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The Brain Stem

In primitive vertebrates—reptiles, amphibians, and fish—the forebrain is only a small part of the brain and is devoted mainly to olfactory processing and to the integration of autonomic and endocrine function with the basic behaviors necessary for survival. These basic behaviors include feeding, drinking, sexual reproduction, sleep, and emergency responses. Although we are accustomed to thinking that the forebrain orchestrates most human behaviors, many complex responses, such as feeding—the coordination of chewing, licking, and swallowing—are actually made up of relatively simple, stereotypic motor responses governed by ensembles of neurons in the brain stem.

The importance of this pattern of organization in human behavior is clear from observing infants born without a forebrain (hydranencephaly). Hydranencephalic infants are surprisingly difficult to distinguish from normal babies. They cry, smile, suckle, and move their eyes, face, arms, and legs. As these sad cases illustrate, the brain stem can organize virtually all of the behavior of the newborn.

In this chapter, we describe the functional anatomy of the brain stem, particularly the cranial nerves, as well as the ensembles of local circuit neurons that organize the simple behaviors of the face and head. Finally, we consider the modulatory functions of nuclei in the brain stem that adjust the sensitivity of sensory, motor, and arousal systems.

The brain stem is the rostral continuation of the spinal cord, and its motor and sensory components are similar in structure to those of the spinal cord. But the portions of the brain stem that control the cranial nerves are much more complex than the corresponding parts of the spinal cord that control the spinal nerves because cranial nerves mediate more complex behaviors. The core of the brain stem, the *reticular formation*, is homologous to the intermediate gray matter of the spinal cord but is also more complex. Like the spinal cord, the reticular formation contains ensembles of local-circuit interneurons that generate motor and autonomic patterns and coordinate reflexes and simple behaviors. In addition, the brain stem contains glutamatergic and GABAergic circuitry that regulates arousal, wake–sleep cycles, breathing, and other vital functions, as well as monoaminergic modulatory neurons that act to optimize the functions of the nervous system.

The Cranial Nerves Are Homologous to the Spinal Nerves

Because the spinal nerves reach only as high as the first cervical vertebra, the cranial nerves provide the somatic and visceral, sensory and motor innervation for the head. Two cranial nerves, the glossopharyngeal and vagus nerves, also supply visceral sensory and motor innervation of the neck, chest, and most of the abdominal organs with the exception of the pelvis. In addition, some cranial nerves are associated with specialized functions, such as vision or hearing, that go beyond the sensory and motor plan of the spinal cord.

Assessment of the cranial nerves is an important part of the neurological examination because abnormalities of function can pinpoint a site in the brain stem that has been damaged. Therefore, it is important to know the origins of the cranial nerves, their intracranial course, and where they exit from the skull.

The cranial nerves are traditionally numbered I through XII in rostrocaudal sequence. Cranial nerves I and II enter at the base of the forebrain. The other cranial nerves arise from the brain stem at characteristic locations (Figure 40–1). All but one exit from the ventral surface of the brain stem (Figure 40–2). The exception is the trochlear (IV) nerve, which leaves the midbrain from its dorsal surface just behind the inferior colliculus and wraps around the lateral surface of the brain stem to join the other cranial nerves concerned with eye movements. The cranial nerves with sensory functions (V, VII, VIII, IX, and X) have associated sensory ganglia that operate much as dorsal root ganglia do for spinal nerves. These ganglia are located along the course of individual nerves as they enter the skull.

The olfactory (I) nerve, which is associated with the forebrain, is described in detail in Chapter 29; the optic (II) nerve, which is associated with the diencephalon, is described in Chapters 21 and 22. The spinal accessory (XI) nerve can be considered a cranial nerve anatomically but actually is a spinal nerve originating from the higher cervical motor rootlets. It runs up into the skull before exiting through the jugular foramen to innervate the trapezius and sternocleidomastoid muscles in the neck.

Cranial Nerves Mediate the Sensory and Motor Functions of the Face and Head and the Autonomic Functions of the Body

Three ocular motor nerves control movements of the eyes. The *abducens (VI) nerve* has the simplest action; it contracts the lateral rectus muscle to move the globe laterally. The *trochlear (IV) nerve* also innervates a single muscle, the superior oblique, which both depresses the eye and rotates it inward depending on the eye's position. The *oculomotor (III) nerve* supplies all of the other muscles of the orbit, including the retractor of the lid. It also provides the parasympathetic innervation responsible for pupillary constriction in response to light and accommodation of the lens for near vision. The ocular motor system is considered in detail in Chapter 35.

