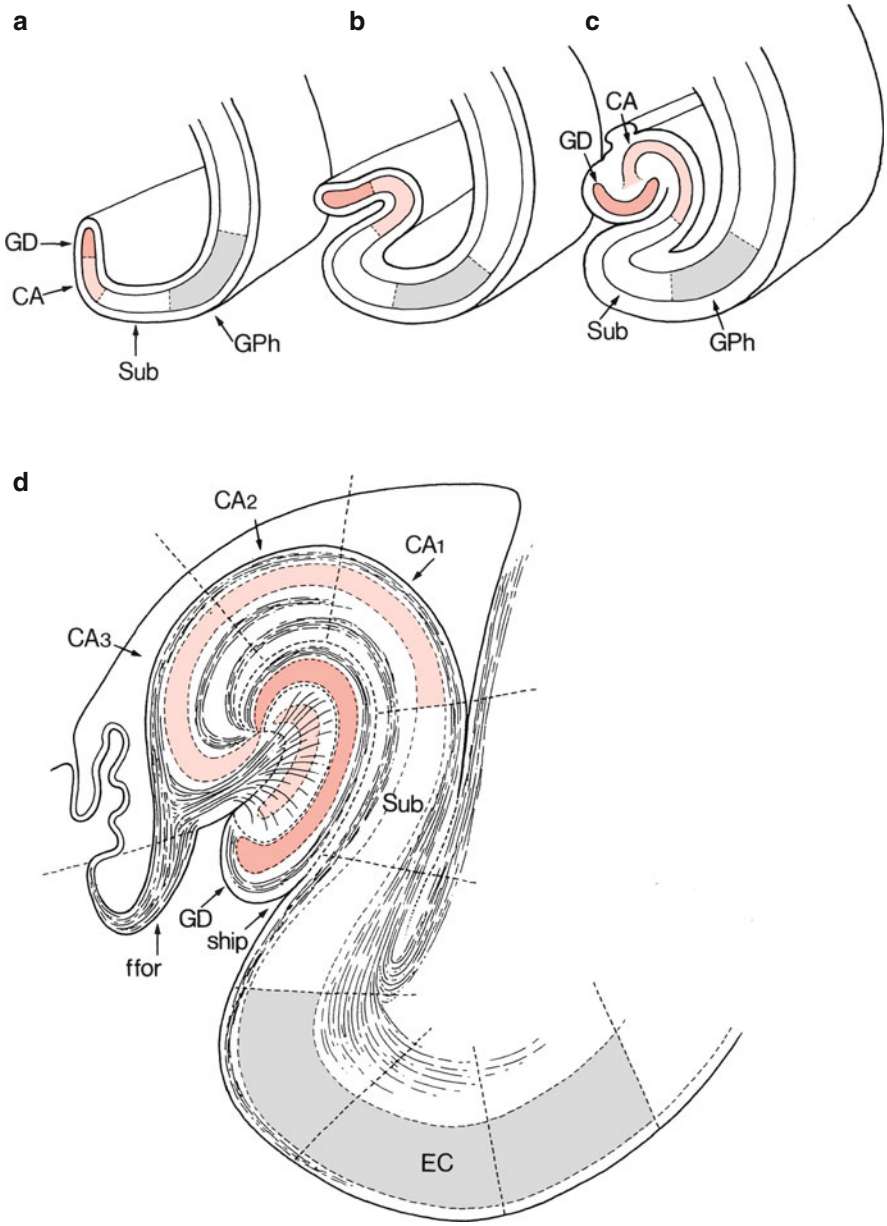

Fig. 1.23 Development (**a**–**c**) and structure (**d**) of the human hippocampal formation. The cornu ammonis (*CA*) is indicated in *light red*, the dentate gyrus (*GD*) in *red* and the entorhinal cortex (*EC*) in *grey*. *CA1-3* cornu ammonis subfields, *ffor* fimbria fornicis, *GPh* gyrus parahippocampalis, *ship* sulcus hippocampi, *Sub* subiculum

The **hippocampal formation** or **formatio hippocampi** comprises the dentate gyrus, the hippocampus, the subiculum and the parahippocampal gyrus. These structures develop from the medial pallium and are originally adjacent cortical areas (Fig. 1.23). During the outgrowth of the cerebral hemispheres, first caudalwards and subsequently ventralwards and rostralwards, the *retrocommissural part* of the hippocampal formation becomes situated in the temporal lobe (Stephan 1975; Duvernoy 1998). Rudiments of the *supracommissural part* of the hippocampus can be found on the medial side of the hemisphere on top of the corpus callosum: the *indusium griseum*, a thin cell layer, flanked by the *stria longitudinalis medialis* and *lateralis* of Lancisi (Chap. 10). At the beginning of the fetal period, the hippocampal formation contains four layers (Humphrey 1966; Kahle 1969; Arnold and Trojanowski 1996): a ventricular zone, an intermediate layer, a hippocampal plate comprised of bipolar-shaped neurons, and a marginal zone. At 15–19 weeks of gestation, individual subfields can be distinguished. A distal-to-proximal gradient of cytoarchitectonic and neuronal maturity is found, with the subiculum appearing more developed than the ammonic subfields (CA1-CA3). The dentate gyrus is the latest area to develop. Most pyramidal cells in the cornu ammonis fields are generated in the first half of pregnancy and no pyramidal neurons are formed after the 24th gestational week (Seress et al. 2001). Granule cells of the dentate gyrus proliferate at a decreasing rate during the second half of pregnancy and after birth but still occur at a low percentage during the first postnatal year (Seress et al. 2001). The postnatal development of the human hippocampus has been described by Insausti et al. (2010; Chap. 10).

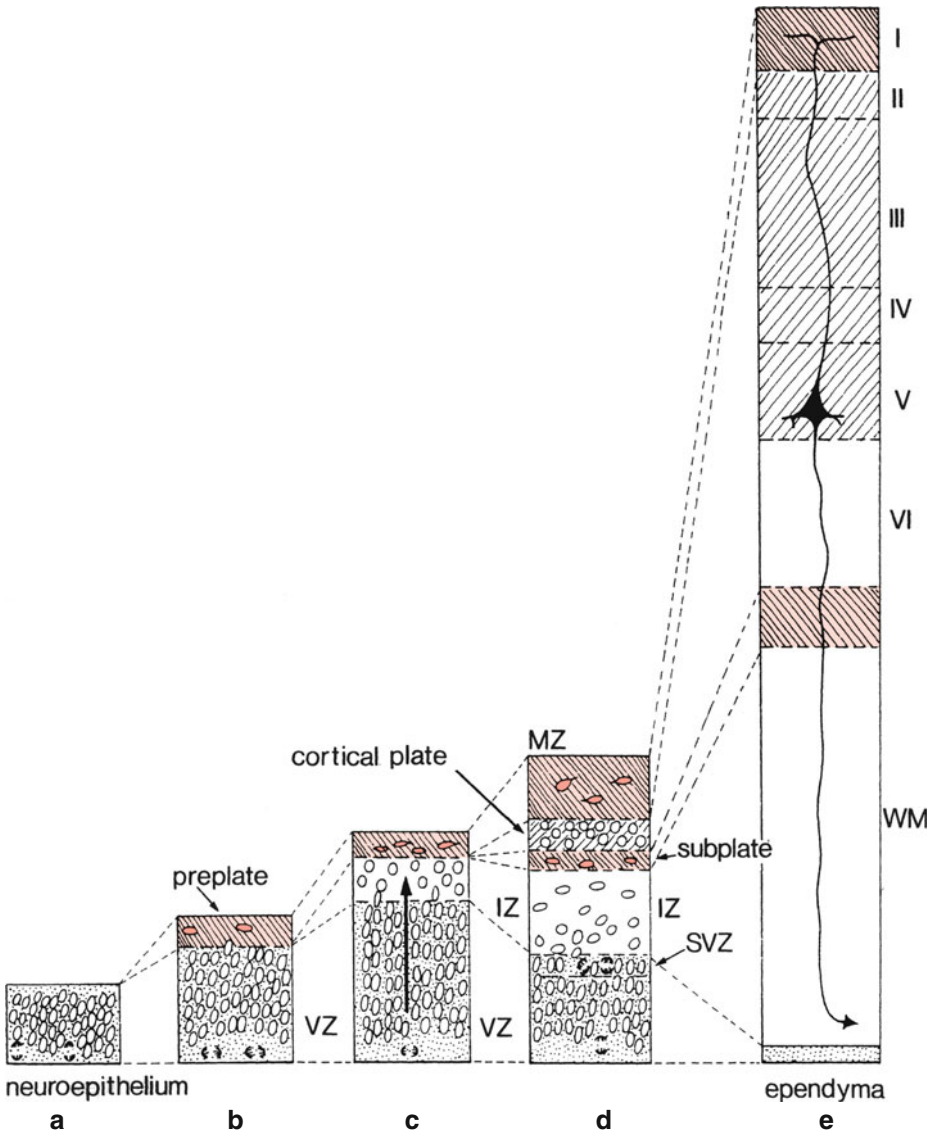

Fig. 1.24 Histogenesis of the cerebral cortex. (**a**–**c**) The neuroepithelium forms three zones, the ventricular zone (*VZ*), the intermediate zone (*IZ*) and the preplate. During the eighth to 18th weeks of development, neurons migrate from the ventricular zone and form the cortical plate (**d**). The preplate becomes divided into the marginal zone (*MZ*) and the subplate. A second compartment for cell division, the subventricular zone (*SVZ*), is mainly involved in the production of glial cells. Finally (**e**), the marginal zone forms the molecular layer (layer *I*) and the cortical plate layers *II-VI*. The intermediate zone forms the subcortical white matter (*WM*). The subplate disappears (After O'Rahilly and Müller 1999)

Reciprocal entorhinal-hippocampal connections are established by fetal midgestation (Hevner and Kinney 1996). Fibres connecting the entorhinal cortex, hippocampus and subiculum are present by about 19 weeks of gestation. The perforant path, connecting the entorhinal cortex with the dentate gyrus, and all connections with the neocortex are only beginning at 22 weeks of gestation.

The **histogenesis** of the six-layered cerebral cortex is shown in Fig. 1.24. The developing cerebral wall contains several transient embryonic zones: (1) the ventricular zone, which is composed of dividing neural progenitor cells; (2) the subventricular zone, which acts early in corticogenesis as a secondary neuronal progenitor compartment and later in development as the major source of glial cells; (3) the intermediate zone, through which migrating neurons traverse along radial glial processes; (4) the subplate, thought to be essential in orchestrating thalamocortical connectivity and pioneering corticofugal projections (Chap. 2); (5) the cortical plate, the initial condensation of postmitotic neurons that will become layers II-VI of the mature cortex; and (6) the marginal zone, the superficial, cell-sparse layer that is important in the establishment of the laminar organization of the cortex.

This terminology largely goes back to the Boulder Committee (1970), although the preplate and subplate were not known then. The last decennia, a wealth of studies have advanced our knowledge of the timing, sequence and complexity of cortical histogenesis, and also emphasized important inter-species differences. Bystron et al. (2008) proposed a revision of the terminology of the Boulder Committee. New types of transient neurons and proliferative cells outside the classic neuroepithelium, new routes of cellular migration and additional cellular compartments were found (Smart et al. 2002; Zecevic et al. 2005, 2011; Bystron et al. 2006;

Carney et al. 2007; Hansen et al. 2010; Lui et al. 2011). The revisions of the Boulder model include:

1. A transient layer with predecessor neurons and Cajal-Retzius cells forms between the neuroepithelium and the pial surface before the appearance of the cortical plate. The term **preplate** is already widely used for this layer.
2. The **subventricular zone** appears as a distinctive proliferative layer *before* the emergence of the cortical plate, earlier than previously recognized. It has increased in size and complexity during evolution and its cellular organization in primates is different from that in rodents.
3. Since there is no distinct cell-sparse layer under the pial surface before the cortical plate forms, the term **marginal zone** should be used only to refer to the residual superficial part of the preplate *after* the appearance of the cortical plate. The marginal zone becomes the layer I of the mature cortex.
4. The term **intermediate zone** should be reserved for the heterogeneous compartment that lies between the proliferative layers and the postmigratory cells above. The intermediate zone contains radially and tangentially migrating cells and a thickening layer of extrinsic axons that eventually constitutes the white matter.
5. The **subplate** is a distinctive and functionally important transient layer, located directly below the cortical plate. In rodents and carnivores, most subplate neurons are born before the first cortical plate cells. In humans, preplate cells also contribute to the subplate but its substantial thickening at later stages probably involves the addition of later-born neurons.

