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CNS development: An overview

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Abstract
The basic principles of the development of the central nervous system (CNS) are reviewed, and their implications for both normal and abnormal development of the brain are discussed. The goals of this review are (a) to provide a set of concepts to aid in understanding the variety of complex processes that occur during CNS development, (b) to illustrate how these concepts contribute to our knowledge of the normal anatomy of the adult brain, and (c) to provide a basis for understanding how modifications of normal developmental processes by traumatic injury, by environmental or experiential influences, or by genetic variations may lead to modifications in the resultant structure and function of the adult CNS.

The human central nervous system (CNS) is, without a doubt, the most complex organ in the body, and the processes involved in its development are commensurately complex. These processes are often treated in a cursory fashion in the early chapters of developmental psychology textbooks, and, as a result, the changes in the "hardware" that occur as cells make and become the adult brain are poorly understood by nonspecialists. The recognition that these changes place constraints on behavioral development is now well recognized, and the nature versus nurture controversy that pervaded biology and psychology in years past has now come to deal with the fact that external influences on the organism can only change behavior by modifying the development of the brain in some way (i.e., that nature and nurture interact). Thus, the current focus of this controversy in this field is directed toward understanding the contributions of processes *intrinsic* to the CNS, such as genes, cell–cell interactions, etc., relative to the contributions of influences from *extrinsic* sources, such as behavioral experience, trauma, nutrition, hormonal states, etc. In other words, in contemporary neurobiology the issue is not whether nature or nurture is the major contributor but which contributes what to the development of specific structures and areas. For the developing CNS, this analysis continues on a variety of levels ranging from the level of the organism (influences intrinsic to the organism vs. influences from the environment), through the level of the organ (influences intrinsic to the brain vs. influences from elsewhere in the body), through the level of a given structure (influences intrinsic to one brain structure vs. influences from other parts of the brain), to the level of interactions between cells (influences intrinsic to a single cell vs. influences on that cell from other cells).

Clearly, the links between the biological processes occurring during CNS development and behavioral pathologies or behavioral capacities exhibited by adults or during behavioral development are not easy to establish. However, although it may not be intuitively obvious, the only way that diversity in the

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structure of the brain can be generated during development is to modify one or more of the basic developmental processes of cell proliferation, cell migration, cell differentiation, or cell death. Thus, in order to arrive at an understanding of how a modification in a developmental process exerts its influence on a particular behavior, it is necessary to understand where the developmental process is being modified (e.g., which kinds of cells and in which part of the brain), how the structure (e.g., the "wiring," etc.) of the mature brain will be changed, and also how the structural changes that are produced will change the ability of the brain to process the information it confronts during a complex behavioral task (for a review see Nowakowski, 1987)). Therefore, in this review the relationship between the basic organization of the embryonic CNS and the adult CNS will be described in order to provide a useful and, by necessity, simplified set of principles for understanding the complex anatomy of the adult brain. Also, the special embryological mechanisms that are involved in generating the diversity that characterizes the adult CNS will be reviewed in order to provide a set of concepts to aid in understanding the variety of complex processes occurring during CNS development. Finally, included in this discussion will be examples describing how modifications of the normal development of the CNS by traumatic injury, by environmental and experiential influences, and by genetic variation may affect and modify the development of the CNS and thereby influence the resultant structure and function of the adult CNS. (Note, however, that the effects of early behavioral experience will not be discussed.) It cannot be emphasized too strongly that the kind of modifications resulting from any particular intervention are directly related to (a) *what* is happening in the developing CNS at the time that the intervention occurs and (b) *which* cell types and developmental processes are affected by the intervention.

The Problem and Its Magnitude

Perhaps the most perplexing aspect of the organization of the CNS is the fact that each division and subdivision of the brain has its own characteristic structure and function. The problem faced by the neuroembryologist is to try to understand (a) how this tremendous diversity in form is generated and (b) how each portion of the CNS is integrated into the whole to produce a functional entity. Clearly, these are not trivial issues, especially since modern biology requires that they be addressed not only in terms of relatively gross changes in the architecture of the developing CNS but also in terms of the "behavior" of its cellular constituents and of changes in gene expression within the cells.

The magnitude of this problem is at least partially reflected in the facts that there are between 10 and 20 billion (i.e., approximately 10^{10}) neurons in the cerebral cortex alone of an adult human brain (N.B., this is *not* the whole brain) and 5–10 times as many glial cells (Blinkov & Glezer, 1968). Although the glial cells certainly contribute in important ways (Kuffler, Nicholls, & Martin, 1984), it is the diversity in shape, form, and interconnections of the neurons that is ultimately responsible for the ability of the CNS to process all of the various sorts of information that it confronts every minute of every day, and any changes in these properties of neurons will alter function. For this reason, the "life history" of the neurons of the CNS is of primary importance in understanding CNS development because the neurons are the components that are "assembled" into a information processing network that controls function. In particular, it is important to define the common features, influences, and capabilities of the differentiating neurons of the CNS. As is true in any developmental analysis, the elucidation of such similarities provides a set of "concepts" or "rules" that make understanding a complex system easier.

Another reflection of the importance of these issues is that the recent advances in molecular genetics have identified numerous genes that are expressed in the developing brain and that control CNS development. These advances have in the past few years dramatically changed our understanding of CNS development and the relationship of genetics to normal and abnormal development.

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This progress will certainly accelerate in the future, and the basis of this progress is a firm foundation of the understanding of normal development.

The Basic Questions

The assembly of the brain from its component parts can be conceptualized using a simple metaphor: the building of a house. The parallels are (a) the genome serves as the blueprint for the brain; (b) the neurons and glia serve as the bricks and mortar, lumber, etc., and (c) axons, dendrites, and synaptic connections among neurons serve as the wiring for electricity, telephone, etc. Just as in the construction of a house, events and processes must occur in a particular sequence and at particular times. Thus, a framework for understanding CNS development is provided by a set of simple questions: *When? Where? What?* Answers to these questions provide a reasonably complete description of the phenomena underlying CNS development. They do not come simply, however, because there are multiple and simultaneously occurring processes that must be considered. Furthermore, the answers are the essential background needed to ask another "simple" question: *How*? Or, how are processes during CNS development controlled? How do cells and cellular interactions influence the fate of other cells? How is gene expression controlled? How does the maturation of one region of the CNS affect the maturation of other regions of the CNS? In the following paragraphs these four simple questions—*When? Where? What?* and *How?*—will be used to describe the major issues confronted by contemporary neuroembryologists. When possible, relevant work in human development will be cited.

When: A Question of Time and Timing

In a developmental sense there are two aspects of "when" — the absolute time that an event occurs and the time relative to other events. The absolute time frame of development for both humans and most experimental animals is usually measured as days (or some other convenient unit) after conception and days after birth. The gestation periods of humans and, for comparison, some common laboratory animals are listed in Table 1. Sometimes, however, staging systems are used for greater precision in order to reduce problems resulting from differences in diet or environment, different rates of development in various strains, or simply because some species develop rapidly. Staging systems are based on readily observable features of the embryo (eye opening, fusion or separation of fingers and toes, etc.). For the staging of human embryos and fetuses the same principles apply except that gestation is generally measured from the time of occurrence of the last menstrual period rather than from the day of conception. With this method human gestation is considered to be 40 weeks long, even though the conceptus is present for only 38 weeks, and the gestation period of humans is generally divided into trimesters each lasting about 13 weeks. The staging system for human embryos and fetuses (Olivier & Pineau, 1961) relies upon easily measurable features such as greatest length (GL) or crown-to-rump length (CRL).