The *trigeminal (V) nerve* is a mixed nerve (containing both sensory and motor axons) that leaves the brain stem in two roots. The motor root innervates the muscles of mastication (the masseter, temporalis, and pterygoids) and a few muscles of the palate (tensor veli palatini), inner ear (tensor tympani), and upper neck (mylohyoid and anterior belly of the digastric muscle). The sensory fibers arise from neurons in the trigeminal ganglion, located at the floor of the skull in the middle cranial fossa.

Three branches emerge from the trigeminal ganglion. The *ophthalmic division* (V_1) runs with the ocular motor nerves through the superior orbital fissure (Figure 40–2A) to innervate the orbit, nose, and forehead and scalp back to the vertex of the skull (Figure 40–3). Some fibers from this division also innervate

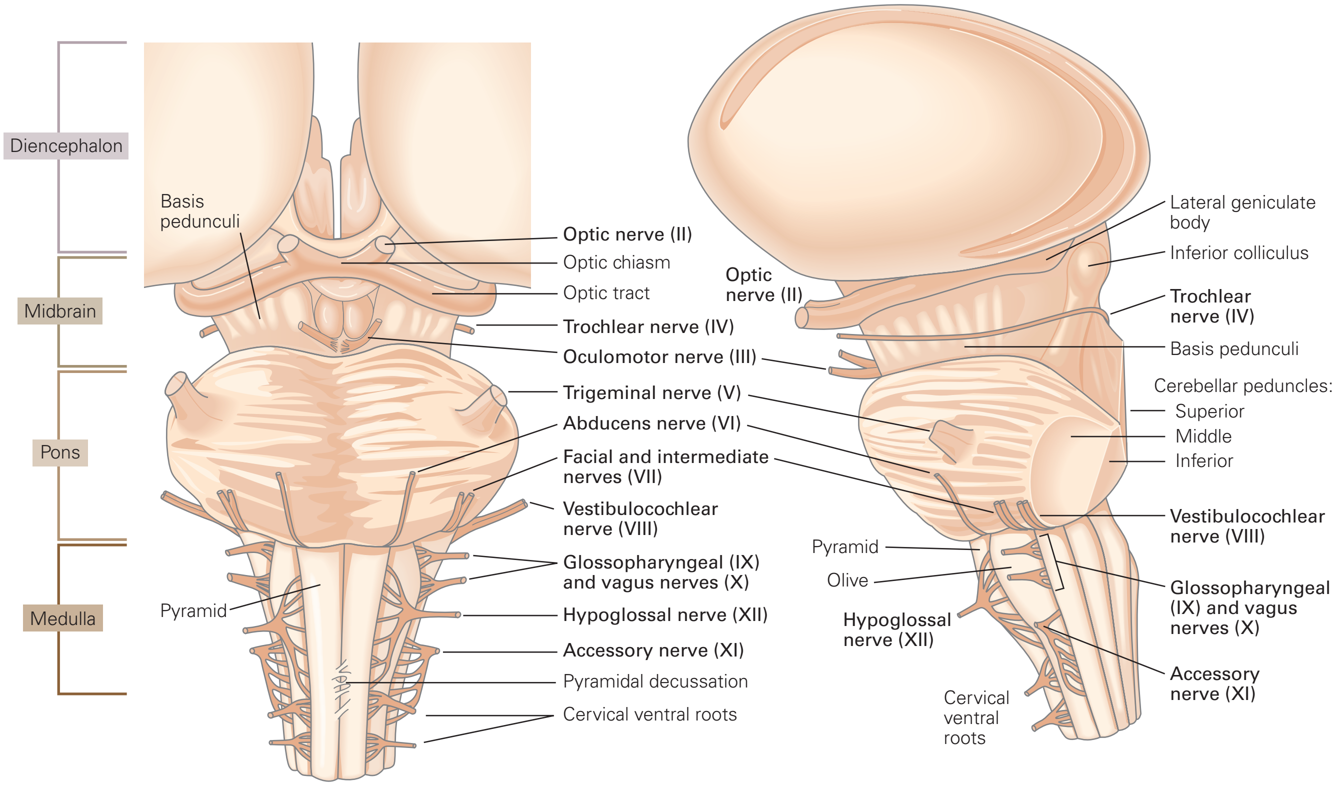

Figure 40–1 The origins of cranial nerves in the brain stem (ventral and lateral views). The olfactory (I) nerve is not shown because it terminates in the olfactory bulb in the forebrain. All of the cranial nerves except one emerge from the ventral surface of the brain; the trochlear (IV) nerve originates from the dorsal surface of the midbrain.

the meninges and blood vessels of the anterior and middle intracranial fossas. The *maxillary division* (V_2) runs through the round foramen of the sphenoid bone to innervate the skin over the cheek and the upper portion of the oral cavity. The *mandibular division* (V_3), which also contains the motor axons of the trigeminal nerve, leaves the skull through the oval foramen of the sphenoid bone. It innervates the skin over the jaw, the area above the ear, and the lower part of the oral cavity, including the tongue.