Cortical neurons are generated in the ventricular zones of the cortical walls and ganglionic eminences, and reach their destination by radial and tangential migration, respectively. The first postmitotic cells form the **preplate** or **primordial plexiform layer** (Marín-Padilla 1998; Meyer and Goffinet 1998; Supèr et al. 1998; Zecevic et al. 1999; Meyer et al. 2000; Meyer 2007, 2010). Then, cells from the ventricular zone migrate to form an **intermediate zone** and, towards the end of the embryonic period, the **cortical plate**. This plate develops within the preplate, thereby dividing the preplate into a minor superficial component, the marginal zone and a large deep component, the subplate. The **marginal zone** is composed largely of **Cajal-Retzius neurons** (Meyer et al. 1999; Meyer 2007, 2010), secreting the extracellular protein Reelin, and the subplate contains pioneer projection neurons. Reelin is required for the normal inside-to-outside positioning of cells as they migrate from the ventricular zone. Another source of Cajal-Retzius cells is the **cortical hem**, a putative signalling centre at the interface of the future hippocampus and the choroid plexus (Meyer 2010; Chap. 10). The formation of the cortical plate takes place from approximately 7–16 weeks. The first cells to arrive will reside in the future layer VI. Cells born later migrate past the already present cortical cells to reside in progressively more superficial layers. In this way, the cortical layers VI-II are subsequently formed. The marginal zone becomes layer I, i.e. the molecular or plexiform layer. The subplate gradually disappears. The ventricular zone becomes the ependyma and the intermediate zone the subcortical white matter. A transient cell layer, the **subpial granular layer** (**SGL**) of Ranke (1910), originates from the basal periolfactory subventricular zone (Brun 1965; Gadisseux et al. 1992; Meyer and Wahle 1999). It migrates tangentially beneath the pia to cover the neocortical marginal zone from the 14th gestational week onwards. The SGL provides a constant supply of Reelin-producing cells during the critical period of cortical migration, keeping pace with the dramatic growth and surface expansion during corticogenesis. Naturally occurring cell death is an active mechanism contributing to the disappearance of the SGL (Spreafico et al. 1999).

Primate corticogenesis is distinguished by the appearance of a large **subventricular zone** that has inner and outer regions (Smart et al. 2002; Zecevic et al. 2005). Recent observations in human, non-human primate, carnivore and marsupial embryos and fetuses reveal how differences in neural progenitor cell populations can result in neocortices of variable size and shape (Lui et al. 2011; Chap. 10). Increases in neocortical volume and surface area are related to the expansion of progenitor cells in the outer subventricular zone during development (Smart et al. 2002; Fietz et al. 2010; Hansen et al. 2010; Lui et al. 2011).

The **subplate** is a largely transient zone containing precocious neurons involved in several key stages of corticogenesis (Kostović and Rakic 1990; Kostović and Jovanov-Milošević 2006; Kostović and Judaš 2007, 2010; Judaš et al. 2010; Fig. 1.25). In rodents, the majority of subplate neurons form a compact layer (Allendoerfer and Shatz 1994; Kanold and Luhmann 2010; Wang et al. 2010), but they are dispersed throughout a much larger zone in primates including humans. In rodents, subplate neurons are among the earliest born neocortical cells, whereas in primates, neurons are added to the subplate throughout cortical neurogenesis. Histochemical studies and magnetic resonance imaging (Figs. 1.29 and 1.30) show that the human subplate grows in size until the end of the second trimester (Kostović and Jovanov-Milošević 2006; Prayer et al. 2006; Radoš et al. 2006; Kostović and Vasung 2009). **Transient laminae** containing circuitry elements (synapses, postsynaptic neurons and presynaptic axons) appear in the cerebral wall from the 8th postconceptional week and disappear with the resolution of the subplate after the 6th postnatal month (Kostović and Jovanov-Milošević 2006; Kostović and Judaš 2007, 2010). Transient neuronal circuitry underlies transient functions during the fetal, perinatal and early postnatal life and determines developmental plasticity of the cerebral cortex and moderates

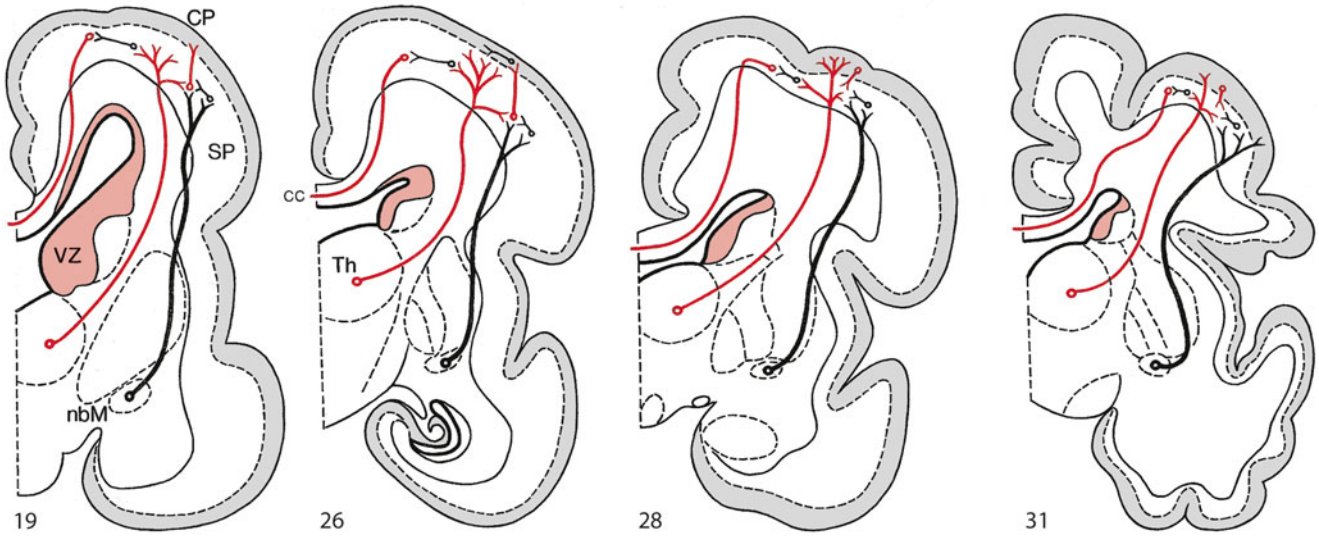

Fig. 1.25 The organization of afferent systems and transient cortical circuitry in human fetuses and preterm infants (19, 26, 28 and 31 post-conceptional weeks). Glutamatergic projections arising in the thalamus (*Th*) and the contralateral hemisphere, passing via the corpus callosum (*cc*), are indicated in *red*, GABAergic in *black* and cholinergic projections from the basal nucleus of Meynert (*nbM*) in *thick black lines*. The cortical afferents initially synapse in the large subplate (*SP*) before reaching the cortical plate. *CP* cortical plate (in *light grey*), *nbM* nucleus basalis of Meynert, *VZ* ventricular zone (in *medium red*) (After Kostović and Judaš 2010)

effects of lesions of the developing brain (Kostović and Jovanov-Milošević 2006; Kostović and Judaš 2007, 2010).

In the telencephalon, **radial migration** is the primary mechanism by which developing neurons arrive at their final position (Rakic 1972). The newly born neuroblasts associate with specialized glial cells known as the radial glial cells. **Radial glial cells** are bipolar cells with one short process extended to the adjacent ventricular surface and a second projecting to the pial surface (Chap. 2). A two-way signalling process between the migrating neuron and the radial glial fibre permits the neuroblast to migrate, and provides a signal to maintain the structure of the radial glial fibre (Hatten 1999). This process requires known receptors and ligands such as neuregulin and Erb4, cell adhesion molecules, putative ligands with unknown receptors such as astrotactin, and extracellular matrix molecules and their surface receptors. Blocking any of these components can slow or prevent radial cell migration (Pilz et al. 2002). Recent data have shown a much more prominent role for radial glial cells as **primary progenitors** or **neural stem cells** (reviewed by Kriegstein and Alvarez-Buylla 2009; Chap. 2). In development and in the adult brain, many neurons and glial cells are not the direct progeny of neural stem cells, but instead originate from transit amplifying **intermediate progenitor cells** (IPCs). IPCs can generate neurons (nIPCs) or generate glial cells, including oligodendrocytes (oIPCs) or astrocytes (aIPCs; Chap. 2).

Cell migration perpendicular to the radial axis, i.e. **tangential migration** (Fig. 1.26), differs from radial cell migration in the direction of movement and in the mechanism of cell guidance. Instead of radial glia, axons appear to be the substrate for at least some non-radial cell migration (Pearlman et al. 1998). Non-radial cell migration provides most, if not all, GABAergic interneurons of the cerebral cortex. This population of cortical neurons migrates from the ganglionic eminences along non-radial routes to reach the cerebral cortex (Anderson et al. 1999, 2001; Lavdas et al. 1999; Marín and Rubinstein 2001). The medial ganglionic eminence is the source of most cortical interneurons, and is also a major source of striatal interneurons (Marín et al. 2000). The tangential migration of postmitotic interneurons from the ganglionic eminences to the neocortex occurs along multiple paths, and is directed in part by members of the Slit and semaphorin families of guidance molecules (Marín et al. 2001). More recently, it has been shown that in the human forebrain (Fig. 1.27) interneurons arise both in the ganglionic eminences as well as locally in the ventricular and subventricular zones of the dorsal telencephalon under the neocortex (Letinić et al. 2002; Zecevic et al. 2005, 2011; Fertuzinhos et al. 2009; Rakic 2009; Chaps. 9 and 10).

Malformations of **cortical development** may be divided into several categories, based on the stage of development (cell proliferation, neuronal migration, cortical organization) at which cortical development was first affected (Barkovich et al. 2001, 2012; Chap. 10). Malformations due to abnormal proliferation or apoptosis may lead to extreme microcephaly. Malformations due to abnormal migration, i.e. ***neuronal migration disorders*** have been extensively studied (Gleeson and Walsh 2000; Barkovich et al. 2001, 2012; Olson and Walsh 2002; Pilz et al. 2002). Malformations due to abnor-

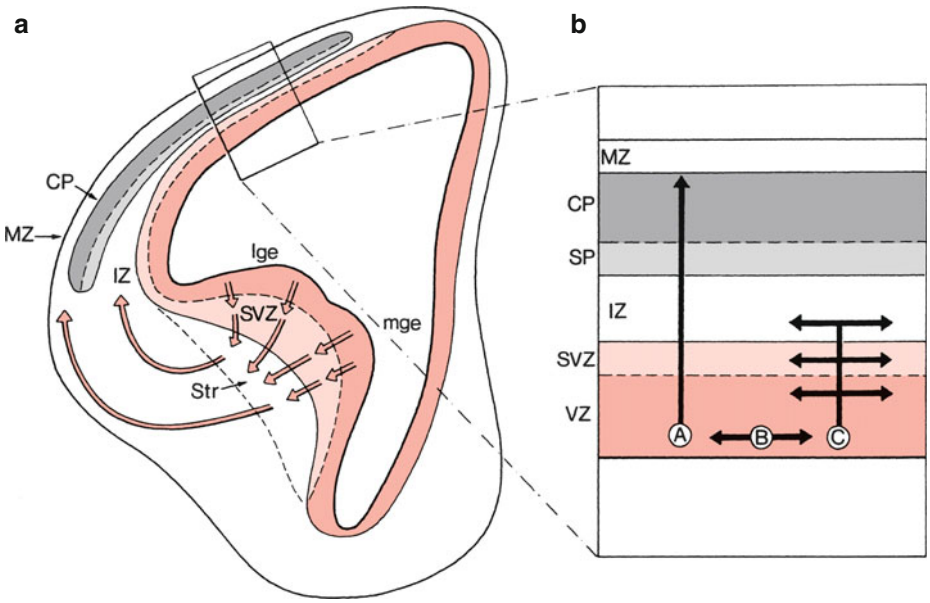

Fig. 1.26 Radial and tangential migration of cortical neurons. (**a**) The proliferative compartments of the murine telencephalon are shown: the ventricular zone (*VZ*, *red*) and the subventricular zone (*SVZ*, *light red*). Postmitotic GABAergic neurons leave the lateral (*lge*) and medial (*mge*) ganglionic eminences and reach the striatum (*Str*) and through tangential migration the marginal zone (*MZ*) and the intermediate zone (*IZ*). (**b**) Part of the cortex is enlarged in which radial migration of neurons (*A*) through the subplate (*SP*) to the cortical plate (*CP*) and tangential migration, occurring in the ventricular, subventricular and intermediate zones (*B*, *C*), is indicated (After Pearlman et al. 1998)

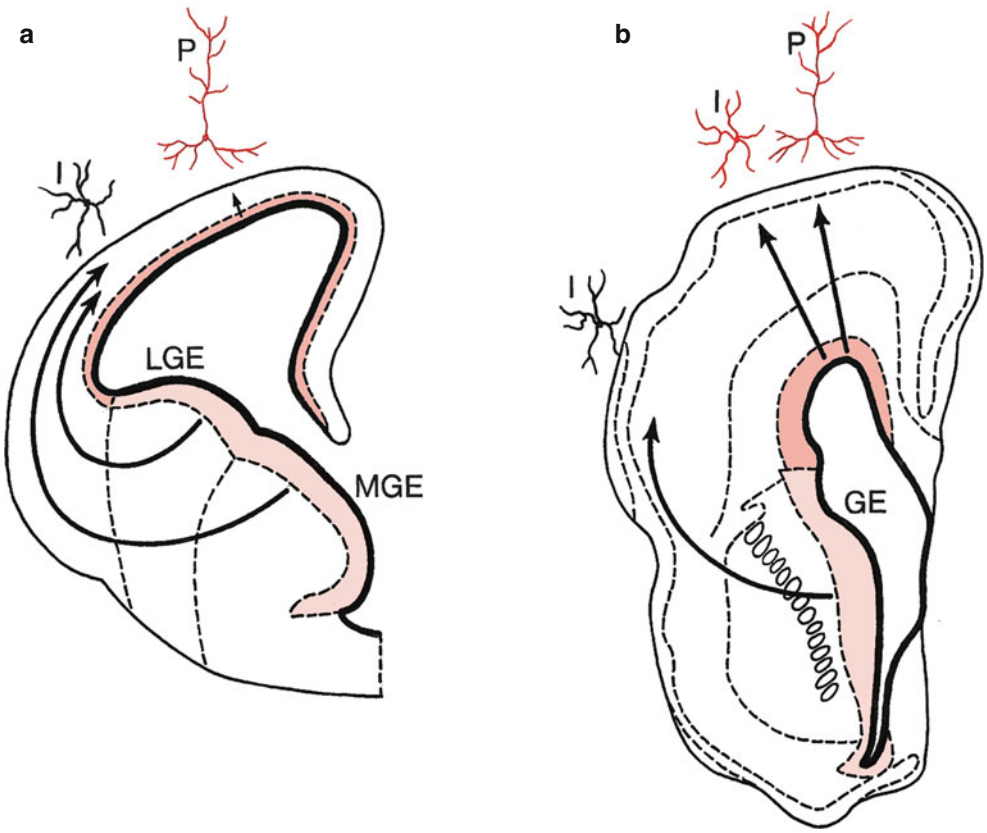

Fig. 1.27 Rodent (**a**) and human (**b**) fetal forebrains at the peak of corticogenesis, showing the sources of cortical interneurons. In rodents, projection neurons (*P*) arise in the ventricular and subventricular zones (in *medium red*), and cortical interneurons (*I*) in the lateral (*LGE*) and medial (*MGE*) ganglionic eminences (in *light red*). In the human brain, cortical interneurons arise not only from the ganglionic eminence (*GE*) but also from the dorsal ventricular and subventricular zones (in *medium red*) (After Rakic 2009)

mal cortical organization include the polymicrogyrias and schizencephalies (Barkovich et al. 2001, 2012).