It is of great significance that the development of the human CNS is not confined to the gestational period. For example, during the intrauterine period the brain grows from nothing to about 350 g (Blinkov & Glezer, 1968). During this period, most of the neurons of the CNS are produced (see below). However, after birth the brain continues to grow, reaching a size of about 1350 g at 20 years of age (Blinkov & Glezer, 1968). Most of the postnatal growth occurs within the first 3 or 4 years after birth (Blinkov & Glezer, 1968), but changes in myelination (Yakovlev & Lecours, 1967) and in other measures (cortical surface area, numbers of glial cells, etc.) continue to be apparent even 70 to 80 years after birth (Blinkov & Glezer, 1968). While this review focuses on the early prenatal period of CNS development, it should be emphasized that the time of birth is not correlated with most measures of the maturity of the CNS. This means, for example, that events occurring prenatally in some species may occur postnatally in another species. One example of this variation is the maturation of the cere-

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Table 1. *Developmental period of various species*

Species	Length of Relevant Developmental Period	Staging System
Xenopus	—[a]	Nieuwkoop & Faber (1956)
Frog (*Rana pipiens*)	—[a]	Shumway (1940)
Chick	21 days[b]	Hamburger & Hamilton (1951)
Mouse	19 days	Theiler (1972)
Rat	21–22 days	—
Chinese hamster	13 days	—
Rhesus monkey	165 ± 5 days[c]	—
Human	40 weeks after last menstrual period (38 weeks after conception)	Streeter (Olivier & Pineau, 1961; O'Rahilly, Muller, Hutchins, & Moore, 1984)

[a]Absolute times are rarely used for these species because the rate of development is too dependent upon the ambient temperature.
[b]The early development of the chick embryo is so rapid that the staging system of Hamburger and Hamilton is invariably used.
[c]From Macdonald (1971).

bral cortex. In rats and mice most of the cells destined to comprise the cerebral cortex are generated during the second half of gestation, ending only a few days before birth (Angevine, 1965; Berry & Rogers, 1965; Miller, 1985). In contrast, in monkeys and humans these same events are completed about the time of the end of the second trimester, well before birth (Kostovic & Rakic, 1980; Rakic, 1974, 1975b). For this reason, it is critical to consider the species being examined before a general conclusion is made.

The *relative timing* or sequence of occurrence of events is a second critical component of "when." The general principle is that development occurs as a cascade of events and that any one event *may* influence those that follow it but not those that precede it. Knowledge of the order of occurrence of developmental events can provide information about the presence or absence of a causal relationship between the two events. Relative timing can be thought of as a simple cascade of events, such as A → B → C (Figure 1A). If event A occurs before event B, then it is possible for A to influence B but *not* for B to influence A (Figure 1B). In addition, events that occur simultaneously can influence each other (Figure 1C). Thus, although additional evidence other than relative timing is needed to establish if events are in a cascade, rather than simply in sequence, relative timing can be used

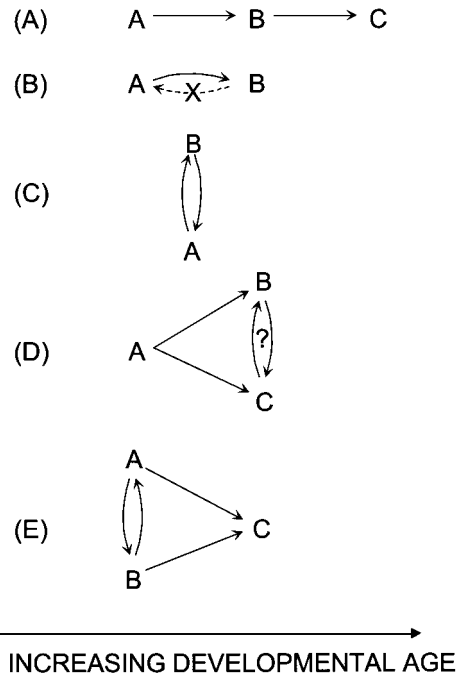


Figure 1. Examples of how events during development influence each other in different ways. (A) Events which follow each other in a sequence can be causally related. (B) A late-occurring event cannot influence an event occurring earlier. (C) Two events occurring at the same time can influence each other. (D) One early-occurring event can influence two (or more) events occurring later, which may or may not influence each other. (E) One event may be dependent on the interaction of two (or more) events occurring earlier.

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to eliminate events from a cascade. In other words, the fact that A precedes B and C does not necessarily mean that A influences either B or C. In addition, cascades are not necessarily simple or direct; one early-occurring event can influence two or more later-occurring events which may or may not interact (Figure 1D), or two early-occurring events might need to interact in order for some later event to occur (Figure 1E). A general corollary to the cascade concept is that the earlier during development that a particular event occurs, the greater is its *potential* influence on subsequently occurring events and the greater the likelihood that it will have a greater effect on the adult structure than the disruption of a later occurring event. For example, if A is the production of neurons and B is the subsequently occurring process of neuronal cell death, then both events A and B influence the total *number* of neurons in the adult animal. Additional events (C, D, etc.) could also affect neuron number, but *only events occurring prior to or during* the time that event A occurs could affect neuron number by affecting cell proliferation. It is, perhaps, useful to emphasize that a large number of "events" influence the development of any given region of the nervous system and even of any given cell type and that it is the summation of these events which produces the mature, functioning whole. In addition, there may be interaction between and among various regions of the brain.

A potentially important use for the knowledge of *when* something occurs is to corroborate or eliminate possible biological bases for behavioral critical periods. For example, Greer, Diamond, and Tang (1982) have shown that an enriched behavioral experience during the developmental period can increase cell number in the adult rat neocortex. It is known that the cells comprising the adult neocortex are generated *before* this critical period. This knowledge definitively eliminates an influence on cell proliferation as being responsible; the likely mechanism is, therefore, a reduction in cell death (i.e., hypothanasia; Hollyday & Hamburger, 1976). Cell death is a normal aspect of CNS development and is found in most regions (Oppenheim, 1991) including the neocortex (Finlay & Slattery, 1983; Thomaidou, Mione, Cavanagh, & Parnavelas, 1997). More recent experiments have shown that behavioral experience can modify *both* cell proliferation and decreased cell death (i.e., increased survival) in the dentate gyrus (Kempermann, Brandon, & Gage, 1998; Kempermann, Kuhn, & Gage, 1997b), a structure in which cell proliferation continues even in the adult (Kempermann, Kuhn, & Gage, 1997a). Knowledge of the time that something occurs is also important when assessing the possible trauma of events such as the development of a tumor (Gilles, 1985), malnutrition (Morgane et al., 1993; Smart, 1991), or exposure to alcohol (Luo & Miller, 1998) or radiation (Otake & Schull, 1984). For the last example mentioned, a particularly striking relationship has been shown between mental retardation in children who were exposed in utero to the high radiation levels associated with the atomic bombs dropped on Hiroshima and Nagasaki and the *gestational age* of the children at the time of the exposure. Otake and Schull (1984) showed that during a critical period lasting from the 8th to the 15th week of gestation the risk of developing mental retardation later in life was directly proportional to the dose of radiation received. However, for embryos exposed before the 8th week there was no risk of developing mental retardation, and for embryos exposed after the 15th week the risk of developing mental retardation was less than one-fifth that of the risk associated with the critical period. The time of occurrence of this critical period allowed Otake and Schull (1984) to hypothesize that the proliferation and migration of neurons destined for the cerebral cortex were severely compromised by the radiation (see below for a description of these processes).

Where: The Three Dimensions of the Neural Tube

An analysis of the structural and functional diversity of the various subdivisions of the CNS requires that at different times during development each subdivision be recognizable and localizable for analysis. Consequently, *where* in the CNS a particular event

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occurs is defined by regional variation in development that delineates subdivisions. This is useful because (a) developmental subdivisions precede and presage functional subdivisions and (b) it becomes somewhat easier to understand the organization of the adult CNS once the organization of the simpler, developing CNS is understood. The three dimensions of the CNS are defined in the neural tube, the end result of the process of neurulation which marks the earliest appearance of the CNS in the embryo (Figure 2A–C). The neural tube, like any other tube, has three dimensions: a longitudinal dimension or length, a circumferential or tangential dimension, and a radial or laminar dimension (Figure 2D). During subsequent development the cavity of the neural tube becomes the ventricles of the brain and the central canal of the spinal cord. Differentiation of the wall of the neural tube along these three dimensions is a useful way to conceptualize the primitive organization of the mammalian CNS (Figure 2D). Along the length of the neural tube the major divisions of the nervous system are produced; around its circumference functionally distinct subdivisions within each division arise; and along the radial dimension, the wall of the neural tube develops laminae or layers that are distinct for each subdivision.