Complete trigeminal sensory loss results in numbness of the entire face and the inside of the mouth. One-sided trigeminal motor weakness does not cause much weakness of jaw closure because the muscles of mastication on either side are sufficient to close the jaw. Nevertheless, the jaw tends to deviate toward the side of the lesion when the mouth is opened because the internal pterygoid muscle on the opposite side, when unopposed, pulls the jaw toward the weak side.

The *facial (VII) nerve* is also a mixed nerve. Its motor root innervates the muscles of facial expression as well as the stapedius muscle in the inner ear, stylohyoid muscle, and posterior belly of the digastric muscle in the upper neck. The sensory root runs as a separate bundle, the intermediate nerve, through the internal auditory canal and arises from neurons in the geniculate ganglion, located near the middle ear. Distal to the geniculate ganglion, the sensory fibers diverge from the motor branch. Some innervate skin of the external auditory canal while others form the chorda tympani, which joins the lingual nerve and conveys taste sensation from the anterior two-thirds of the tongue. The *autonomic component* of the facial nerve includes parasympathetic fibers that travel through the motor root to the sphenopalatine and submandibular ganglia, which innervate lacrimal and salivary glands (except the parotid gland) and the cerebral vasculature.

The facial nerve may suffer isolated injury in Bell palsy, a common complication of certain viral infections. Early on, the patient may complain mainly of the face pulling toward the unaffected side because of the weakness of the muscles on the side of the lesion. Later, the ipsilateral corner of the mouth droops, food falls out of the mouth, and the eyelids no longer close on that side. Loss of blinking may result in drying