The **olfactory bulbs** evaginate after olfactory fibres penetrate the cerebral wall at the ventrorostral part of the hemispheric vesicles (Pearson 1941). By the end of the sixth week, several bundles of fibres arising in the olfactory placodes have reached the forebrain vesicles. A few days later, a shallow protrusion appears at the site of contact, and between 8 and 13 weeks, the cavity of the evagination enlarges and becomes the olfactory ventricle. The olfactory bulbs gradually elongate rostralwards along the base of the telencephalon. Mitral cells arise from the surrounding ventricular zone. As the olfactory bulbs form, future granule and preglomerular cells are generated in the subventricular zone of the lateral

ganglionic eminences, and migrate into each bulb along a rostral migratory stream (Hatten 1999). These neurons move rapidly along one another in chain formations, independent of radial glia or axonal processes. In rats and primates, this migration persists into adulthood (Doetsch et al. 1997; Kornack and Rakic 2001; Brazel et al. 2003). Numerous cells of the **piriform cortex** originate close to the corticostriatal boundary (Bayer and Altman 1991). They reach the rostrolateral telencephalon via a lateral cortical stream (de Carlos et al. 1996; Chap. 2).

1.8.3 Cerebral Commissures

Cerebral commissures arise in a thin plate, the **embryonic lamina terminalis**, i.e. the median wall of the telencephalon rostral to the chiasmatic plate. It is also known as the lamina reuniens or *Schlussplatte* (His 1889, 1904; Hochstetter 1919; Rakic and Yakovlev 1968; Paul et al. 2007; Raybaud 2010; Chap. 10). At approximately 5 weeks (stage 16), the **commissural plate** appears as a thickening in the embryonic lamina terminalis. The remainder of the lamina then constitutes the adult lamina terminalis (*Endplatte* of His 1889, 1904). The commissural plate gives rise to (Fig. 1.28) (1) the anterior commissure, which appears at the end of the embryonic period and connects the future temporal lobes, (2) the hippocampal commissure, which appears several weeks later and connects the crura of the fornix, and (3) the corpus callosum, which appears early in the fetal period and connects the cerebral hemispheres. The **corpus callosum** is first identified at 11–12 weeks after ovulation, and gradually extends considerably caudalwards. The overlying part of the commissural plate becomes thinned to form the septum pellucidum. Within the septum a narrow cavity appears, the cavum septi pellucidi. The corpus callosum appears to be fully formed by the middle of prenatal life. Mechanisms of the formation of the corpus callosum are discussed in Chap. 2. Partial or complete ***absence*** of the ***corpus callosum*** is not uncommon (Aicardi 1992; Norman et al. 1995; Kollias and Ball 1997; Barkovich 2000; Paul et al. 2007; Raybaud 2010). Every disorder that influences the development of the commissural plate may lead to this malformation. Dysgenesis of the corpus callosum occurs in approximately 20 % as an isolated disorder, but in about 80 % of cases in combination with other disorders of the brain (Chap. 10).

1.8.4 Imaging of the Fetal Brain

Fetal magnetic resonance images at 20 and 35 weeks of development are shown in Figs. 1.29 and 1.30, respectively. At 20 weeks of development, cortical layers, the hypodense

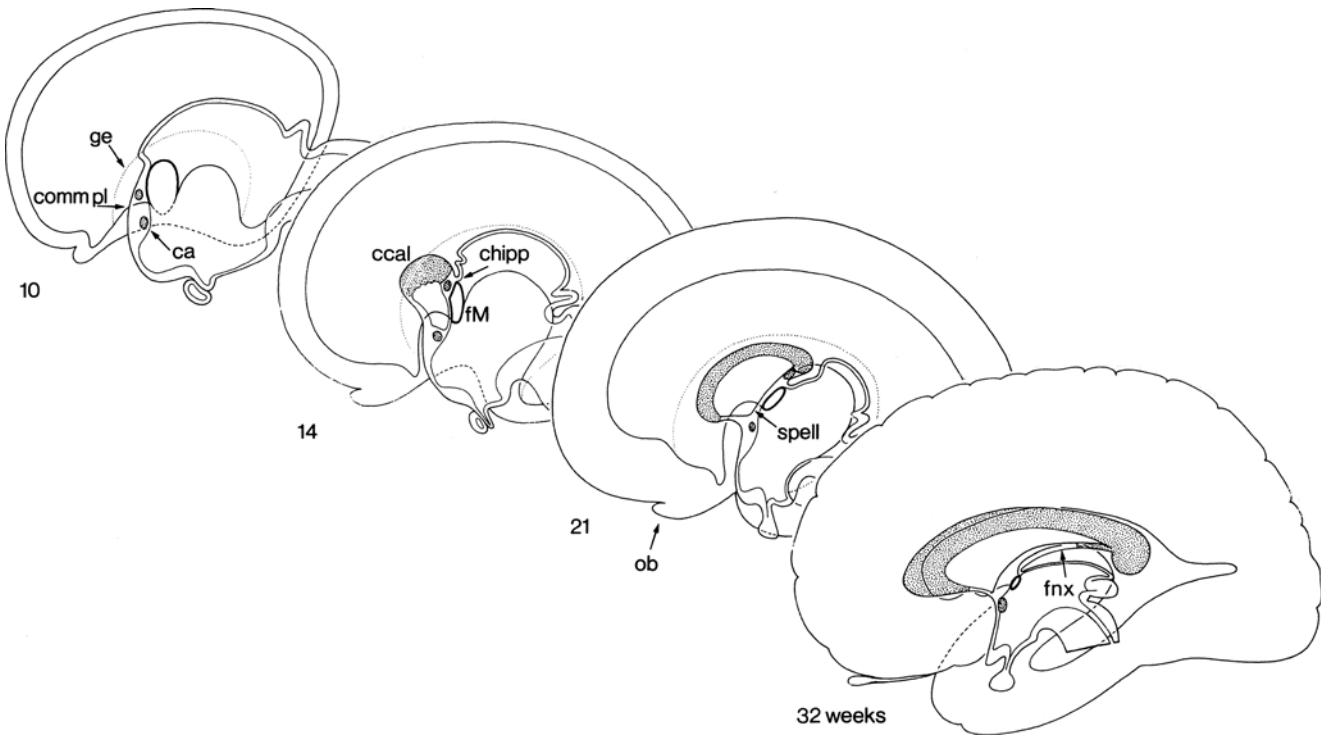

Fig. 1.28 Development of the cerebral commissures at the 10th, 14th, 21th and 32th week of development. *ca* commissura anterior, *ccal* corpus callosum, *chipp* commissura hippocampi, *comm pl* commissural plate, *fM* foramen of Monro, *fnx* fornix, *ge* ganglionic eminence, *ob* olfactory bulb, *spell* septum pellucidum (After Streeter 1911, 1912)

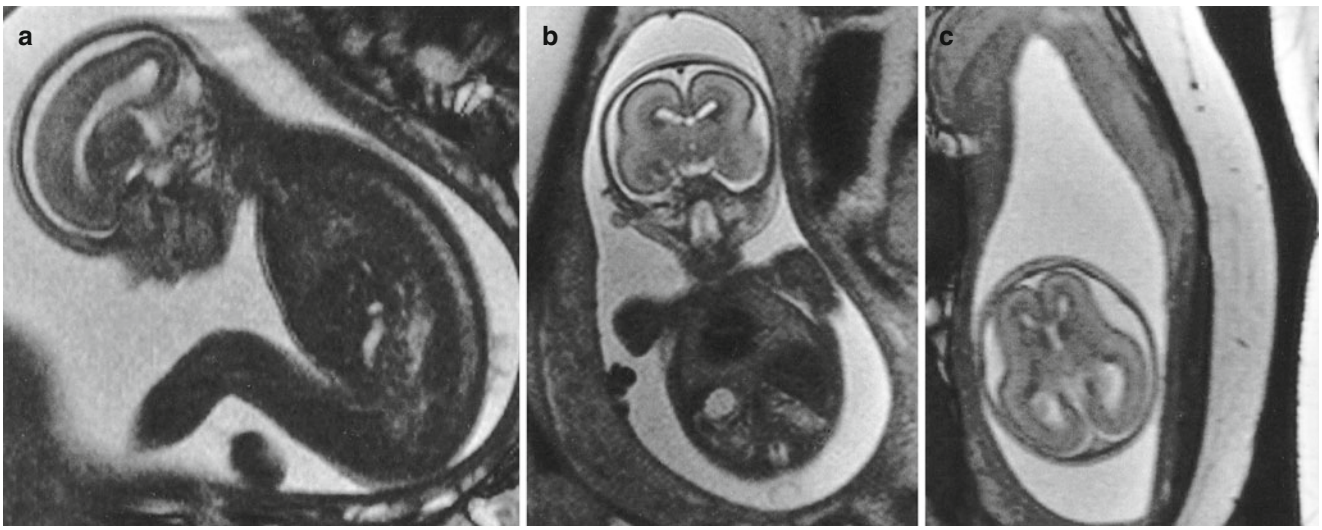

Fig. 1.29 Fetal T2-weighted MRI taken at the 20th week of development: (**a**) sagittal section; (**b**) frontal (or coronal) section; and (**c**) horizontal (or axial) section. There is a smooth cerebral surface without gyration. The thick periventricular germinal layer has a low-signal intensity. A thin cortical layer is present, below which the large subplate can be recognized

subplate in particular, can be easily distinguished in the smooth cerebral cortex. Germinal zones are hyperdense. A 35-week-old brain shows the extensive changes that appear in the cerebrum in the second half of pregnancy. Garel's (2004) MRI atlas presents the fetal brain in detail from 20 weeks of development until birth. Kostović and Vasung (2009) analyzed in vitro fetal magnetic resonance imaging of cerebral development. With 7.0 T MRI, Meng et al. (2012) displayed the development of subcortical brain structures in postmortem fetuses from 12 weeks gestational age onwards. For ultrasound data on the fetal brain, see Monteagudo and Timor-Tritsch (2009) and Pooh and Kurjak (2009).

1.9 Development of the Meninges and Choroid Plexuses

The **cranial meninges** originate from several sources such as the prechordal plate, the parachordal mesoderm and the neural crest (O'Rahilly and Müller 1986). The loose mesenchyme around most of the brain at 5 weeks of development (stage 15) forms the primary meninx. At 6 weeks (stage 17), the dural limiting layer is found basally and the skeletogenous layer of the head becomes visible. At 7 weeks (stage 19), the cranial pachymeninx and leptomeninx are distinguishable. Hochstetter (1939) showed that, as the dural reflections develop, the posterior point of attachment between the tentorium cerebelli and the falx cerebri gradually moves to a more caudal position in the skull, thereby producing a continual reduction in the size of the posterior cranial fossa relative to the supratentorial fossae. Increases of supratentorial volume relative to infratentorial volume affect such an inferoposterior rotation of the human fetal tentorium cerebelli (Jeffery 2002). Klintworth (1967) found the tentorium cerebelli at stage 20 as a bilateral, three-layered structure. The two tentorial precursors were visible macroscopically by stage 23. They fuse at 55-mm crown-rump length (CRL) to create the straight sinus (Streeter 1915). It is now clear that the meninges of the forebrain and hindbrain serve as a signalling centre coordinating developmental events between the cortex and the skull by releasing a variety of secreted factors (Siegenthaler and Pleasure 2011).

The development of the **spinal meninges** has been studied by Hochstetter (1934) and Sensenig (1951). The future pia mater appears as neural crest cells by stage 11, and at 5 weeks (stage 15) the primary meninx is represented by a loose zone between the developing vertebrae and the neural tube. After 6 weeks (stage 18), the mesenchyme adjacent to the vertebrae becomes condensed to form the dural lamella. At the end of the embryonic period (stage 23), the dura completely lines the wall of the vertebral canal. The spinal arachnoid, however, does not appear until either the third trimester or postnatally (O'Rahilly and Müller 1999).