Differentiation along the longitudinal dimension

Already at the time of neurulation the head and tail ends of the embryo have been determined, and, in fact, neurulation proceeds at different rates in the different parts of the neuraxis. Eventually about 50% of the tail or caudal end of the neural tube becomes the spinal cord, which is organized segmentally in repeated units (called segments), each of which is associated with the sensory and motor innervation of a small part of the body. The head or cephalic portion of the neural tube becomes the brain. Most of the head or cephalic portion of the neural tube acquires a suprasegmental organization, which means (a) that its organization does not repeat, and (b) that a substantial portion of its innervation and output is not devoted to or derived from a single body seg-

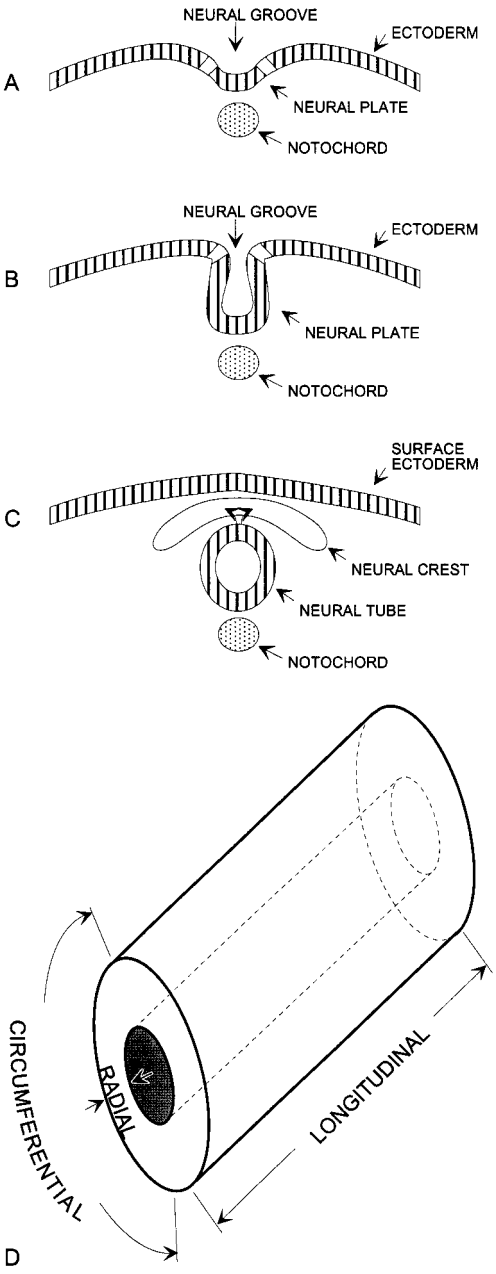


Figure 2. Neurulation. The process of neurulation begins at the end of the 3rd week after conception. During the next few days the outer surface of the embryo (or ectoderm) folds in upon itself to form the neural tube. (A) At the beginning of neurulation a shallow groove appears to mark the position of the neural plate. (B) Subsequently, the groove deepens, and (C) the lateral edges of the neural plate fuse to become the neural tube. A small group of cells just lateral to the edge of the neural plate and some cells from the dorsalmost portion of the neural tube (arrows in C) become the neural

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ment but rather provides input to and receives output from the segmental parts of the nervous system. It should be noted that the brainstem (i.e., the adult medulla, pons, and midbrain), which develops from intermediate portions of the neural tube, acquires a pattern of organization which is in part segmental (i.e., the motor and sensory components of the cranial nerves) and in part suprasegmental. The molecular basis of the segmental organization of the brainstem and spinal cord has been shown to lie, in part, in the segmentally restricted expression of numerous genes from the Hox and other gene families (Lee & Jessell, 1999; Lumsden & Krumlauf, 1996; Rubinstein & Shimamura, 1997; Studer, Lumsden, Ariza–McNaughton, Bradley, & Krumlauf, 1996).

In humans, it is the cephalic portions of the neural tube that grow tremendously, and this disproportionate emphasis of the suprasegmental portions of the neural tube is referred to as "encephalization." Even before the closure of the neural tube is complete, the cephalic end of the neural tube differentiates into three primary vesicles (i.e., "bulges") that form from its wall (see Figure 3). From rostral-to-caudal (i.e., from front-to-back, literally "beak-to-tail") these vesicles are (a) the prosencephalon or forebrain, (b) the mesencephalon or midbrain, and (c) the rhombencephalon or hindbrain (Table 2). Subsequently, the prosencephalon becomes subdivided into the telencephalon and the diencephalon, and the rhombencephalon becomes subdivided into the metencephalon and myelencephalon,

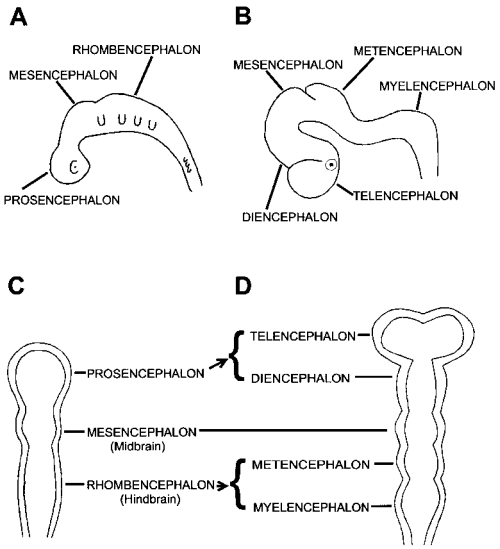


Figure 3. Longitudinal differentiation of the neural tube. (A) A drawing of a lateral view of the brain of a 4-week-old human embryo. This is only shortly after neurulation, and already the three primary brain vesicles (the prosencephalon, mesencephalon, and rhombencephalon) are present. (B) A drawing of a lateral view of the brain of a 5-week-old human embryo. At this age the prosencephalon has become divided into the telencephalon and diencephalon, and the rhombencephalon has become divided into the metencephalon and myelencephalon. (C) A stretched-out and cut-away dorsal view of the 4-week-old brain. (D) A stretched-out and cut-away dorsal view of the 5-week-old brain.

thereby forming *five* secondary vesicles. In the human embryo, these five secondary vesicles are already recognizable at the 5th week of gestation (Hochstetter, 1919). Thus, at a very early stage in development the major structural subdivisions of the adult brain are defined by these vesicles. In fact, their names are used to refer to parts of the adult brain. Examples of major adult structures derived from each of these secondary vesicles are (a) the cortex, derived from the telencephalon; (b) the thalamus and hypothalamus, derived from the diencephalon; (c) the midbrain, derived from the mesencephalon; (d) the pons and cerebellum, derived from the metencephalon; and (e) the medulla, derived from the myelencephalon.

Once these basic longitudinal subdivisions have appeared, each of them is subsequently

crest. The neural tube is the forerunner of the central nervous system (i.e., the brain and spinal cord), whereas the neural crest cells produce most of the peripheral nervous system. Together the neural tube and the neural crest are often referred to as the neuroectoderm. (D) Once closed the neural tube, just like any other tube, can be considered to have three dimensions: length or a longitudinal dimension, a circumferential or tangential dimension, and a radial dimension. Differentiation of the neural tube along these three dimensions is a useful way to conceptualize the primitive organization of the mammalian CNS. See the text for further details.

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Table 2. *The "encephalons"*

Prosencephalon:	"forebrain"	= *proso,* forward + *enkephalos*
Telencephalon:	"endbrain"	= *telos,* end + *enkephalos*
Diencephalon:	"throughbrain"	= *dia,* through or across + *enkephalos* (Many ascending and descending pathways cross or pass through the diencephalon on their way to or from the telencephalon.)
Mesencephalon:	"midbrain"	= *mesos,* middle + *enkephalos*
Rhombencephalon:	"rhombic-brain"	= *rhombos,* rhombic + *enkephalos* (At this level of the brain, the ventricle is shaped like a rhombus.)
Metencephalon:	"afterbrain"	= *meta,* after or post + *enkephalos*
Myelencephalon:	"medulla"	= *myelos,* marrow + *enkephalos* (The spinal cord is the marrow of the vertebral column and the medulla is the spinalmost portion of the brain.)

Note: At first, the names of the subdivisions of the embryonic brain seem formidable, but an examination of their root meanings facilitates becoming comfortable with their usage. In all cases, the second part of the name is derived from the Greek word *enkephalos* (*en,* in + *kephalos,* head). Each prefix has a similarly descriptive root that is derived either from its relative position in the neural tube or some other salient feature. See Figure 3.

modified by further differentiation in the other two dimensions of the neural tube. However, developmental *errors* in neural tube closure and in the subsequent longitudinal parcellation of the nervous system lead to profound disturbances of the nervous system, presumably because these are among the earliest events of CNS development. The closure of the neural tube begins in the vicinity of the future medulla and pons and moves downward and upward from there (sort of like a zipper). Thus, the two most common places for the failure of the neural tube to close are at its two ends (i.e., in the spinal cord and prosencephalon; Friede, 1989). When the neural tube fails to close at the caudal end, a severe form of spina bifida known as rachischisis occurs. In rachischisis, the spinal cord, the vertebrae, and the overlying skin are malformed such that the central canal of the spinal cord (i.e., the cavity of the neural tube) is open (Friede, 1989). As a result, this malformation is detectable by ultrasonography or by measurement of serum alpha-fetoprotein (Bell & Gosden, 1978). Rachischisis is the result of a very early failure of neural-tube closure; later closure failures result in less deleterious forms of spina bifida (Friede, 1989). Similar malformations occurring at the rostral end of the neural tube result in anencephaly, which is a malformation in which the derivatives of the prosencephalon do not form (Friede, 1989).