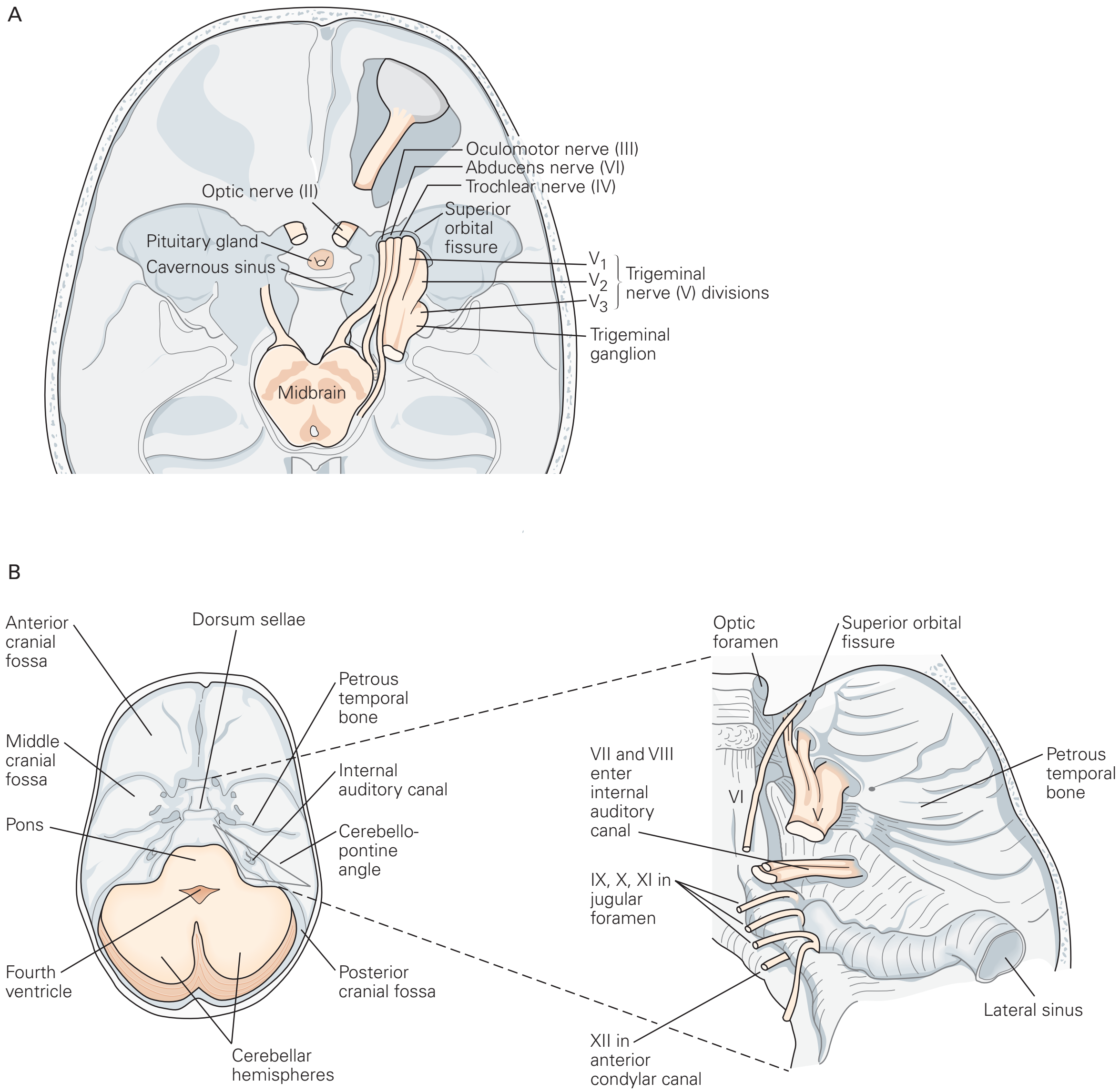

Figure 40–2 The cranial nerves exit the skull in groups.

A. Cranial nerves II, III, IV, V, and VI exit the skull near the pituitary fossa. The optic (**II**) nerve enters the optic foramen, but the oculomotor (**III**), trochlear (**IV**), and abducens (**VI**) nerves, and the first division of the trigeminal (**V**) nerve leave through the superior orbital fissure. The second and third divisions of the trigeminal nerve exit through the round and oval foramina, respectively.

B. In the posterior fossa, the facial (**VII**) and vestibulocochlear (**VIII**) nerves exit through the internal auditory canal, whereas the glossopharyngeal (**IX**), vagus (**X**), and accessory (**XI**) nerves leave through the jugular foramen. The hypoglossal nerve (**XII**) has its own foramen.

and injury to the cornea. The patient may complain that sound has a booming quality in the ipsilateral ear because the stapedius muscle fails to tense the ossicles in response to a loud sound (the stapedial reflex). Taste may also be lost on the anterior two-thirds of the tongue on the ipsilateral side. If the Bell palsy is caused by a herpes zoster infection of the geniculate ganglion, small blisters may form in the outer ear canal, the ganglion's cutaneous sensory field.

The *vestibulocochlear (VIII) nerve* contains two main bundles of sensory axons from two ganglia. Fibers from the vestibular ganglion relay sensation of angular and linear acceleration from the semicircular canals, utricle, and saccule in the inner ear. Fibers from the cochlear ganglion relay information from the cochlea concerning sound. A vestibular schwannoma, one of the most common intracranial tumors, may form along the vestibular component of cranial nerve VIII

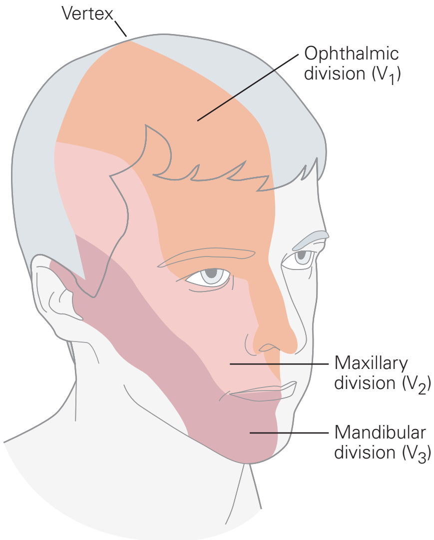

Figure 40–3 The three sensory divisions of the trigeminal (V) nerve innervate the face and scalp. The V_2 and V_3 divisions also innervate the upper and lower parts of the oral cavity, including the tongue. The C2 cervical root innervates the back of the head. The area around the ear is innervated by branches of the VII and X nerve.

as it runs within the internal auditory meatus. Most patients complain only about hearing loss, as the brain is usually able to adapt to the gradual loss of vestibular input from one side.

The *glossopharyngeal (IX) nerve* and *vagus (X) nerve* are mixed nerves and provide parasympathetic autonomic input to thoracic and visceral organs. These closely related nerves transmit sensory information from the pharynx and upper airway as well as taste from the posterior third of the tongue and oral cavity. The glossopharyngeal nerve transmits visceral information from the neck (for example, information on blood oxygen and carbon dioxide from the carotid body, and arterial pressure from the carotid sinus), whereas the vagus nerve transmits visceral information from the thoracic and abdominal organs except for the distal colon and pelvic organs. Both nerves include parasympathetic motor fibers. The glossopharyngeal nerve provides parasympathetic control of the parotid salivary gland, whereas the vagus nerve innervates the rest of the internal organs of the neck, thorax, and abdomen. The glossopharyngeal nerve innervates only one muscle of the palate, the stylopharyngeus, which raises and dilates the pharynx. The remaining striated muscles of the larynx and pharynx are under control of the vagus nerve.