A **choroid plexus** first appears in the roof of the fourth ventricle at stage 18, in the lateral ventricles at stage 19, and in the third ventricle at stage 21 (Ariëns Kappers 1958; Bartelmez and Dekaban 1962). The primordia appear as simple or club-shaped folds protruding into the ventricles. During stage 21, the choroid plexuses become vascularized. The early choroid plexus of the lateral ventricle is lobulated with vessels running in the mesenchymal stroma and forming capillary nets under the single-layered ependyma.

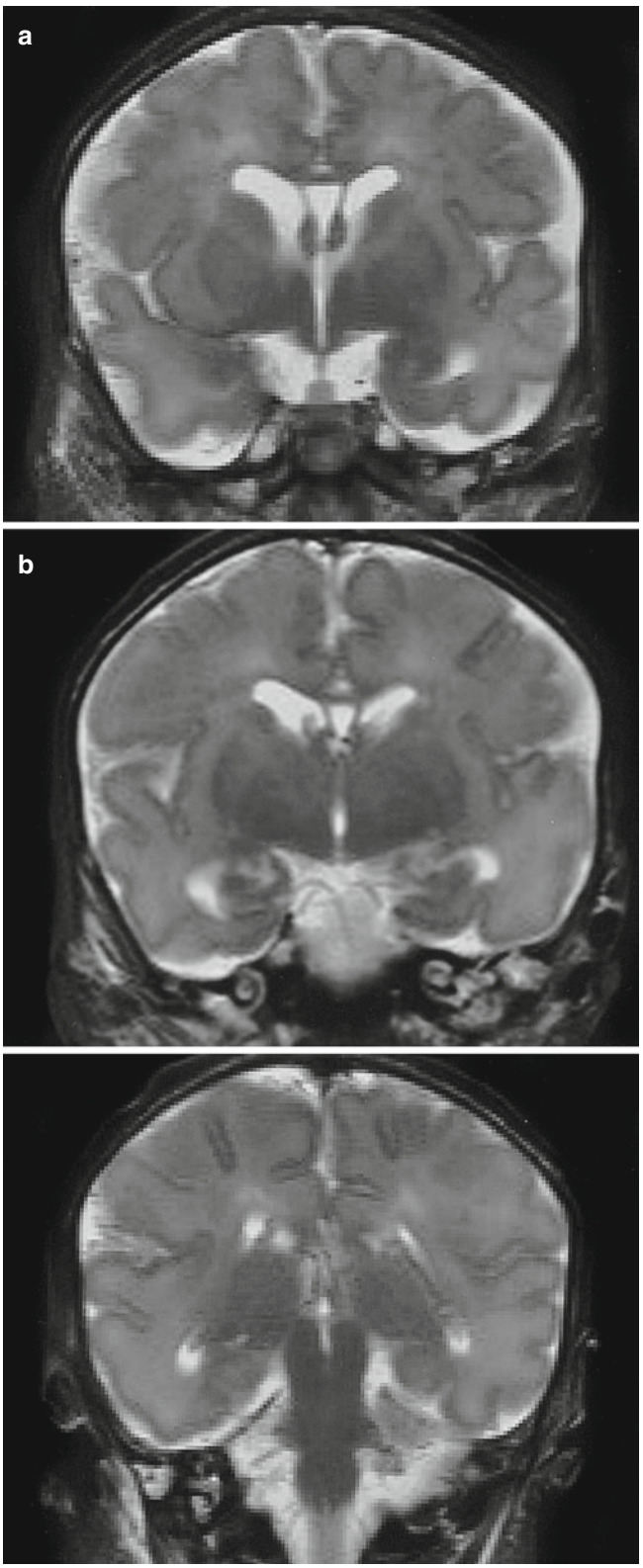

Fig. 1.30 Fetal T2-weighted MRI taken at the 35th week of development. The three frontal (or coronal) sections show increasing development of the insulae and lateral fissures, and an increasing number of gyri and sulci. The basal ganglia (in **a**), the amygdala (in **a**) and the hippocampal region (in **b**) are easily recognized. Note the large cavum septi pellucidi and the prominent fornices (in **a** and **b**). The corpus callosum is visible in (a) and (b)

The embryonic choroid plexus is converted into the fetal type during the ninth week of development as the embryonic capillary net is replaced by elongated loops of wavy capillaries that lie under regular longitudinal epithelial folds (Kraus and Jirásek 2002). The stroma of the plexus originates from extensions of the arachnoid into the interior of the brain that form the **vela interposita**. This may explain the origin of the sporadically occurring intraventricular meningiomas, most commonly found in the trigone of the third ventricle (Nakamura et al. 2003).

1.10 Development of the Blood Supply of the Brain

The brain is supplied by two pairs of internal carotid and vertebral arteries, connected by the circle of Willis. During the closure of the neural tube, primordial endothelial blood-containing channels are established. From these all other vessels, arteries, veins and capillaries are derived. At stage 12, capital venous plexuses, the capital vein and three aortic arches are present (Streeter 1918; Congdon 1922; Padget 1948, 1957; Fig. 1.31). The internal carotids develop early (stages 11–13), followed by the posterior communicating artery, the caudal branch of the internal carotid at stage 14, the basilar and vertebral arteries (stage 16), the main cerebral arteries (stage 17) and finally the anterior communicating artery, thereby completing the circle of Willis (Evans 1911, 1912; Padget 1948; Gillilan 1972). Bilaterally, longitudinal arteries are established at stage 13 and are connected with the internal carotids by temporary trigeminal, otic and hypoglossal arteries. At first, the posterior communicating artery provides the major blood supply of the brain stem. Anastomotic channels unite the two longitudinal arteries, thereby initiating the formation of the basilar artery. The temporary arteries are gradually eliminated, but each of them may persist. The primitive trigeminal artery is the most common of the primitive carotid-basilar anastomoses that persist into adulthood, with an incidence of 0.1–1.0 % (Wollschlaeger and Wollschlaeger 1964; Lie 1968; Salas et al. 1998; Suttner et al. 2000; Fig. 1.32). The persistence of a primitive otic artery is shown in Fig. 1.33. The development of the large vessels can be studied with 3D-ultrasound (Pooh 2009; Pooh et al. 2011).

Capillaries at the level of the cerebral hemispheres begin to appear at 5 weeks, and probably earlier in the brain stem (Padget 1948; O'Rahilly and Müller 1999). By 5 weeks (stage 16), many of the definitive arteries are present and are being transformed into the definitive pattern. At the end of the embryonic period, an anular network of **leptomeningeal arteries** arises from each middle cerebral artery and extends over each developing hemisphere (Van den Bergh and Vander Eecken 1968). Similar meningeal branches, originating from the vertebral and basilar arteries, embrace the brain stem and

cerebellum. From these leptomeningeal arteries branches grow into the brain. Both supratentorially and infratentorially, **paramedian**, **short circumferential** and **long circumferential arteries** can be distinguished. The first vessels penetrate the telencephalon in the seventh week of gestation, form a subventricular plexus at about 12 weeks of gestation (Duckett 1971). The paramedian branches of the anterior cerebral artery have a short course before they penetrate the cerebral parenchyma, whereas the short circumferential arteries such as the striate artery have a slightly longer course and the long circumferential arteries may reach the dorsal surface of the cerebral hemispheres. At 16 weeks of gestation, the anterior, middle and posterior cerebral arteries, contributing to the formation of the circle of Willis, are well

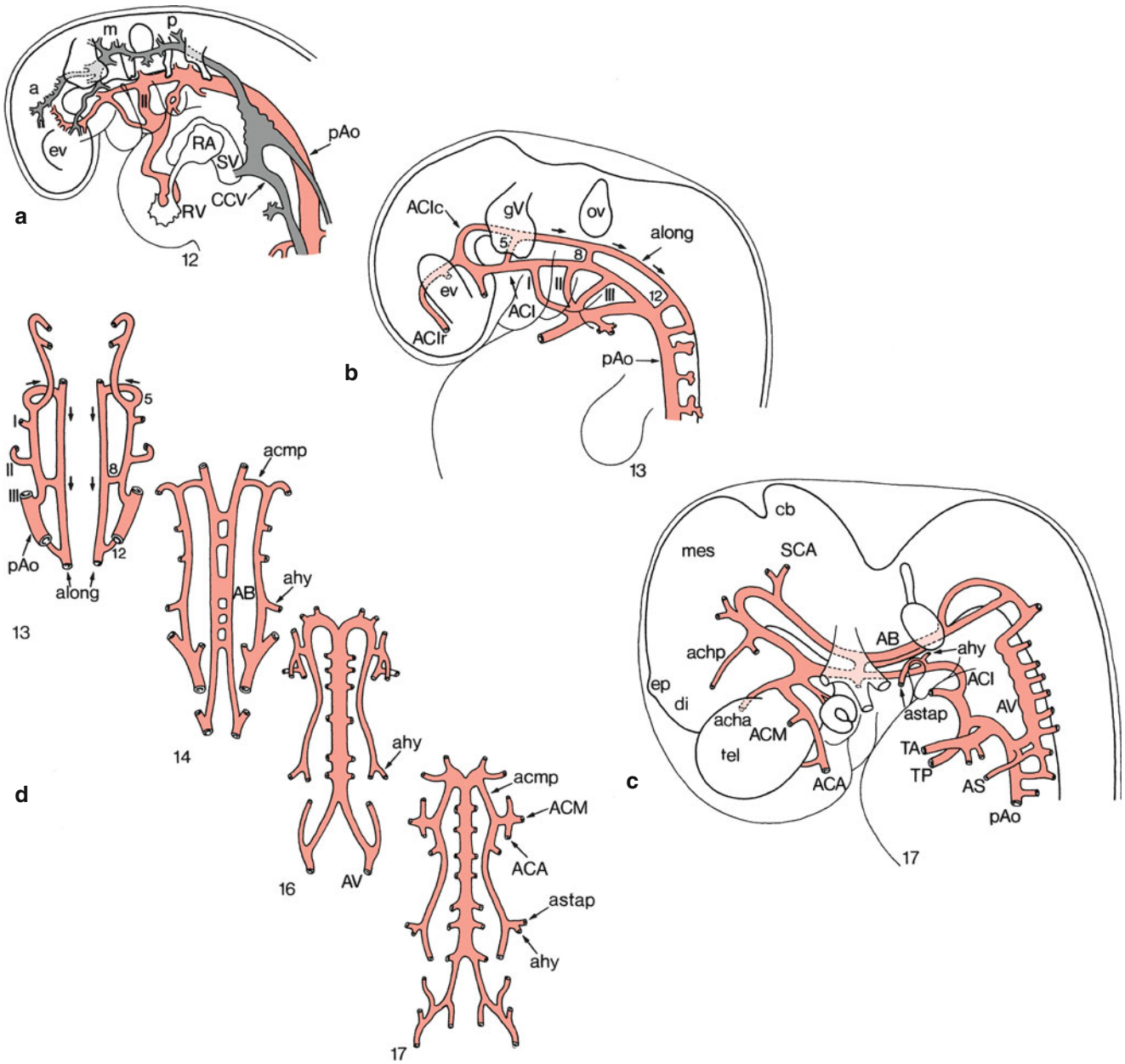

Fig. 1.31 Overview of the development of the blood supply of the human brain from stage 12 until the neonatal period. Arteries are in *red*, veins in *grey*. *a* anterior capital plexus, *AA* aortic arch, *AB* a. basilaris, *ACA* a. cerebri anterior, *ACE* a. carotis externa, *acha* anterior choroidal artery, *achp* posterior choroidal artery, *ACI* a. carotis interna, *ACIc* caudal branch of a. carotis interna, *ACIr* rostral branch of a. carotis interna, *ACM* a. cerebri media, *acmp* a. communicans posterior, *ACP* a. cerebri posterior, *ahy* hyoid artery, *AICA* anterior inferior cerebellar artery, along a. longitudinalis, *AS* a. subclavia, *astap* a. stapedia, *AV* a. vertebralis, *cb* cerebellum, *cc* corpus callosum, *CCV* common cardinal vein, *DA* ductus arteriosus, *di* diencephalon, *ep* epiphysis, *ev* eye vesicle, *gV* trigeminal ganglion, *m* middle capital plexus, *mes* mesencephalon, *OA* ophthalmic artery, *ov* otic vesicle, *p* posterior capital plexus, *pAo* posterior aorta, *PICA* posterior inferior artery, *plch* plexus choroideus, *RA* right atrium, *RV* right ventricle, *SCA* superior cerebellar artery, *SV* sinus venosus, *TA* truncus arteriosus, *tel* telencephalon, *TP* truncus pulmonalis, *I-III* aortic branches, *5*, *8*, *12* temporary trigeminal, otic and hypoglossal arteries (After Padget 1948; O'Rahilly and Müller 1999)