Differentiation in the circumferential or tangential dimension

Specializations also develop *circumferentially* around the neural tube (i.e., *tangential* to its surface; Figure 4). The significance of this circumferential differentiation is that (a) it *precedes* the *functional* organization of the CNS into sensory and motor subdivisions and other functional subdivisions, and (b) it reflects developmental processes that extend beyond the borders of any single longitudinal subdivision. These specializations are most easily described for the future spinal cord, which can be divided into four circumferentially defined zones or "plates" (Kingsbury, 1922): the floor plate, paired lateral plates, and the roof plate (Figure 4A). Each lateral plate is usually divided into a basal plate and an alar plate. The adult spinal cord (Figure 4B) is derived primarily from the alar and basal plates, which become the dorsal and ventral horns of the spinal cord, respectively. The pattern formation underlying the circumferential divisions of the spinal cord occurs early during development, concomitant with neurulation. The first step is the induction of neural tube formation by signals arising from the notochord and other mesodermal structures (Figure 2A). Chief among these signals is a molecule called "sonic hedgehog" (shh) that induces the formation of the floor plate and initiates a cascade of events that acts to

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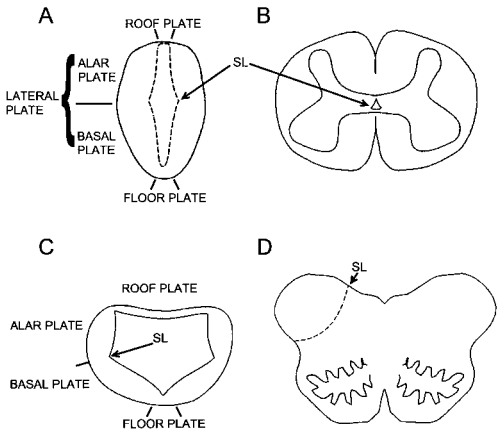


Figure 4. Circumferential differentiation of the neural tube. (A,B) The circumferential zones or "plates" are best seen in the developing spinal cord, where there are four of them: a floor plate, two paired lateral plates, and a roof plate. Each lateral plate is usually divided at the sulcus limitans into a basal plate and an alar plate, which become the motor and sensory portions of the spinal gray, respectively. The names of these plates are derived from their positions around the tube (*alar* is derived from the Latin word *ala,* "wing"). (C,D) In the medulla, the roof plate becomes wide and attenuated and displaces the alar and basal plates laterally. Nevertheless, the sulcus limitans continues to mark the border between the basal and alar plates; in the adult, the morphological relationship between the sensory and motor derivatives of these two plates is similar to that found in the spinal cord, except that they are displaced laterally by the extension of the roof plate, and, thus, their relationship shifts from dorsoventral in the spinal cord to lateromedial in the medulla.

assign a "ventral" fate to the cells of the floor and basal plates (Dodd, Jessell, & Placzek, 1998; Lee & Jessell, 1999; Tanabe & Jessell, 1996). As the neural tube closes, other signaling factors are secreted by the cells of the overlying ectoderm that is first lateral to the neural plate and then overlies the neural tube (Figure 2A–C). These factors include members of the bone morphogenetic protein family (the "BMPs") which act on the roof plate (and may also be propagated by it) and the adjacent portions of the alar plate to induce a cascade of responses that leads to the specification of "dorsal" fates in these cells and their progeny (Lee & Jessell, 1999). It seems that induction by signaling factors arising both ventrally and dorsally is essential for normal spinal cord development (Lee & Jessell, 1999; Tanabe & Jessell, 1996), which is an example of an interaction in a cascade in which distinct early events must both occur and interact for normal development to occur (Figure 1E).

The same four circumferential subdivisions can be identified in the lower brainstem (Figure 4C), and, despite the fact that the roof and floor plates distort the shape of the neural tube, the relationship of sensory and motor functions to the structures derived from alar and basal plate is retained (Figure 4D). In addition, signaling by both ventrally and dorsally derived factors continues to play a role in specifying the fates of neurons in the brainstem including the cerebellum and midbrain (Lee & Jessell, 1999). In contrast, in the prosencephalic derivatives it is difficult to define the extension of the alar, basal, roof, and floor plates (His, 1904; Johnston, 1902; Kingsbury, 1922; Schulte, Von, & Tilney, 1915). However, differentiation in the tangential dimension is still obvious in these regions. For example, in the diencephalon, His (1904) defined three sulci that divide the wall of the diencephalon into four zones that become the epithalamus, dorsal thalamus, ventral thalamus, and hypothalamus, respectively (Kuhlenbeck, 1973; Miura, 1933; Sidman & Rakic, 1982). Similarly, in the telencephalon the archicortex is derived from the medial wall of the lateral hemisphere, the neocortex from the dorsolateral wall, and the paleocortex from the lateral wall of the hemisphere (Kuhlenbeck, 1977; Polyakov, 1949; Sidman & Rakic, 1982). The molecular and cellular interactions that produce these tangential zones is a "hot topic" that, although complicated, is beginning to be revealed by molecular and genetic analysis (Lee & Jessell, 1999; Lumsden & Krumlauf, 1996; Rubinstein & Shimamura, 1997). Indeed, it has been proposed that the combination of molecular markers of longitudinal and tangential subdivisions of the neural tube divide the wall of the neural tube into a gridlike pattern of domains that define a gridlike pattern of fates (Rubinstein & Shimamura, 1997).

Differentiation in the radial or laminar dimension

From the description outlined above, it should be clear that the different areas of the CNS

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are discernible very early during development and that differentiation of the neural tube along its length and circumference defines its basic organizational plan. However, tremendous further refinement in the structure of the CNS must occur before it can be considered to be mature. For the most part, this additional differentiation consists of a series of changes in the radial dimension to produce a variety of laminar schemes in various parts of the neural tube. *What* is happening to produce this variety of lamination patterns in the various parts of the CNS is discussed in the following section.

What: Cellular Actions and Interactions During Development

The question "What is happening in a particular part of the developing CNS at a particular time?" can best be answered in terms of cellular processes. At the simplest level of analysis, there are four of these processes to consider: cell proliferation, cell migration, cell differentiation, and, for some cells, cell death. Needless to say, each of these processes includes a complicated set of events, and the "life history" of any single neuron or glial cell can be traced by considering each of these processes as a developmental "step" through which each cell passes. Thus, as discussed earlier, these steps represent a cascade of developmental events of which the earliest occurring ones may influence the subsequently occurring ones, but the later occurring ones cannot influence the earlier occurring ones. In addition, as will become clear in the descriptions that follow, cell proliferation, cell migration, cell differentiation, and sometimes cell death occur simultaneously in every division and subdivision of the developing CNS. This is simply because different cells in the population are passing through different portions of their life histories at any given time. For this reason, in order to complete the description of CNS development in cellular terms, it is necessary to add the additional concept of intercellular interactions as a way for one cell to influence the fate of another cell. Intercellular interactions can occur between cells in the same state of maturation (e.g., one differentiating cell can influence another) or between cells of different levels of maturation (e.g., a migrating cell can interact with a differentiated cell). In the following paragraphs the processes and events associated with cell proliferation, cell migration, cell differentiation, and cell death are described. Emphasis will be placed on these processes as they apply to neurons, and, in general, the opportunities for intercellular interactions will be pointed out only when especially good examples are known.