The vagal sensory neurons innervate the length of the gastrointestinal tract and thus are able to regulate multiple postprandial functions. One excellent example is the role of vagal afferents in regulating food intake following a meal. Cholecystokinin (CCK) is an endogenous peptide secreted by duodenal enteroendocrine cells during meals, which helps to induce satiety. CCK acts (at least in part) via action on vagal afferents in the gut, stimulating a feeling of fullness. Exogenous electrical stimulation of the vagus nerve is now being used clinically to treat a wide variety of conditions including obesity, intractable epilepsy, and even depression. However, the neuroanatomic and molecular mechanisms underlying these effects remain poorly understood. Similarly, bariatric surgery remains one of the most widely used and effective strategies to combat obesity. Some studies have suggested that surgical alterations in the responsiveness of vagal afferents to gut signals may contribute to the sustained weight loss following these surgeries.

Because many of the functions of nerves IX and X are bilateral and partially overlapping, unilateral injury of nerve IX may be difficult to detect. Patients with unilateral cranial nerve X injury are hoarse, because one vocal cord is paralyzed, and they may have some difficulty swallowing. Examination of the oropharynx shows weakness and numbness of the palate on one side.

The *spinal accessory (XI) nerve* is purely motor and originates from motor neurons in the upper cervical spinal cord. It innervates the trapezius and sternocleidomastoid muscles on the same side of the body. Because the mechanical effect of the sternocleidomastoid is to turn the head toward the opposite side, an injury of the left nerve causes weakness in turning the head to the right. A lesion of the cerebral cortex on the left will cause weakness of voluntary muscles on the entire right side of the body except for the sternocleidomastoid; instead, the ipsilateral sternocleidomastoid will be weak (because the left cerebral cortex is concerned with muscles that interact with the right side of the world, and the left sternocleidomastoid turns the head to the right).

The *hypoglossal (XII) nerve* is also purely motor, innervating the muscles of the tongue. When the nerve is injured, for example during surgery for head and neck cancer, the tongue atrophies on that side. The muscle fibers exhibit twitches of muscle fascicles (fasciculations), which may be seen clearly through the thin mucosa of the tongue.

Cranial Nerves Leave the Skull in Groups and Often Are Injured Together

In assessing dysfunction of the cranial nerves, it is important to determine whether the injury is within the brain or further along the course of the nerve. As cranial nerves leave the skull in groups through specific foramina, damage at these locations can affect several nerves.

The cranial nerves concerned with orbital sensation and movement of the eyes—the oculomotor, trochlear, and abducens nerves, as well as the ophthalmic division of the trigeminal nerve—are gathered together in the *cavernous sinus*, along the lateral margins of the sella turcica, and then exit the skull through the *superior orbital fissure* adjacent to the optic foramen (Figure 40–2A). Tumors in this region, such as those arising from the pituitary gland, often make their presence known first by pressure on these nerves or the adjacent optic chiasm.

Cranial nerves VII and VIII exit the brain stem at the *cerebellopontine angle*, the lateral corner of the brain stem at the juncture of the pons, medulla, and cerebellum (Figure 40–2B), and then leave the skull through the internal auditory meatus. A common tumor of the cerebellopontine angle is the vestibular schwannoma (sometimes erroneously called an "acoustic neuroma"), which derives from Schwann cells in the vestibular component of nerve VIII. A large tumor of the cerebellopontine angle may not only impair the function of nerves VII and VIII but may also press on nerve V near its site of emergence from the middle cerebellar peduncle, causing facial numbness, or compress the cerebellum or its peduncles on the same side, causing ipsilateral clumsiness.

The lower cranial nerves (IX, X, and XI) exit through the *jugular foramen* (Figure 40–2B) and are vulnerable to compression by tumors at that site. Nerve XII leaves the skull through its own (hypoglossal) foramen and is generally not affected by tumors located in the adjacent jugular foramen, unless the tumor becomes quite large. If a tumor involves nerves IX and X, but nerve XI is spared, it is generally within or near the brain stem rather than near the jugular foramen.

The Organization of the Cranial Nerve Nuclei Follows the Same Basic Plan as the Sensory and Motor Areas of the Spinal Cord

Cranial nerve nuclei are organized in rostrocaudal columns that are homologous to the sensory and motor laminae of the spinal cord (Chapters 18 and 31). This pattern is best understood from the developmental plan of the caudal neural tube that gives rise to the brain stem and spinal cord.