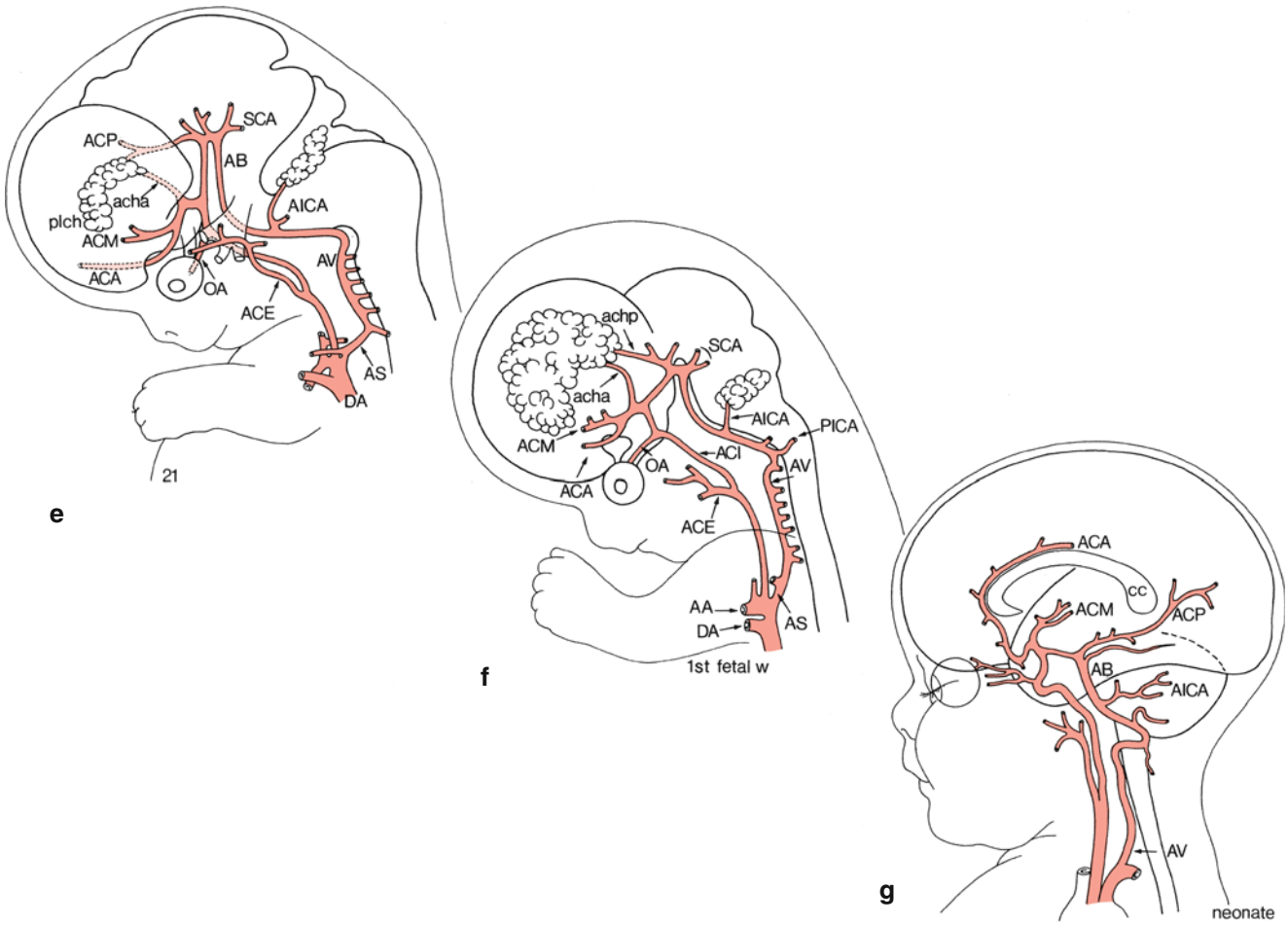

Fig. 1.31 (continued)

established (Padget 1948; Van den Bergh and Vander Eecken 1968). During the further fetal period the relatively simple leptomeningeal arteries increase in tortuosity, size and number of branches. Their branching pattern is completed by 28 weeks of gestation (Takashima and Tanaka 1978).

The leptomeningeal perforating branches pass into the cerebral parenchyma as **cortical**, **medullary** and **striate branches** (Fig. 1.34). The cortical vessels supply the cortex via short branches, whereas the medullary branches supply the underlying white matter. The striate branches penetrate into the brain via the anterior perforate substance and supply the basal ganglia and internal capsule. The cortical and medullary branches supply cone-shaped areas along the periphery of the cerebrum also known as **ventriculopetal arteries**. Striate branches arborize close to the ventricle and supply a more central part of the cerebrum. Together with branches of the tela choroidea, they were supposed to give rise to **ventriculofugal arteries**, supplying the ventricular zone or germinal matrix (Van den Bergh and Vander Eecken 1968; De Reuck 1971; De Reuck et al. 1972). According to their accounts, ventriculopetal and ventriculofugal arteries made no anastomotic connections and formed a deep white matter border zone. The presence of such arteries could not be confirmed by Gilles and co-workers (Kuban and Gilles 1985; Nelson et al. 1991; Gilles and Nelson 2012). More likely, the central parts are supplied by deep penetrating branches (Rorke 1992; Gilles and Nelson 2012). Smooth muscle is present at the basal ends of striatal arteries by midgestation and extends well into the vessels in the caudate nucleus by the end of the second trimester (Kuban and Gilles 1985). The intracortical vessels also develop gradually (Allsop and Gamble 1979). From the 13th to 15th weeks, radial arteries without side branches course through the cortex. By 20 weeks of gestation, horizontal side branches and recurrent collaterals appear, and from 27 weeks to term, shorter radial arteries increase in number. Growth of the intracortical capillaries continues well after birth (Norman and O'Kusky 1986). In the fetal brain, the density of capillaries is much higher in the ventricular zone than in the cortical plate until 17 weeks (Duckett 1971; Allsopp and Gamble 1979; Norman and O'Kusky 1986). After 25 weeks, increasing vascularization of the cortical areas occurs.

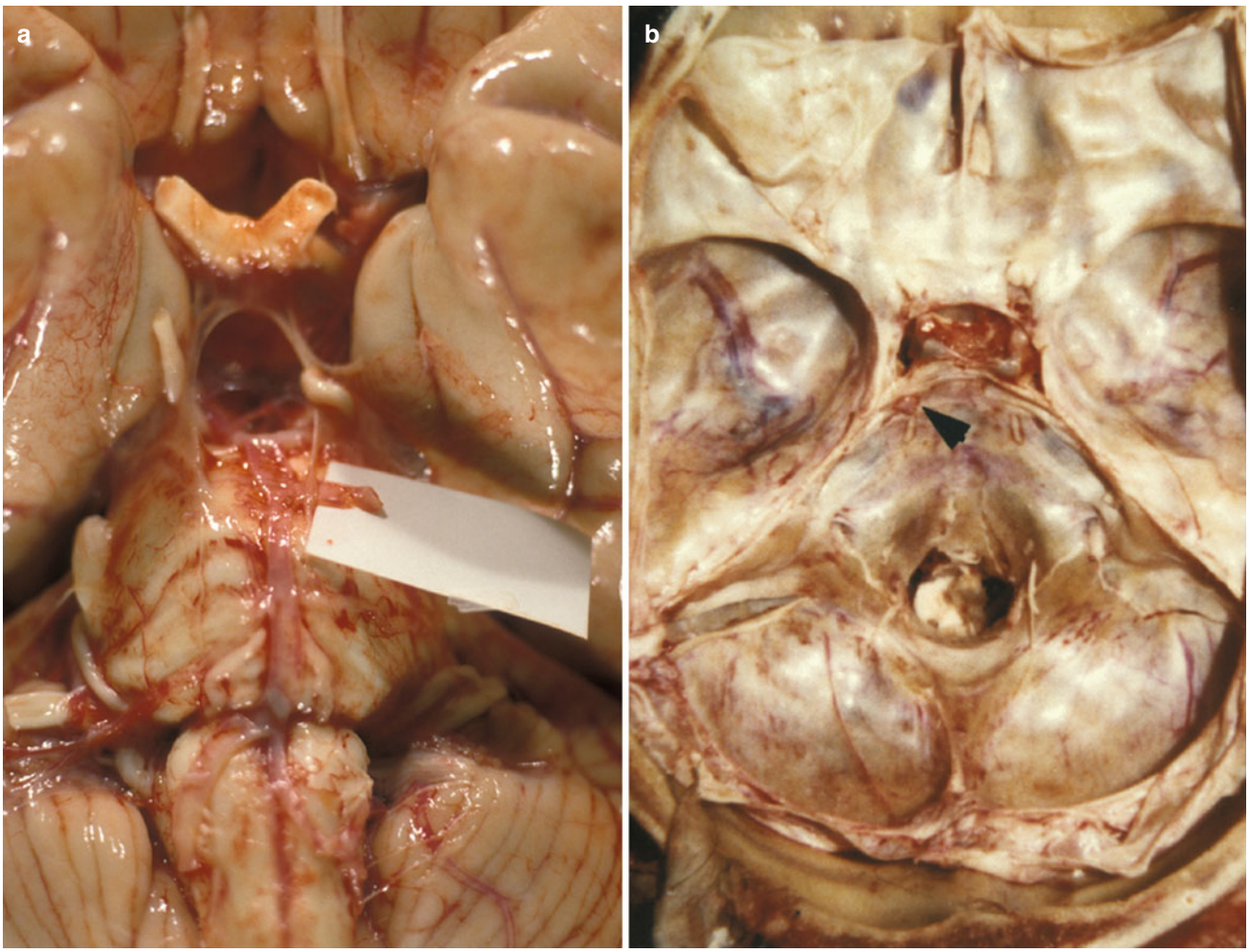

Fig. 1.32 Persistence of the primitive trigeminal artery. Occasional autopsy finding by Akira Hori in a 42-year-old woman

At 24 weeks of gestation, a large part of the basal ganglia and internal capsule is supplied by a prominent **Heubner's artery**, arising from the anterior cerebral artery (Hambleton and Wigglesworth 1976). The capillary bed in the ventricular zone is supplied mainly by Heubner's artery and terminal branches of the lateral striate arteries from the middle cerebral artery (Wigglesworth and Pape 1980). The cortex and the underlying white matter are rather poorly vascularized at this stage of development. Gradually, the area supplied by the middle cerebral artery becomes predominant when compared to the territories supplied by the anterior and posterior cerebral arteries (Okudera et al. 1988). Early arterial anastomoses appear around 16 weeks of gestation. The sites of arterial anastomoses between the middle and the anterior cerebral arteries move from the convexity of the brain towards the superior sagittal sinus and those between the middle and posterior cerebral arteries move towards the basal aspect of the brain. By 32–34 weeks of gestation, the ventricular zone involutes and the cerebral cortex acquires its complex gyral pattern with an increased vascular supply. The ventricular zone capillaries blend with the capillaries of the caudate nucleus and the territory of Heubner's artery becomes reduced to only a small medial part of the caudate nucleus. In the cortex, there is progressive elaboration of the cortical blood vessels (Van den Bergh and Vander Eecken 1968; Hambleton and Wigglesworth 1976; Weindling 2002). Towards the end of the third trimester, the balance of cerebral circulation shifts from a central, ventricular zone oriented circulation to a circulation predominant in the cerebral cortex and white matter. These changes in the pattern of cerebral circulation are of major importance in the pathogenesis and distribution of hypoxic/ischaemic lesions in the developing human brain.

Cerebrovascular density correlates with regional metabolic demand (Pearce 2002). Correspondingly, cerebrovascular conductance in the vertebrobasilar and carotid systems increases more slowly than brain weight, particularly during the postnatal period of rapid cerebral growth, myelination and differentiation. As part of normal development, most immature human cerebral arteries appear to have regions of

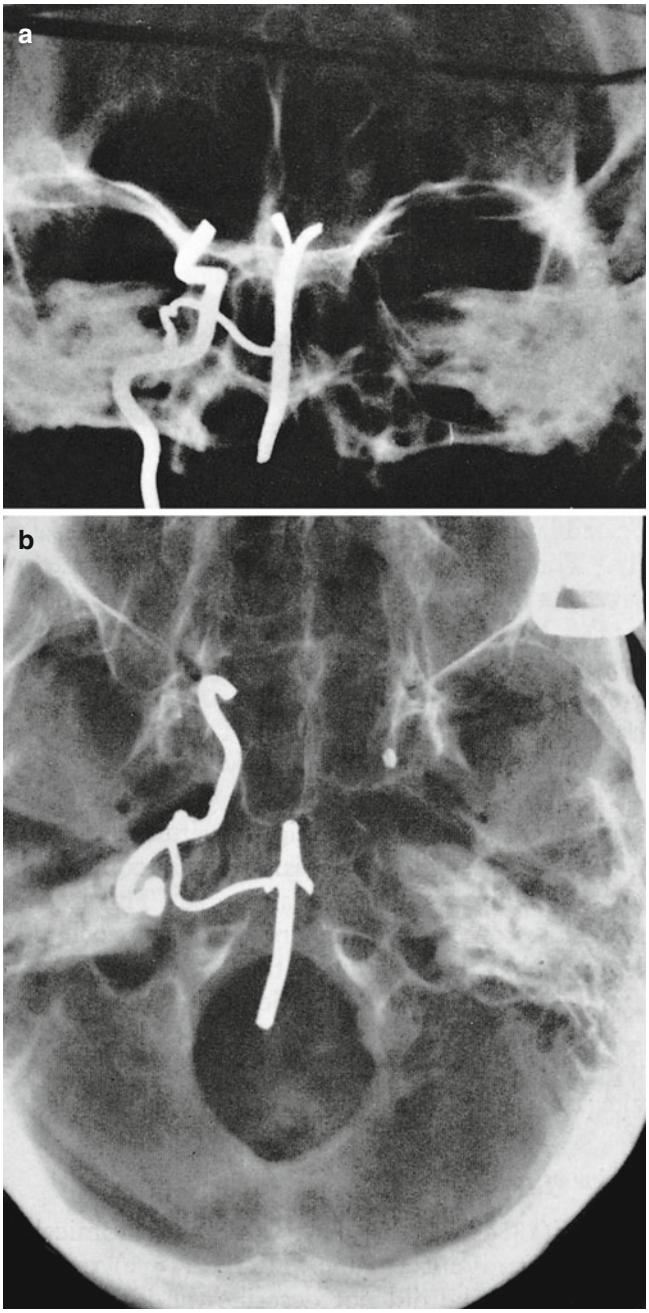

Fig. 1.33 Persistence of the primitive otic artery (From Lie 1968)

weakened media near vessel bifurcations. These weakened areas are reinforced during maturation via the deposition of additional smooth muscle, but can comprise areas of heightened vulnerability to rupture during early postnatal development (Pearce 2002).