Cell proliferation

Most of the neurons of the adult CNS are produced during the prenatal period (Nowakowski, 1987). Shortly after closure of the neural tube, the tube's wall becomes specialized such that the proliferating cells are found surrounding the lumen of the tube (see Figure 5). With only a few exceptions, most of the cells of the CNS are produced by one of two proliferative zones adjacent to the future ventricular system. The first of these two zones to appear is the "ventricular zone" (Boulder Committee, 1970), which is a pseudostratified columnar epithelium (for explanation, see Figure 5). In some parts of the developing CNS the ventricular zone is the only proliferative zone to appear, and, thus, it is reasonable to assume that it produces all of the cell types (Figure 5A–E). In other parts of the developing CNS, however, a second proliferative zone appears (Figure 5F,G). This second zone, known as the subventricular zone, differs in several ways from the ventricular zone (Figure 5). It is attractive to speculate that the subventricular zone is a phylogenetically recently acquired specialization. For example, the hippocampus is classified as an archicortical (i.e., "old" cortex) structure, and the neurons of its major subdivisions (areas CA1, CA2, and CA3) are all derived from the ventricular zone (Nowakowski & Rakic, 1981). In contrast, in the neocortex (i.e., "new" cortex) the subventricular zone is substantial, and, although it is unlikely to contribute large numbers of neurons (Takahashi, Nowakowski, & Caviness, 1995b), it produces glial cells. A similar contrast occurs in the developing diencephalon,

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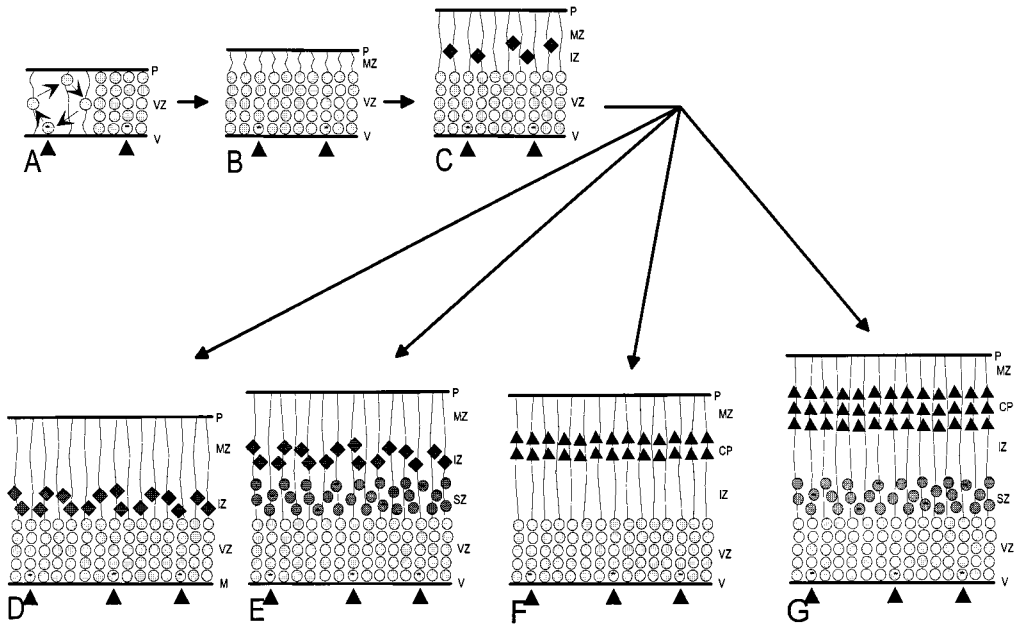


Figure 5. Radial differentiation of the neural tube. (A–C) Schematic diagrams of the early stages of the radial differentiation of the neural tube through which every part of the CNS passes. (D–G) Schematic diagrams of various options for the later stages of the radial differentiation of the neural tube. Each of these options is characteristic of a different part of the neural tube. (A) At the time of closure of the neural tube its wall consists of a population of proliferating cells organized into a pseudostratified columnar epithelium, known as the ventricular zone (VZ). In this proliferative zone the nuclei of the cells are stratified, but each cell has processes that contact the ventricular (V) and pial (P) surfaces of the neural tube. As diagramed on the right-hand side of the drawing, mitosis occurs at the pial surface (asterisks), and during the cell cycle the nucleus of each cell moves to a different level. DNA synthesis, for example, occurs in the outer half of the ventricular zone. This to-and-fro movement of the cell nuclei is known as interkinetic nuclear migration, and means that all cells even though they are apparently at different levels are part of the proliferative population. (B) The next zone to appear during the radial differentiation of the neural tube is the marginal zone (MZ), which is an almost cell-free zone between the ventricular zone and the pial surface. (C) The intermediate zone (IZ), which contains the first postmitotic cells in the nervous system, is the next to form. This zone is located between the ventricular zone and the marginal zone. (D) In some parts of the neural tube, such as the spinal cord, the postmitotic cells derived from the ventricular zone aggregate and mature in a densely populated intermediate zone. (E) In some areas, such as the dorsal thalamus, a second proliferative zone, the subventricular zone (SZ), is formed between the ventricular zone and the intermediate zone. In the subventricular zone, interkinetic nuclear migration does not occur; instead, mitotic figures (asterisks) are found scattered throughout the thickness of the zone. (DNA synthesis also occurs throughout the thickness of the subventricular zone.) The postmitotic cells derived from both the ventricular and subventricular zones aggregate and mature in a densely populated intermediate zone. (Note, however, that any cells derived from the ventricular zone must cross the subventricular zone.) (F) In the hippocampus, the postmitotic cells derived from the ventricular zone migrate across a sparsely populated intermediate zone to form a cortical plate (CP). (G) In the cerebral cortex, postmitotic cells derived from both the ventricular and subventricular zones migrate across a sparsely populated intermediate zone to form a cortical plate.

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in which the hypothalamus lacks a subventricular zone, whereas other diencephalic subdivisions have both ventricular and subventricular zones (Rakic, 1977). The fact that these differences in cell proliferation arise just as the first neurons are being produced (Nowakowski & Rakic, 1981) indicates that one level of functional differentiation, the development of the major subdivisions of the CNS, is well underway even at a very early stage. (In humans this would be occurring during the 2nd month of gestation.)

The cells of the ventricular zone are organized into a pseudostratified epithelium, which means that while the nuclei appear to be at different levels each cell maintains attachments to both the ventricular and pial surfaces. Thus, the proliferating cells of the ventricular zone comprise a proliferative ventricular epithelium (PVE). The nuclei of the PVE move up and down (i.e., ab-and adventricularly) as they move through the cell cycle (Sauer, 1936; Sidman, 1970). At the beginning of the cell cycle (i.e., just as the cell leaves M and enters G1), the nucleus of a PVE cell is located at the ventricular surface (Figure 6). As the cell moves through G1 and enters S, it moves away from the ventricular surface, reaching its maximum distance as it enters S (Takahashi, Nowakowski, & Caviness, 1993; 1996a). The nucleus again moves towards the ventricular surface during G2, and the cell divides during M at the ventricular surface (Figure 6). With each pass through the cell cycle, the cell must decide whether or not it will continue to proliferate and reenter the S phase or stop proliferating to become a postmitotic neuron (a Q cell) and migrate out of the ventricular zone towards its final destination. The dynamics of the cell cycle for both the PVE and the proliferating cells of the subventricular zone in developing neocortex are now well known (Caviness, Takahashi, & Nowakowski, 1995; Takahashi et al., 1995b; Takahashi, Nowakowski, & Caviness, 1995a, 1996b, 1997); studies have shown that during mouse neocortical development the cell cycle progressively lengthens from about 8 hr to about 20 hr during a 6-day period when neurons are being produced (Caviness et al., 1995; Takahashi et al., 1995a, 1995b, 1996b, 1997). Thus, during this 6-day period the cells of the PVE make 11 trips through the cell cycle. In addition, at each pass through the cell cycle the population produces an ever-increasing proportion of postmitotic neurons (Figure 6; Caviness et al., 1995; Takahashi et al., 1997). The cell cycle is longer in the primate (Kornack & Rakic, 1998), and in the human the comparable period of time during which neurons are produced is much longer, about 120 days (Caviness et al., 1995). From this it has been estimated that about 34–35 cell cycles would be required to make all of the neurons of the human neocortex (Caviness et al., 1995).

The cells of the subventricular zone, in contrast, neither maintain an attachment to the ventricular or pial surfaces nor do their nuclei move as they move through the cell cycle (Sidman, 1970). In the neocortical proliferative zones the lengths of the cell cycle of the ventricular and subventricular zones are similar (Takahashi et al., 1995b). The contribution of the subventricular zone to the adult brain is important, and most of the glia for most of the brain are produced there (Goldman, 1995). In addition, in some areas of the brain a significant number of neurons are also produced in the subventricular zone (Garcia–Verdugo, Doetsch, Wichterle, Lim, & Alvarez–Buylla, 1998).