The transverse axis of the embryonic caudal neural tube is subdivided into alar (dorsal) and basal (ventral) plates by the sulcus limitans, a longitudinal groove along the lateral walls of the central canal, fourth ventricle, and cerebral aqueduct (Figure 40–4). The alar plate forms the sensory components of the dorsal horn of the spinal cord, whereas the basal plate forms the motor components of the ventral horn. The intermediate gray matter is made up primarily of the interneurons that coordinate spinal reflexes and motor responses.

The brain stem shares this basic plan. As the central canal of the spinal cord opens into the fourth ventricle, the walls of the neural tube are splayed outward

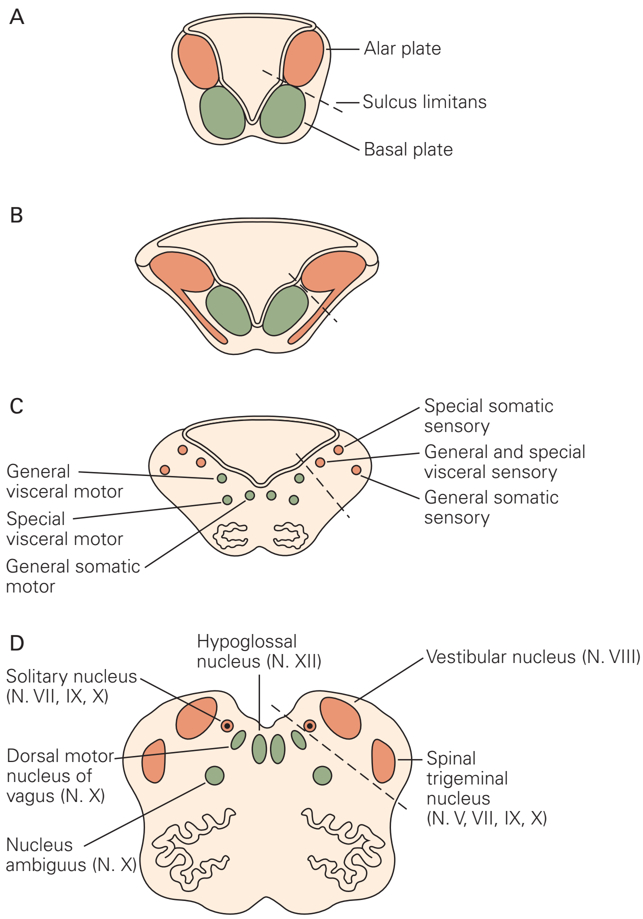

Figure 40–4 The developmental plan of the brain stem is the same general plan as that of the spinal cord.

A. The neural tube is divided into a dorsal sensory portion (the alar plate) and a ventral motor portion (the basal plate) by a longitudinal groove, the sulcus limitans.

B–D. During development, the sensory and motor cell groups migrate into their adult positions but largely retain their relative locations. In maturity (part **D**), the sulcus limitans (**dashed line**) is still recognizable in the walls of the fourth ventricle and the cerebral aqueduct, demarcating the border between dorsal sensory (**orange**) and ventral motor (**green**) structures. The section in part D is from the rostral medulla.

so that the dorsal sensory structures (derived from the alar plate) are displaced laterally, whereas the ventral motor structures (derived from the basal plate) remain more medial. The nuclei of the brain stem are divided into *general nuclei*, which serve functions similar to those of the spinal cord laminae, and *special nuclei*, which serve functions unique to the head, such as hearing, balance, taste, and control of the musculature related to the jaw, face, oropharynx, and larynx.

Embryonic Cranial Nerve Nuclei Have a Segmental Organization

Although the columns of sensory and motor nuclei in the adult hindbrain are organized rostrocaudally, the arrangement of neurons at each level derives from a strikingly segmental pattern in the early embryo. Before neurons appear, the future hindbrain region of the neural plate becomes subdivided into a series of eight segments of approximately equal size, known as *rhombomeres* (Figure 40–5A).

Each rhombomere develops a similar set of differentiated neurons, as if the developing hindbrain is made up of series of modules. Pairs of rhombomeres are associated with specific sets of muscles derived from the embryonic branchial arches (eg, rhombomeres 2 and 3 with the muscles of mastication and 4 and 5 with the muscles of facial expression) (Figure 40–5A). The even-numbered rhombomeres differentiate ahead of the odd-numbered ones. Rhombomeres 2, 4, and 6 form the branchial motor nuclei of the trigeminal, facial, and glossopharyngeal nerves, respectively. Later, rhombomeres 3, 5, and 7 contribute motor neurons to these nuclei, again respectively; in each case, the axons of individual motor neurons from odd-numbered rhombomeres extend rostrally as they join those of their even-numbered neighbors.