In younger premature infants (22–30 weeks old), the blood vessels of the germinal, periventricular zone and the perforating ventriculopetal vessels are particularly vulnerable to ***perinatal asphyxia*** (Marín-Padilla 1996; Volpe 1998; Weindling 2002). Damage to these vessels often causes focal haemorrhagic lesions. In **older premature infants** (30–34 weeks), the fetal white matter seems to be particularly vulnerable to hypoxic-ischaemic injury, leading to ***periventricular leukomalacia*** or ***PVL*** (Chap. 3), and often resulting in infarction (necrosis) and cavitation (Banker and Larroche 1962; Marín-Padilla 1997, 1999; Volpe 2001, 2009; Squier 2002; Weindling 2002; Rutherford et al. 2010). PVL refers to necrosis of white matter in a characteristic distribution, i.e. in the white matter dorsal and lateral to the external angles of the lateral ventricles. The corticospinal tracts run through the periventricular region. Therefore, ***impaired motor function*** is the most common neurologic sequela of periventricular white matter injury (Banker and Larroche 1962; Aida et al. 1998; Staudt et al. 2000). Periventricular white matter lesions account for the pathogenesis of a large number of children with spastic hemiparesis (Niemann et al. 1994). In **younger premature infants** with very low birth weight (less than 1,500 g), however, ***cognitive deficits*** without major motor deficits are by far the dominant neurodevelopmental sequelae in infants (Woodward et al. 2006; Volpe 2009). In PVL, the primary event is most likely to be a destructive process and the subsequent developmental disturbances are secondary. The necrosis involves all cellular elements, and, therefore, focal loss of premyelinating oligodendrocytes, axons and perhaps late-migrating interneurons (Fig. 1.35). ***Cystic PVL*** probably accounts for the small group of infants who show spastic diplegia, whereas ***non-cystic PVL*** correlates with the cognitive deficits observed later, usually in the absence of major motor deficits. The consequences will be similar to, but quantitatively less than, the wider cellular effects of diffuse PVL (Volpe 2009; Chap. 3).

Dural plexuses associated with the precardinal veins become modified to form the various dural sinuses around the brain (Streeter 1915, 1918; Lindenberg 1956; Padget 1957). Definitive venous channels emerge from the primitive vascular net later than the arteries do. Moreover, the complicated venous anastomoses are essential to facilitate a greater adjustment to the changing needs of their environment over a considerably longer period (Padget 1957). The development of the human **cranial venous system** is summarized in Fig. 1.36. During Padget's venous stage 1 (Carnegie stage 12), **capital venous plexuses** and the **capital vein** are forming (Fig. 1.36a). By venous stage 2 (Carnegie stage 14), three relatively constant **dural stems**, anterior, middle and posterior, are present draining into a **primary head sinus** (capital or 'head' vein) that is continuous with the anterior cardinal vein. During venous stages 3 and 4 (Carnegie stages 16 and 17), the dural venous channels come to lie more laterally as the cerebral hemispheres and the cerebellar anlage expand and the otic vesicles enlarge (Fig. 1.36c). The head sinus and the primitive internal jugular vein also migrate laterally. By

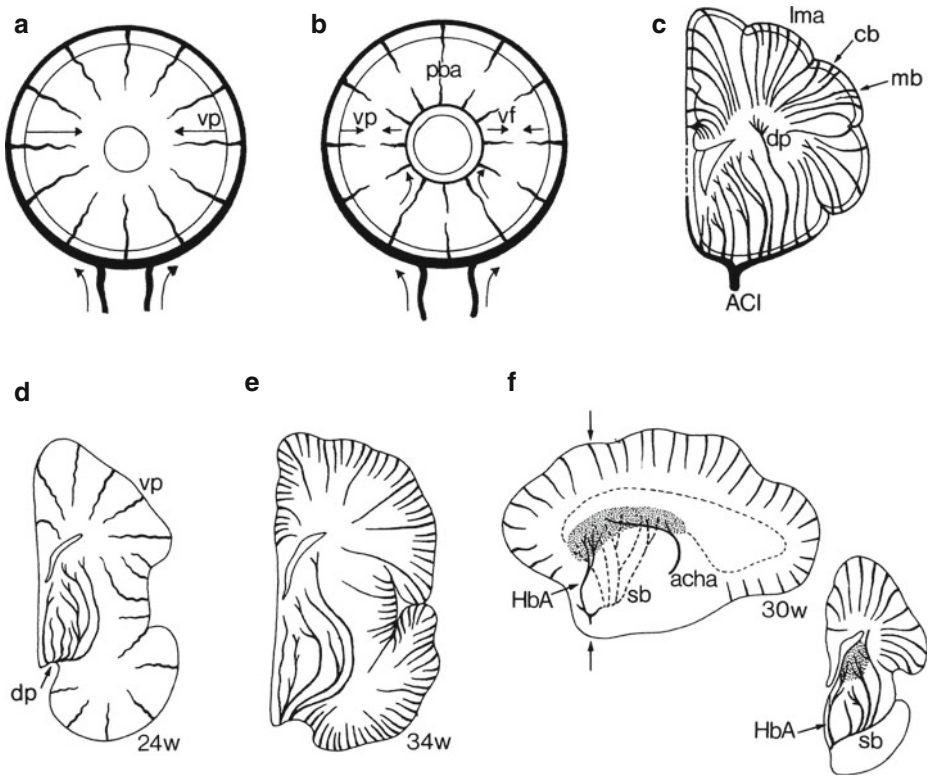

Fig. 1.34 Development of cerebral blood vessels. The brain is surrounded by a system of leptomeningeal arteries, which is supplied by afferent trunks at the base of the brain, and gives off ventriculopetal arteries (*vp*) towards the lateral ventricle (**a**). A few deep-penetrating arteries supply periventricular parts of the brain and were supposed to send ventriculofugal arteries (*vf*) towards the ventriculopetal vessels, without making anastomoses (**b**). Between these two systems there may be a periventricular border area. Deep penetrators (*dp*) more likely supply the periventricular parts of the brain. (**c**) The arrangement of both types of vessels around a cerebral hemisphere is shown. (**d**, **e**) Changes in the arterial pattern of the cerebrum between 24 and 34 weeks of gestation. (**f**) Blood supply to the basal ganglia at 20 weeks of gestation. *acha* anterior choroidal artery, *ACI* internal carotid artery, *cb* cortical branches, *HbA* Heubner's artery, *lma* leptomeningeal arteries, *mb* medullary branches, *pba* periventricular border area, *sb* striate branches of middle cerebral artery (After Van den Bergh and Vander Eecken 1968; Hambleton and Wigglesworth 1976)

venous stage 5 (Carnegie stage 19), the head sinus is replaced by a secondary anastomosis, the **sigmoid sinus**. Moreover, more cranially the **primitive transverse sinus** is formed. During venous stage 6 (Carnegie stage 21), the external jugular system arises (Fig. 1.36d). Most parts of the brain, except for the medulla, drain into the junction of the sigmoid sinus with the primitive transverse sinus. Meanwhile, the Galenic system of intracerebral drainage emerges as the result of accelerated growth of the ganglionic eminences. Subsequent venous changes depend largely upon the expansion of the cerebral and cerebellar hemispheres and the relatively late ossification of the skull (Fig. 1.36e, f). One of the most common malformations of the cerebral venous system is the ***vein of Galen malformation*** (Chap. 3).

1.11 Development of Fibre Tracts (Including Development of Myelination)

Early generated, 'pioneer' neurons lay down an axonal scaffold, containing guidance cues that are available to later outgrowing axons (Chap. 2). The first descending brain stem projections to the spinal cord can be viewed as pioneer fibres. They arise in the interstitial nucleus of the fasciculus longitudinalis medialis (flm) and in the reticular formation (Müller and O'Rahilly 1988a, b). At early developmental stages (from stage 11/12 onwards), in the brain stem a ventral longitudinal tract can be distinguished, followed by lateral and medial longitudinal fasciculi at stage 13. Descending fibres from the medullary reticular formation reach the spinal cord in embryos of 10–12-mm CRL (Windle and Fitzgerald 1937). Interstitiospinal fibres from the interstitial nucleus of the flm start to descend at stage 13, i.e. at 28 days. In 12-mm-CRL embryos (about stage 17/18) embryos, vestibulospinal projections were found (Windle 1970). At the end of the embryonic period, the flm is well developed, and receives ascending and descending (the medial vestibulospinal tract) components from the vestibular nuclear complex (Müller and O'Rahilly 1990c). The lateral vestibulospinal tract arises from the lateral vestibular nucleus. Windle and Fitzgerald (1937) also followed the ingrowth of dorsal root projections and the development of commissural, ascending and descending spinal pathways (Chap. 6). Ascending fibres in the dorsal funiculus have reached the brain stem at stage 16 (Müller and O'Rahilly 1989). Decussating fibres, forming the medial lemniscus, were first noted at stage 20 (Müller and O'Rahilly 1990a, b; Chap. 7).

The **corticospinal tract** is one of the latest developing descending pathways (ten Donkelaar 2000). At stage 21, the cortical plate starts to develop, whereas a definite internal capsule is present by stage 22 (Müller and O'Rahilly 1990b).

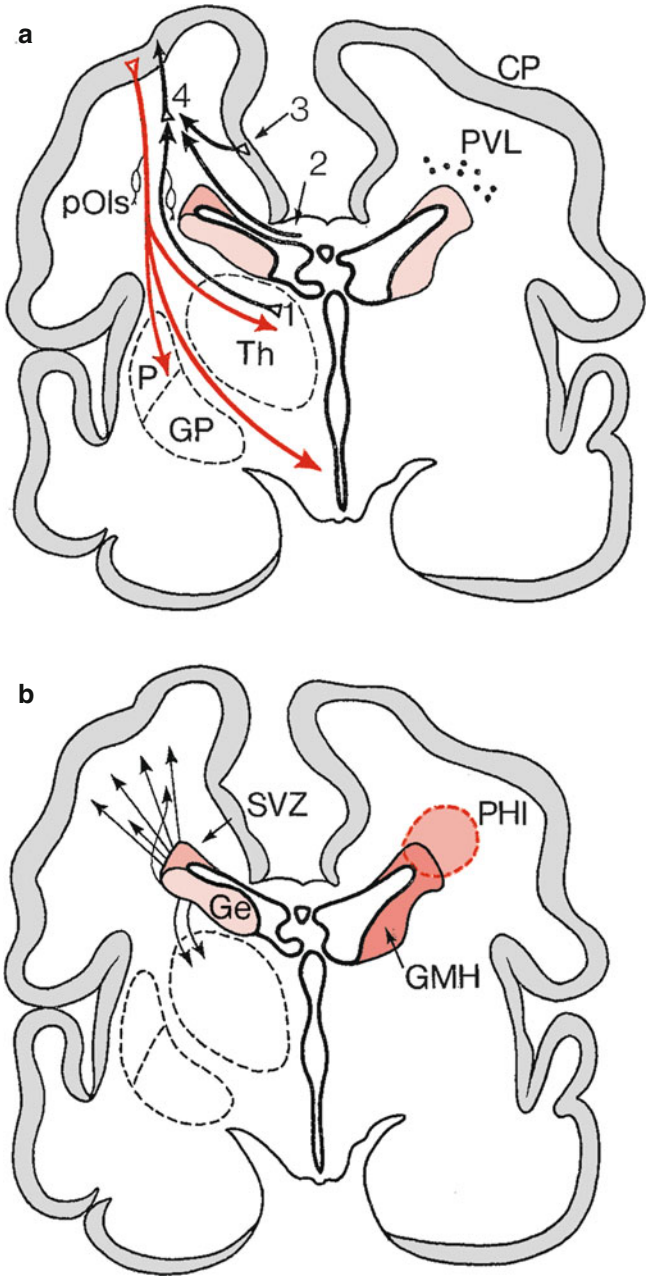

Fig. 1.35 Anatomical relationships between (**a**) the major developmental events (**b**) and the topography of periventricular leukomalacia (*PVL*) and germinal matrix haemorrhage (*GMH*) and periventricular haemorrhagic infarction (*PHI*). The fibre connections that may become involved, arise from *1* the thalamus (*Th*), *2* the contralateral hemisphere via the corpus callosum, *3* the ipsiateral hemisphere, and synapse initially on subplate neurons (*4*). Corticofugal projections are shown in *red*. Premyelinating oligodendrocytes (*pOls*) ensheathe axons before full differentiation to mature myelin-producing oligodendrocytes. *GE* ganglionic eminence, *GP* globus pallidus, *P* putamen, *SVZ* subventricular zone (After Volpe 2009)

Hewitt (1961) found the earliest sign of the internal capsule (probably the thalamocortical component; Yamadori 1965) in stage 18 (13–17-mm CRL). Humphrey (1960) studied the ingrowth of the corticospinal tract into the brain stem and spinal cord with a silver technique (Fig. 1.37). The pyramidal tract reaches the level of the pyramidal decussation at the end of the embryonic period, i.e. at 8 weeks of development (Müller and O'Rahilly 1990c). Pyramidal decussation is complete by 17 weeks of gestation, and the rest of the spinal cord is invaded by 19 weeks (lower thoracic cord) and 29 weeks (lumbosacral cord) of gestation (Humphrey 1960). Owing to this long, protracted development, ***developmental disorders*** of ***the pyramidal tract*** may occur over almost the entire prenatal period, and may include aplasia, hypoplasia, hyperplasia, secondary malformations due to destructive lesions, anomalies of crossing and disorders of myelination (ten Donkelaar et al. 2004). Aplasia of the pyramidal tracts is characterized by the absence of the pyramids (Chap. 6).