Cell migration influences ultimate cell position

As illustrated in Figure 5, the zones where cell proliferation occurs are, in general, physically separate from the ultimate destinations of the cells they produce. This means that the postmitotic young neurons must move from the site of their proliferation to their final position. There are two essentially different ways that cells make this movement. In some parts of the developing nervous system the postmitotic neurons leave the proliferative population (presumably under the influence of some unknown signal or signals) and move only a very short distance from the border of proliferative zone. Subsequently, these cells are displaced outward away from the proliferative zone by newly produced cells (see Fig-

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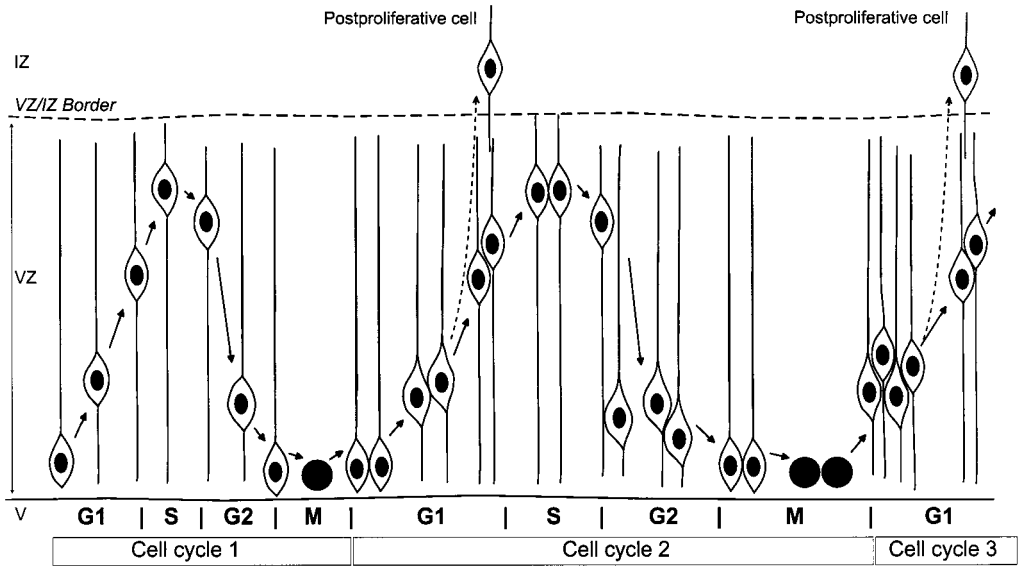


Figure 6. The cell cycle in the ventricular zone of the developing CNS. This schematic diagram illustrates the up-and-down movement of the nuclei of the cells comprising the proliferative ventricular epithelium of the ventricular zone (VZ). With each pass through the cell cycle the nucleus of a single cell moves from its starting position at the ventricular surface at the beginning of G1 to the border of the VZ where it enters S. During G2, the nucleus again moves down to the ventricular surface, where it enters M and divides to form two cells. With each pass through the cell cycle some postmitotic neurons are produced. The postmitotic neurons migrate away from the VZ to produce the structures of the adult brain (in this case, the cerebral neocortex). During the production of the neocortex in the mouse, the cell cycle lengthens with each cell cycle, and there are a total of 11 cell cycles.

ure 7). This type of cell movement does not seem to require active locomotor activity by the moving cell and is generally considered to be a *passive cell displacement*. In the parts of the developing CNS in which passive cell displacement is the only type of cell movement that occurs after the young neurons leave the proliferative population, the neurons that are generated earliest are located farthest away from the proliferative zone, and subsequently generated neurons are found at levels progressively closer to the proliferative zone (Figure 7). This correlation between the distribution of neurons and their time of origin is referred to as an "outside-to-inside" spatiotemporal gradient. In this case, outside and inside are defined with respect to the location of the proliferative zone. (This usually, but not always, corresponds with the outside and inside of the neural tube.) It should be noted, however, that the presence of an outside-to-inside spatiotemporal gradient does not necessarily imply that the neurons of that region moved only by passive displacement. Areas of the nervous system in which the outside-to-inside spatiotemporal pattern is present include the thalamus (Altman & Bayer, 1979; Angevine, 1970; Rakic, 1977), hypothalamus (Ifft, 1972), spinal cord (Nornes & Das, 1974), retina (Sidman, 1961; Walsh, Polley, Hickey, & Guillery, 1983), dentate gyrus of the hippocampal formation (Angevine, 1965; Bayer, Yackel, & Puri, 1982; Nowakowski & Rakic, 1981; Wyss & Sripanidkulchai, 1985), and many regions of the brainstem (Altman & Bayer, 1981; Taber–Pierce, 1972).

In many other parts of the developing nervous system the moving cells play a much more active role in reaching their final position. In these cases the neurons leaving the proliferative zone move a much greater distance and, in addition, in many instances the earliest neurons to be generated are bypassed by the progressively later generated neurons

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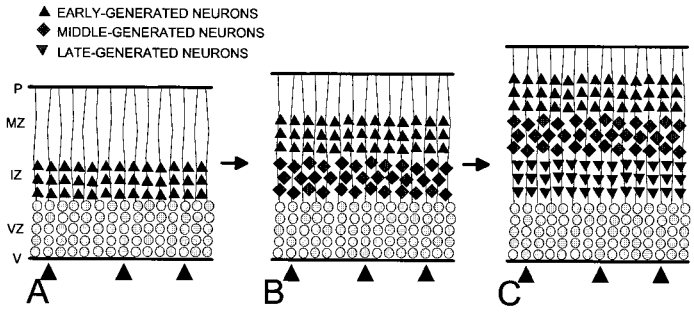


Figure 7. Cell movement by passive displacement. Some cells leave the proliferative zones and move only a short distance from the outer edge of the zone. Subsequently, these cells are displaced outward away from the proliferative zone by newly produced cells. (A–C) This sequence of events is illustrated. (A) The first neurons to leave the ventricular zone are shown as triangles. (B) The next neurons to form (shown as diamonds) move away from the ventricular zone, displacing the earlier generated ones outward. (C) Finally, the last neurons to form (shown as inverted triangles) move away from the ventricular zone and displace both populations of earlier generated neurons. This sequence of events results in a specific distribution of neurons generally known as an outside-to-inside spatiotemporal gradient. V, Ventricular surface; VZ, ventricular zone; IZ, intermediate zone; CP, cortical plate; MZ, marginal zone; P, pial surface.

(Figure 8). This type of cell movement clearly requires the active participation of the moving cell itself in its own displacement. This active process of cell movement is generally referred to as *neuronal migration* (Sidman & Rakic, 1973). When the migrating young neuron bypasses the previously generated cells, the result is an "inside-to-outside" spatiotemporal gradient (Figure 8). This pattern is found in most portions of the cerebral cortex (Angevine, 1965; Angevine & Sidman, 1961; Caviness, 1982; Hinds, 1968; Rakic, 1975b; Rakic & Nowakowski, 1981; Wyss & Sripanidkulchai, 1985) and in several subcortical areas (Cooper & Rakic, 1981; Hickey & Hitchcock, 1984). What these areas have in common is that they are all *well-laminated* structures (which means that they are divided up into tangentially oriented layers that run *parallel* with the surface of the proliferative zone). Structures which are formed by an outside-to-inside spatiotemporal gradient (see previous paragraph) tend to exhibit such well-laminated structure. In other words, the inside-to-outside versus outside-to-inside pattern of distribution of neurons is correlated with the eventual organization of the region of the CNS to which the migrating neurons will eventually belong.

How do migrating neurons "know" when they have reached their final destination? A partial answer was provided by Rakic, who discovered that migrating neurons in the developing cerebral cortex and cerebellar cortex use radial glial fibers as guides during their migration (Rakic, 1971, 1972). This finding has since been confirmed, and it is now widely accepted that during the development of the cerebral cortex young neurons are intimately apposed to radially aligned glial fibers that provide guidance (Nowakowski & Rakic, 1979; Rakic, 1972; Rakic, Cameron, & Komuro, 1994). This interaction of migrating young neurons with radial glial fibers is one of the best-documented examples of cell interactions in the developing CNS. The process of neuronal migration is a complicated process consisting of at least three phases (Figure 9; for reviews, see Hatten, 1999; Nowakowski, 1986; Rakic et al., 1994). First, a young neuron starts its migration. During this phase a cell in the proliferating population makes the transition from neuroblast to young neuron, becomes apposed to a radial glial fiber, and establishes an axis of polarity away from the ventricular surface. In the second or locomotory phase, a young neuron propels itself along the surface of the radial glial cell, while maintaining its apposition to the radial fiber and its axis of polarity. Finally, in the third

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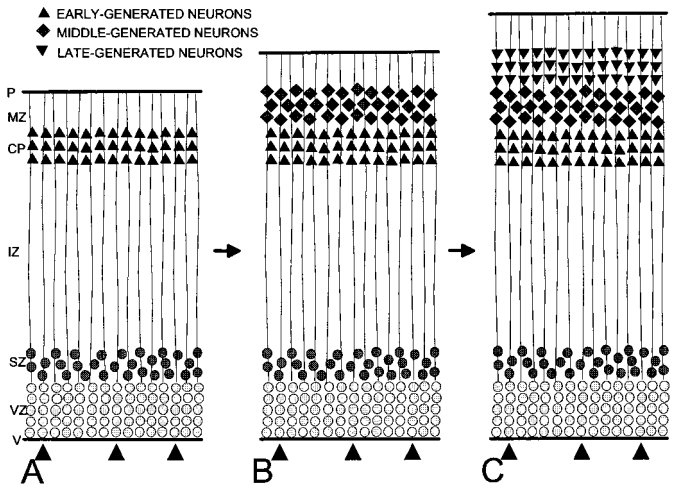