At this developmental stage, each of these nuclei is composed of homologous neurons derived from two adjacent segments. This early transverse segmental organization changes later in development, as rhombomere boundaries disappear and the dorsolateral migration of the cell bodies aligns the cells into rostrocaudal columns. Ultimately, some somatic and parasympathetic motor neurons migrate into the ventrolateral tegmentum; for example, the migration of the facial motor neurons of rhombomere 4 around the abducens nucleus generates the internal genu of the facial nerve (Figure 40–5A). Furthermore, neural crest cells from each rhombomere migrate into the corresponding branchial arches where they provide sensory and autonomic ganglion cells, as well as positional cues for the development of the arch muscles.

Adult Cranial Nerve Nuclei Have a Columnar Organization

Overall, the brain stem nuclei on each side are organized in six rostrocaudal columns, three of sensory nuclei and three of motor nuclei (Figure 40–6). These are considered later, in dorsolateral to ventromedial sequence. Although the columns are discontinuous along the rostrocaudal axis of the brain stem, nuclei with similar functions (sensory or motor, somatic or visceral) have similar dorsolateral-ventromedial positions at each level of the brain stem.

Within each motor nucleus, motor neurons for an individual muscle are also arranged in a cigar-shaped longitudinal column. Thus, each motor nucleus in cross section forms a mosaic map of the territory that is innervated. For example, in a cross section through the facial nucleus, the clusters of neurons that innervate the different facial muscles form a topographic map of the face.

General Somatic Sensory Column

The general somatic sensory column occupies the most lateral region of the alar plate and includes the trigeminal sensory nuclei (N. V). The *spinal trigeminal nucleus* is a continuation of the dorsal-most laminae of the spinal dorsal horn (Figure 40–5A) and is sometimes called the medullary dorsal horn. Along its outer surface lies the spinal trigeminal tract, a direct continuation of Lissauer's tract of the spinal cord (Chapter 20), thus allowing some cervical sensory fibers to reach the trigeminal nuclei and some trigeminal sensory axons to reach the dorsal horn in upper cervical segments. This arrangement allows dorsal horn sensory neurons to have a range of inputs that are much broader than that of individual spinal or trigeminal segments and ensures the integration of trigeminal and upper cervical sensory maps.

The spinal trigeminal nucleus receives sensory axons from the trigeminal ganglion (N. V) and from all cranial nerve sensory ganglia concerned with pain and temperature in the head, including geniculate ganglion (N. VII) neurons that relay information from the external auditory meatus, petrosal ganglion (N. IX) cells that convey information from the posterior part of the palate and tonsillar fossa, and nodose ganglion (N. X) axons that relay information from the posterior wall of the pharynx. The spinal trigeminal nucleus thus represents the entire oral cavity as well as the surface of the face.

The somatotopic organization of the afferent fibers in the spinal trigeminal nucleus is inverted: The forehead