Fibre tracts that appear early in development generally undergo myelination before later-appearing tracts (Flechsig 1920; Yakovlev and Lecours 1967; Gilles et al. 1983; Brody et al. 1987; Kinney et al. 1988; Gilles and Nelson 2012; Fig. 1.38). **Myelination** in the CNS is undertaken by oligodendrocytes, and a very slow process. The presence of myelin has been noted in the spinal cord at the end of the first trimester and proceeds caudorostrally. The motor roots preceed the dorsal roots slightly. In the CNS the afferent tracts become myelinated earlier than the motor pathways. In the brain stem, myelination starts in the flm at eight postovulatory weeks. The vestibulospinal tracts become myelinated at the end of the second trimester, whereas the pyramidal tracts begin very late (at the end of the third trimester), and myelination is not completed in them until about 2 years (Fig. 1.39). Cortical association fibres are the last to become myelinated. The appearance of myelin in MRI lags about 1 month behind the histological time tables (van der Knaap and Valk 1995; Ruggieri 1997). As judged from relative signal intensities, myelin is present at 30–34 weeks of development in the following structures (Sie et al. 1997; van Wezel-Meijler et al. 1998): the medial lemniscus, the superior and inferior colliculi, the decussation of the superior cerebellar peduncles, the crus cerebri, the ventrolateral thalamus, the lateral globus pallidus and dorsolateral putamen, the dentate nucleus, the middle and superior cerebellar peduncles, the vermis, the cortex around the central sulcus and the hippocampus. Between 34 and 46 weeks, myelin appears in the lateral part of the posterior limb of the internal capsule and the central part of the corona radiata; therefore, at birth the human brain is rather immature in regard to the extent of its myelination. The rate of deposition of myelin is greatest during the first two postnatal years (van der Knaap and Valk 1990, 1995). On MR images, a significant decrease in water content leads to a decrease in longitudinal relaxation times (T1) and transverse relaxation times (T2). Consequently, 'adult-like' appearance of T1-weighted and T2-weighted images becomes evident towards the end of the first year of life. Age-related changes in white matter myelination continue during childhood and adolescence (Paus et al. 2001).

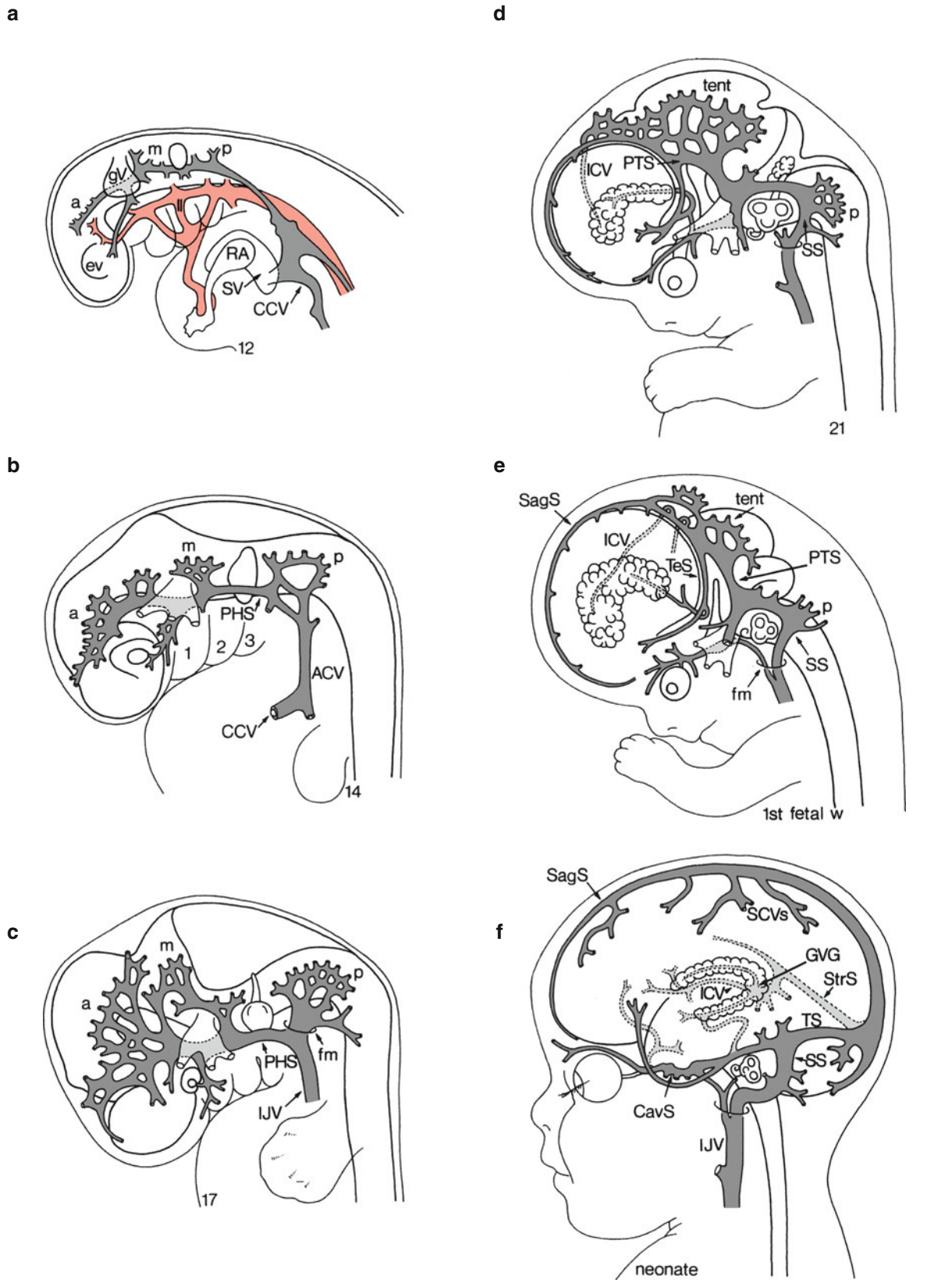

Fig. 1.36 Development of the venous system of the human brain from stage 12 until the neonatal period. Veins are in *grey*, early arteries in *red. a* anterior capital plexus, *ACV* anterior cardinal vein, *CavS* cavernous sinus, *CCV* common cardinal vein, *ev* eye vesicle, *fm* foramen magnum, *GVG* great vein of Galen, *ICV* internal cerebral vein, *IJV* internal jugular vein, *m* middle capital plexus, *p* posterior capital plexus, *PHS* primary head sinus, *PTS* primitive transverse sinus, *RA* right atrium, *SagS* sagittal sinus, *SCVs* superior cerebral veins, *SS* sigmoid sinus, *StrS* straight sinus, *SV* sinus venosus, *tent* tentorial plexus, *TeS* tentorial sinus, *TS* transverse sinus, *II* second aortic branch, *1*, *2*, *3* pharyngeal arches (After Streeter 1918; Padget 1957)

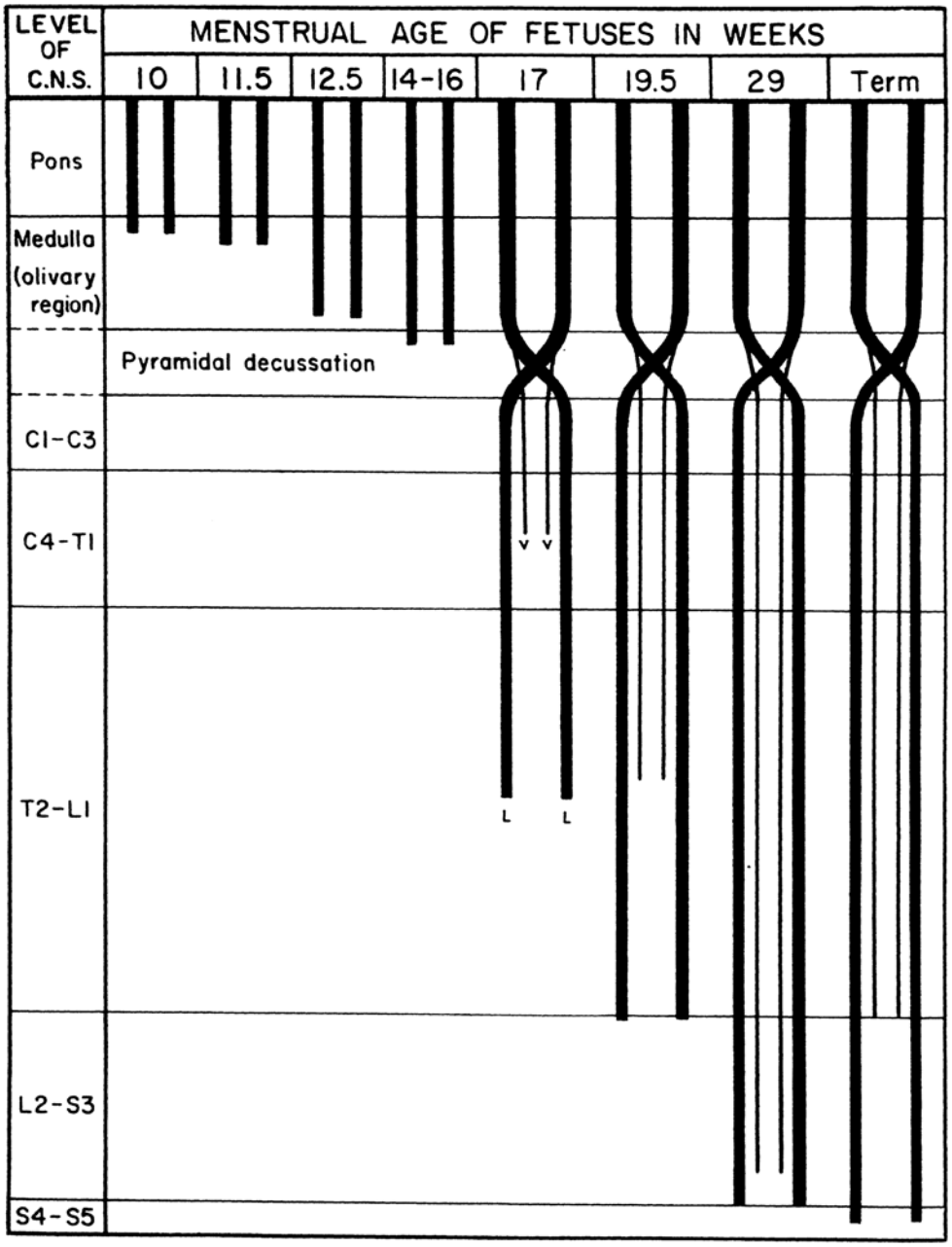

Fig. 1.37 The outgrowth of the human corticospinal tracts (After Humphrey 1960)

With **diffusion tensor imaging** (**DTI**), a novel branch of MRI, anatomical components can be delineated with high contrast and revealed at almost microscopical level (Mori et al. 2005; Catani and Thiebaut de Schotten 2012). Huang et al. (2006, 2009) analyzed DTI data of fixed second-trimester human fetal brains. DTI tractography revealed that important white matter tracts, such as the corpus callosum, the uncinate tract and the inferior longitudinal fascicle, become apparent during this period. Three-dimensional reconstruction of white matter tracts of postmortem fetal brains of 13, 15 and 19 weeks are shown in Fig. 1.40. Vasung et al. (2010) further analyzed the development of axonal pathways in the human fetal fronto-limbic brain, combining histochemical data and DTI (Chap. 10). The DTI technique can also be applied to congenital brain malformations (Wahl and Mukherjee 2009).