Figure 8. Cell movement by active migration. In many parts of the developing nervous system, cells leaving the proliferative population move a considerable distance from the proliferative zone. For example, in the cerebral cortex the later-generated cells bypass the earlier-generated cells and take up a position even more distant from the proliferative zone. (A) The first neurons to leave the proliferative zones are shown as triangles. These cells form a cortical plate between the intermediate and the marginal zones. (B) the next neurons to form (shown as diamonds) leave the proliferative zones and migrate across the intermediate zone and *past* the previously generated cells to the top of the cortical plate. (C) The final neurons to reach the cortical plate are shown as inverted triangles. These cells have also migrated across the intermediate zone and *past* the previously generated cells to the top of the cortical plate. This sequence of events results in a specific distribution of neurons generally known as an inside-to-outside spatiotemporal gradient. V, Ventricular surface; VZ, ventricular zone; SZ, subventricular zone; IZ, intermediate zone; CP, cortical plate; MZ, marginal zone; P, pial surface.

phase of its migration, a young neuron "recognizes" that it has reached its final destination and stops its migration. During this phase the migrating neuron detaches from the radial glial fiber, and the young neuron can continue to differentiate. Also, as a result of this detachment the surface of the radial glial fiber is made available for the guidance of subsequently generated neurons that migrate past those that were previously generated (Pinto–Lord, Evrard, & Caviness, 1982). Guidance and motility of migrating neurons involves a complex interaction of the migrating neuron with the radial glial cell (Hatten, 1999; Rakic et al., 1994). The analysis of neuronal migration in normal and mutant mice and also in human pathological conditions indicates that there are specific molecules which mediate the contact of migrating neurons with radial glial fibers (Hatten, 1999). In addition, guidance may involve ion channels (Komuro & Rakic, 1998a, 1998b), and adhesive interactions may also be mediated in part by specific cell-surface-related molecules (e.g., integrins; Anton & Kreidberg, 1999). Key information about the nature of the signal(s) for detaching from the radial glial fiber has come from the analysis of mutant mice and, in particular, from the reeler mutant mouse which has an "inverted" cortex reflecting abnormalities in neuronal migration (Caviness & Sidman, 1973; Pinto–Lord et al., 1982). Recently, "reelin," the cell-surface molecule that is mutated in reeler, has been identified (Curran & D'Arcangelo, 1998; Lambert de Rouvroit & Goffinet, 1998). Work in progress is certain to reveal how reelin and other molecules aid in directing neurons to their final position.

If neuronal migration is disrupted, an *abnormality in cell position results.* When this happens the neurons are said to be heterotopic or ectopic (Rakic, 1975a). In humans, the best

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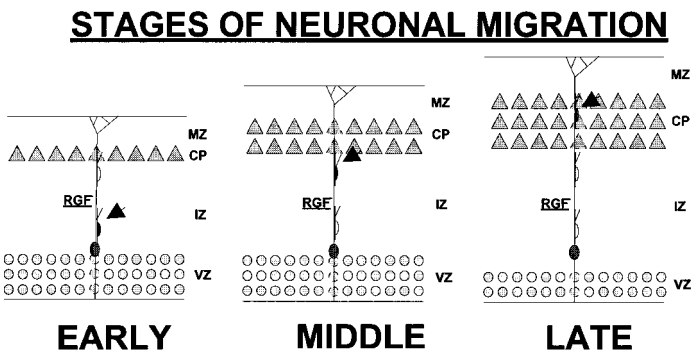


Figure 9. Interaction between migrating neurons and radial glial cells. As a young neuron moves from its site of origin in the proliferative zone to its final position in the cortical plate, it is guided by a radially aligned glial cell. In this figure the movement of a young neuron is depicted by a dark cell (marked by an arrow) in each of the three drawings. This migratory process can be divided into three phases. (A) Initially, a young neuron leaves the proliferative population, becomes apposed to a radial glial fiber, and acquires a polarity directed towards the pial surface. (B) Next, it must traverse the intermediate zone; while doing this, it maintains its apposition to the radial glial fiber and its polarity. (C) Finally, as it reaches the top of the cortical plate, it stops its forward progress, loses it apposition to the radial glial fiber, and reorganizes its polarity in order to become a mature neuron. Disruption of any of these three steps could lead to neuronal heterotopias. V, ventricular surface; VZ, ventricular zone; SZ, subventricular zone; IZ, intermediate zone; CP, cortical plate; MZ, marginal zone; P, pial surface.

studied examples are in the cerebral cortex, where defects in neuronal migration have been associated with a variety of syndromes and diseases ranging from behavioral disorders to extremely severe mental retardation and failure to thrive (for reviews, see Barth, 1987; Dobyns & Truwit, 1995; Pearlman, Faust, Hatten, & Brunstrom, 1998; Rakic, 1975a; Reiner & Sapir, 1998). Behavioral disorders that have been associated with a disruption of neuronal migration include some forms of schizophrenia (Arnold & Trojanowski, 1996; Chua & Murray, 1996), dyslexia (Galaburda & Kemper, 1979; Peterson, 1995), and autism (Bailey et al., 1998; Kemper & Bauman, 1998; Peterson, 1995).

What is the developmental fate of neurons which fail to migrate to their proper position? Do these abnormally positioned neurons make connections with the rest of the brain? If so, do they make connections with their normal targets or some other targets, and how does this affect the function of the area of the brain in which these cells were supposed to have ended up? The answers depend on how the guidance of axons to their final position is affected, and whether input or output is considered. For the input to the ectopic cells, the possibilities are that:

1. the axons of normally positioned cells will follow a normal trajectory and therefore fail to find their normal target (because it is not where it belongs), or
2. the axons of normally positioned cells will follow an abnormal trajectory in order to reach their normal target.

There are also two possibilities for the output from the abnormally positioned cells:

3. the axons of the abnormally positioned neurons successfully find their normal targets, or
4. the axons of the abnormally positioned neurons fail to find their normal targets.

What is the significance of these possibilities for the development of normal functions in the CNS? In order for normal connections to be made and, presumably, for normal func-

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tions to be established, the inputs to a population of abnormally positioned cells and the outputs from the abnormally positioned cells must *both* succeed in finding their normal targets. How do these theoretical possibilities fit with reality? Do axons find their normal targets or not? These possibilities have been addressed to some extent in mutant mice with ectopic cells (Nowakowski, 1987), but relatively little information is available about the connections and capacities of ectopic neurons. Interestingly, the available results indicate that the way that abnormally positioned neurons make and receive connections with other neurons in the brain varies. For example, in the reeler mutant mouse there is a widespread change in relative cell position in many parts of the CNS (for review, see Caviness & Rakic, 1978). For the most part, axons in the reeler mouse find their way to their appropriate target. However, in doing so, these axons may change their normal trajectory considerably in order to reach the appropriate portion of their normal target's dendritic tree (Stanfield, Caviness, & Cowan, 1979). Thus, in reeler, the abnormally positioned neurons find their normal targets (i.e., possibility 3, as listed above), *even though the normal target may also be abnormally positioned*. The functional capacities of these connections has been tested in the visual cortex, and it appears that these connections are capable of processing information normally (Drager, 1981). Importantly, this change in trajectory does not occur everywhere in the brain of the reeler mouse (Devor, Caviness, & Derer, 1975). For example, the axons of the lateral olfactory tract remain a tightly collimated bundle following their normal trajectory, and, as a result, they do *not* contact the appropriate part of the dendrites of their target cell (i.e., possibility 1, as listed above). In another mouse mutant, the *Hld* mouse, the mossy fibers from the dentate gyrus contact the apical dendrites of the late generated cells in *two* places, whereas in the normal mouse the mossy fibers contact both the apical dendrites (in one place) and the basal dendrites of the pyramidal cells. Thus, the bundle of mossy fibers does *not* change its trajectory to make contact with the basal dendrites of the late generated cells that are, in fact, its normal target (Nowakowski & Davis, 1985). Thus, this aspect of the rewiring of the hippocampus as a result of a disruption of a particular population of cells is also consistent with possibility 1 as listed above. It is to be expected that eventually all four of the above possibilities are likely to be demonstrated.