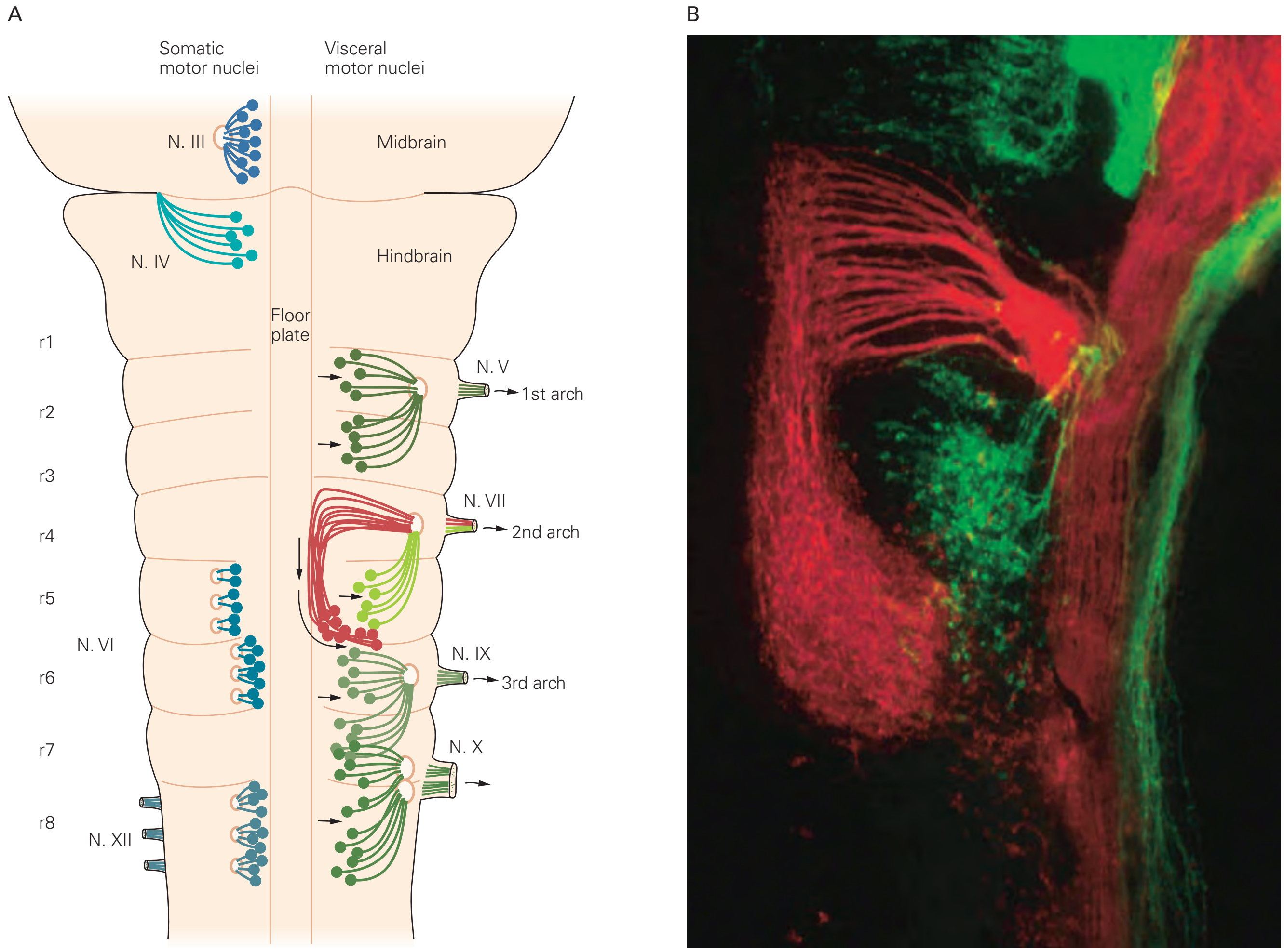

Figure 40–5 **Embryonic cranial nerve nuclei are organized segmentally.**

A. In the developing hindbrain (seen here from the ventral side), special and general visceral motor neurons (represented on the right side of the brain stem) form in each hindbrain segment (rhombomere) except rhombomere 1 (**r1**). Each special visceral motor nucleus comprises neurons in two rhombomeres: the trigeminal motor nucleus is formed by neurons in r2 and r3, the facial nucleus by neurons in r4 and r5, the glossopharyngeal nucleus by neurons in r6 and r7, and the motor nuclei of the vagus by neurons in r7 and r8. Axons of neurons in each of these nuclei course laterally within the brain, leaving the brain through exit points in the lateral neuroepithelium (of r2, r4, r6, and r7) and running together outside the brain to form the respective cranial motor nerves (V, VII, IX, X). The trigeminal (**V**) nerve innervates muscles in the 1st branchial arch, the facial (**VII**) nerve innervates muscles in the 2nd branchial arch, and the glossopharyngeal (**IX**) nerve innervates muscles in the 3rd branchial arch.

All of the visceral motor neurons (various shades of **green**, represented on the right side of the brain stem) develop initially next to the floor plate at the ventral midline; after extending their axons toward their respective exit points, the cell bodies then migrate laterally (**arrows**). Exceptions are the facial motor neurons formed in r4 (**red**); the cell bodies, after extending their axons toward the exit point, migrate caudally to the axial level of r6 before migrating laterally. General visceral (parasympathetic) motor neurons associated with nerve VII (**light green**) take a more conventional course (see panel **B**).

General somatic motor nuclei (**various shades of blue**, represented on the left side of the brain stem) are formed in r1 (trochlear nucleus), r5 and r6 (abducens nucleus), and r8 (hypoglossal nucleus). The cell bodies of these neurons remain close to their place of birth, next to the floor plate. The axons of abducens and hypoglossal neurons exit the brain directly ventrally, without coursing laterally. The axons of trochlear neurons (**light blue**) extend laterally and dorsally within the brain until, caudal to the inferior colliculus, they turn medially, decussate just behind the inferior colliculus, and exit near the midline of the opposite side.

B. The brain stem of a mouse embryo in which fluorescent dyes label different populations of cranial nerve VII motor neurons. A red-fluorescing dye fills the cell bodies of facial motor neurons via retrograde transport from the motor root of the facial nerve. These neurons develop initially in r4 and then migrate posteriorly, alongside the floor plate, to r6 (see **red** neurons in part **A**). A green-fluorescing dye fills the cell bodies of general visceral motor neurons in r5 (see **light green** neurons in part **A**) via retrograde transport from the root of the intermediate nerve (sensory and preganglionic general visceral motor axons). (Micrograph reproduced, with permission, from Dr. Ian McKay.)