Prenatal motor behaviour has been analysed in ultrasound studies. The first, just discernable movements emerge at 6–7 weeks' postmenstrual age (Ianniruberto and Tajani 1981; de Vries et al. 1982; de Vries and Fong 2006, 2007). About 2 weeks later, movements involving all parts of the body appear. Two major forms of such movements can be distinguished, the startle and the general movement (Hadders-Algra and Forssberg 2002). The first movements

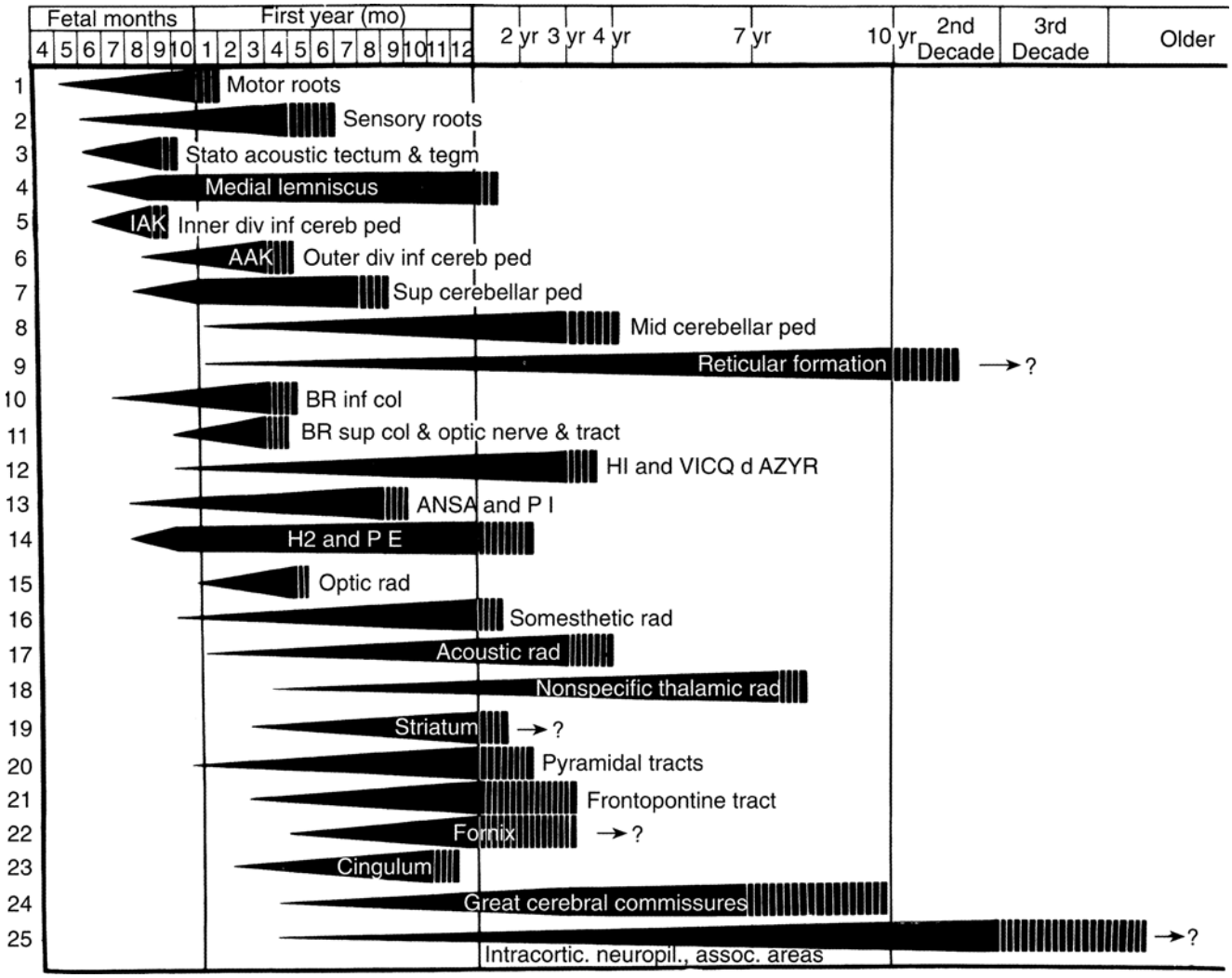

Fig. 1.38 Development of myelination of the main fibre tracts in the human CNS (From Yakovlev and Lecours 1967)

appear prior to the formation of the spinal reflex arc, which is completed at 8 weeks' postmenstrual age (Okado and Kojima 1984). This means that the first human movements, just like those of chick embryos (Hamburger et al. 1966), are generated in the absence of afferent information. During the following weeks, new movements are added to the fetal repertoire such as isolated arm and leg movements, various movements of the head, stretches, periodic breathing movements and sucking and swallowing movements (de Vries et al. 1982; de Vries and Fong 2006, 2007). Arm and leg movements, just like the palmar and plantar grasp reflexes, develop at 9–12 weeks, suggesting that fetal motility develops without a clear craniocaudal sequence. The age at which the various movements develop shows considerable interindividual variation, but at about 16 weeks' postmenstrual age all fetuses exhibit the entire fetal repertoire. This repertoire continues to be present throughout gestation (Hadders-Algra and Forssberg 2002; Kurjak et al. 2009; Salihagic-Kadic et al. 2009). If these movements are diminished or even absent due to cerebral, spinal, nervous or muscular defects, the ***fetal akinesia deformation sequence*** occurs (Moessinger 1983), the phenotype of which was first described as Pena-Shokeir phenotype. This phenotype is characterized by multiple joint contractures, limb pterygia, lung hypoplasia, short umbilical cord, craniofacial deformities, growth retardation, hydrops and polyhydramnios (Hall 1986). The fetal akinesia sequence has been detected by ultrasound as early as 13 weeks of gestation owing to cerebral deformities leading to hydranencephaly (Witters et al. 2002) and at 16 weeks of gestation in a case of muscular origin (Lammens et al. 1997; see also Chap. 6). One of the most promising advances in the field of ultrasonography has been the invention of the new 4D-ultrasound technology (Lee 2001), giving visualization of the intrauterine neurological condition in almost real-time (Kurjak et al. 2009).

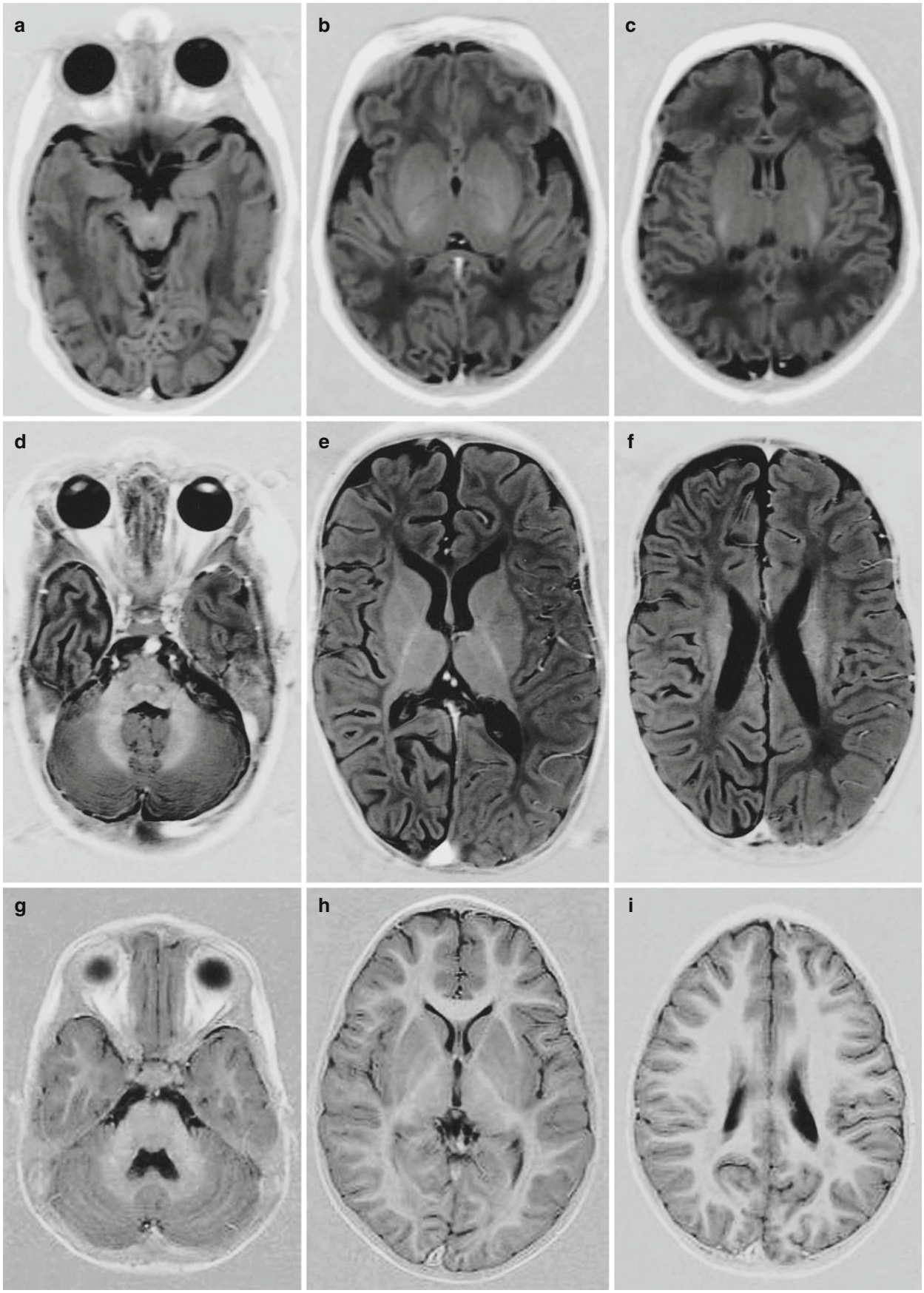

Fig. 1.39 Myelination in T1-weighted horizontal (or axial) images of a newborn (**a**–**c**), a child of 1.5 years of age (**d**–**f**) and a young adult (**g**–**i**). In (**a**) myelination is visible in the decussation of the brachia conjunctiva, and in (**b**) and (**c**) in the posterior limb of the internal capsule. Myelination is far more advanced in the pictures of the infant (**d**–**f**)

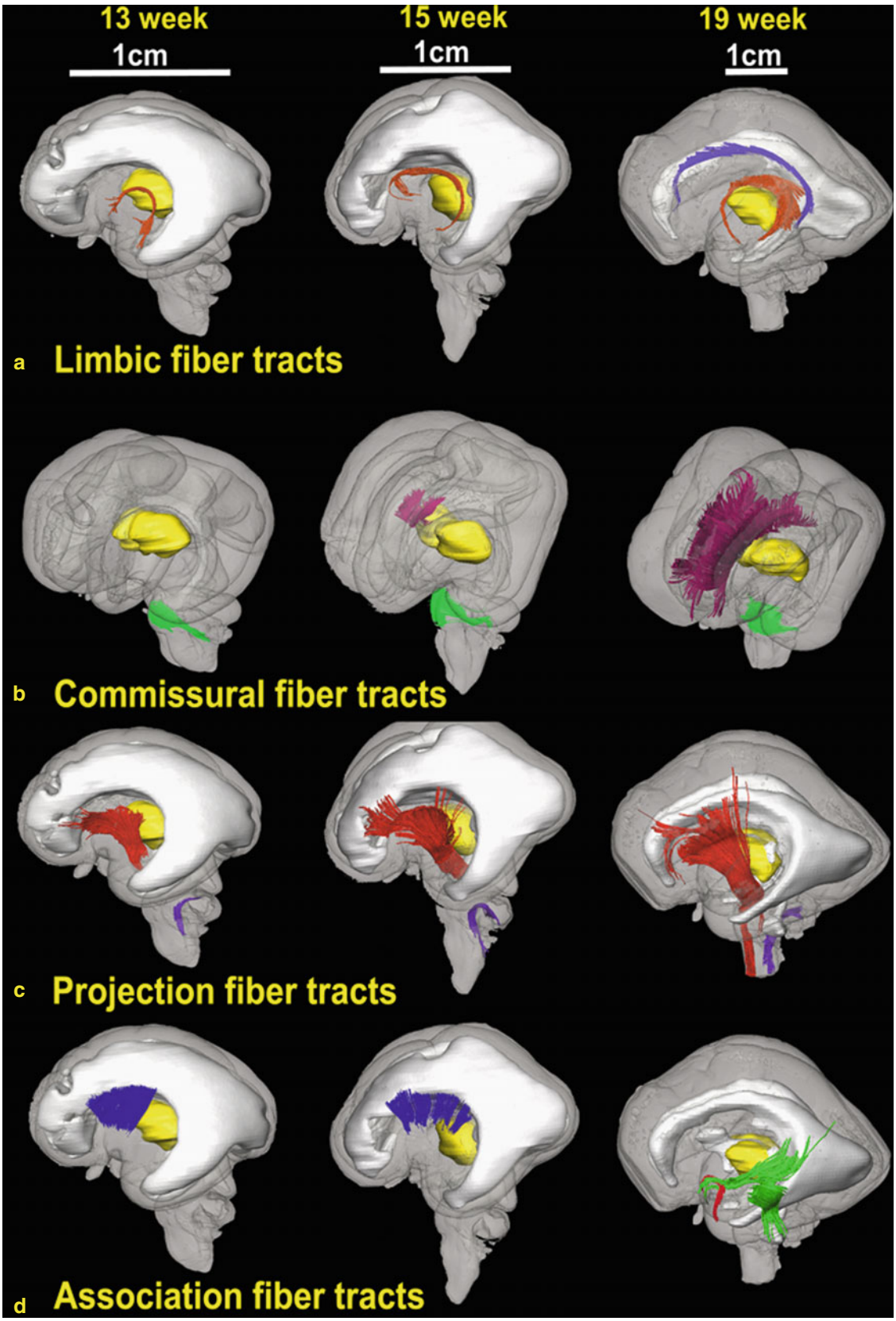

Fig. 1.40 3D depiction of the development of white matter tracts in 13-, 15- and 19-week-old brains. (**a**) Lateral views of limbic tracts with the fornix and stria terminalis in *pink* and the cingulum bundle in *purple*; (**b**) oblique views of commissural fibres with the corpus callosum in *pink* and the middle cerebellar peduncle in *green*; (**c**) lateral views of projection fibres with the cerebral peduncle in *red* and the inferior cerebellar peduncle in *purple*; (**d**) lateral views of association tracts with the extreme capsule in *blue*, the inferior longitudinal fasciculus/inferior fronto-occipital peduncle in *green* and the uncinate fasciculus in *red* (From Huang et al. 2009; kindly provided by Hao Huang; reproduced with permission from the Society for Neuroscience)

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