Cell differentiation is the final complication

Once a neuron or glial cell has left the proliferative population and reached its final position, it enters the final phase in its life history (i.e., its differentiation). The differentiation of neurons and glia is an extraordinarily complicated process that is responsible for the generation of a large proportion of the diversity of the adult CNS. During its differentiation each neuron grows out its axon and its dendrites. In many cases the axon grows a long distance over a complicated terrain before reaching its final target. The dendrites grow out and form their characteristic pattern of arborization for the particular cell class. Each differentiating neuron also must express the specific enzymes it requires in order to produce the neurotransmitter(s) it will use. Also, each postsynaptic site must express the receptors it needs to receive input from its presynaptic partner. In addition, the axons of some neurons will become myelinated, whereas others will not. Simultaneous with the acquisition of mature properties by the neurons, the glial cells are also differentiating into oligodendrocytes that make myelin and astrocytes that perform other functions (Goldman, 1995; Lillien & Raff, 1990; Raff, Durand, & Gao, 1998). For example, in humans the myelination of most pathways in the CNS continues long after birth (for review, see Richardson, 1982), and, in fact, the classical work by Flechsig (1920) on myelination in the developing human cerebral cortex provided the basis of the traditional classification of cortical areas into primary, secondary, and association areas. Many aspects of cell differentiation in the CNS are beyond the scope of this review, and, for this reason, the discussion below will

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be confined to the limited issue of the transient connections made by some axons.

The growth of axons in the CNS involves the extension of a process from the cell body to a target or postsynaptic cell. Each growing axon must find its way through a complicated terrain to its target area, and once there it must select the appropriate target cell and even the appropriate part of the dendritic tree in order to make its synapses. This is clearly a complicated process, and it is likely that the growing axon makes use of a variety of mechanisms to find its way to its final target (Goodman, 1996; Tessier–Lavigne & Goodman, 1996). It is clear, however, that in many parts of the developing CNS the growing axons do not grow directly to their final targets but instead grow "exuberantly," such that they transiently innervate areas and cells that they do not normally contact in the adult. Two types of transient connections are made (see Figure 10): divergent and convergent. Divergence means that one neuron (or population of neurons) innervates more cells (or a greater area) than it normally does in the adult (Figure 10A). During development the extra collaterals of the divergently projecting population are eliminated such that the projection area is reduced to its adult size (Figure 10A′). Convergence means that several neurons (or populations of neurons) innervate one target neuron (or area) (Figure 10B), which in the adult is innervated by only one of these neurons (or populations; Figure 10B′). These two types of transient projections are *not* mutually exclusive, and it is possible that both could be found within a single population of cells (Figure 10C). In this case, both the divergent and convergent projections would have to be eliminated in order to establish the adult pattern of connections (Figure 10C′).

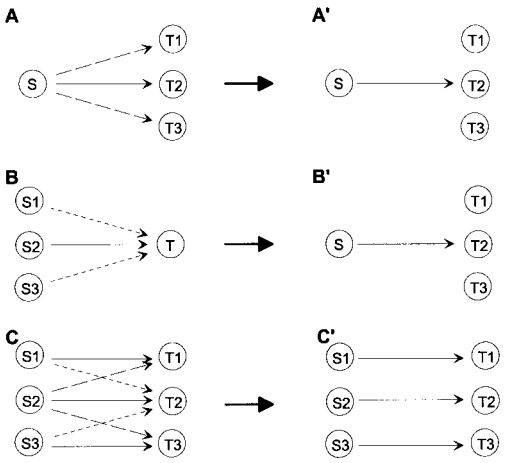


Figure 10. There are two types of exuberant projections which occur during the development of the CNS. (A) the transient *divergence* of a single source of axons is illustrated. In this case, the circle represents a single source of axons (a cell or population of cells) that projects to an area broader than its eventual adult distribution. Subsequently, some portion of the projection is withdrawn (through a variety of mechanisms) to produce (A′) the adult pattern. (B) The transient *convergence* of projections from more than one source (i.e., from more than one cell or population of cells), all termination on a single target, is illustrated. In this case, the projections from some of the sources are lost in order to establish (B′) the adult pattern. (C) The simultaneous presence of both transient divergence and convergence is illustrated. In this case, both types of exuberant projections have to be lost in order to establish (C′) the adult pattern of connections.

Cell Death and Transient Connections

How are transient connections eliminated? There seem to be two distinctly different regressive phenomena responsible: (a) the transient connections can be removed by a retraction of the collaterals of the neuron's axon or by a shrinking of the terminal arborization of the axon, and (b) the transient connections can be removed through selective cell death such that the neurons that are "unsuccessful" in establishing projections to their normal adult territory die. Both of these mechanisms of elimination are known to occur. For example, during the development of the cerebral cortex pyramidal neurons in the visual cortex send collaterals to targets, such as the spinal cord, which they do not ordinarily innervate in the adult animal. As the animal matures, some of the collaterals of these cells are lost, whereas other collaterals persist (O'Leary & Stanfield, 1985; Stanfield & O'Leary, 1985a, 1985b). The refinement of point-to-point connections to the visual cortex from the lateral geniculate nucleus also involves reorganization of the input (Wiesel, 1982). In many other parts of the

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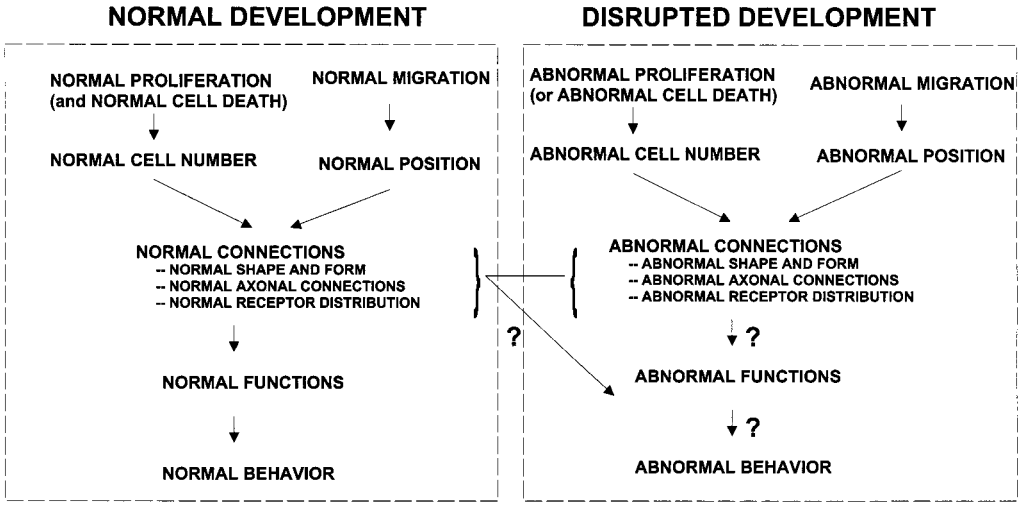


Figure 11. Schematic diagram of the cascade of events associated with normal and disrupted migration in the developing CNS. The diagram on the left shows the normal sequence of events, and the diagram on the right shows the disrupted sequence. If disruption of migration occurs in only one part of the CNS, the connections between the abnormally positioned neurons and their normally positioned counterparts may be affected, and abnormal functions and behavior may result.

CNS, neuron death also contributes to the elimination of divergently projecting collaterals (Burek & Oppenheim, 1996; Cowan, Fawcett, O'Leary, & Stanfield, 1984; O'Leary, 1987; Oppenheim, 1991). Thus, it is of great interest (and some irony) that an important set of processes during the development of the nervous system, which is generally thought of as being a series of *progressive* events, are *regressive* events involving the retraction of axons and the death of cells. There is no doubt, however, that cell death is an important developmental feature because "knockout" mice with deletion genes that control cell death have severe developmental abnormalities in the CNS (Kuida et al., 1998, 1996; Yang et al., 1997).

The Effects of Abnormal Development

"How" are cell proliferation, cell migration, and cell differentiation controlled? As discussed in the introduction to this paper, the simple answer is that they are each controlled by processes intrinsic to the cell or by processes extrinsic to the cell (i.e., by cell–cell interactions, by interactions of cells with hormones, etc.). How do abnormalities in development affect the adult CNS and behavior? The answer to this question is less clear, but abnormalities in cell proliferation, migration, or death clearly produce changes in the connections of the neurons of the adult brain. For example, in disorders in which either cell proliferation or neuronal migration is disrupted in some way, either fewer neurons or abnormally positioned neurons result. As described, these events occur relatively early during the developmental cascade (Figure 1) and, thus, are likely to have further impact on CNS organization. It seems reasonable to suggest that the neurons of the affected regions will not make normal connections, and, as a result, normal functional competence will not be achieved (Figure 11). These changes in connections could involve both the regions in which the primary disruption occurs and also regions that receive connections from or send connections to the affected regions (Figure 11). Unraveling these effects on behavior is the topic of the rest of the papers in this Special Issue.

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