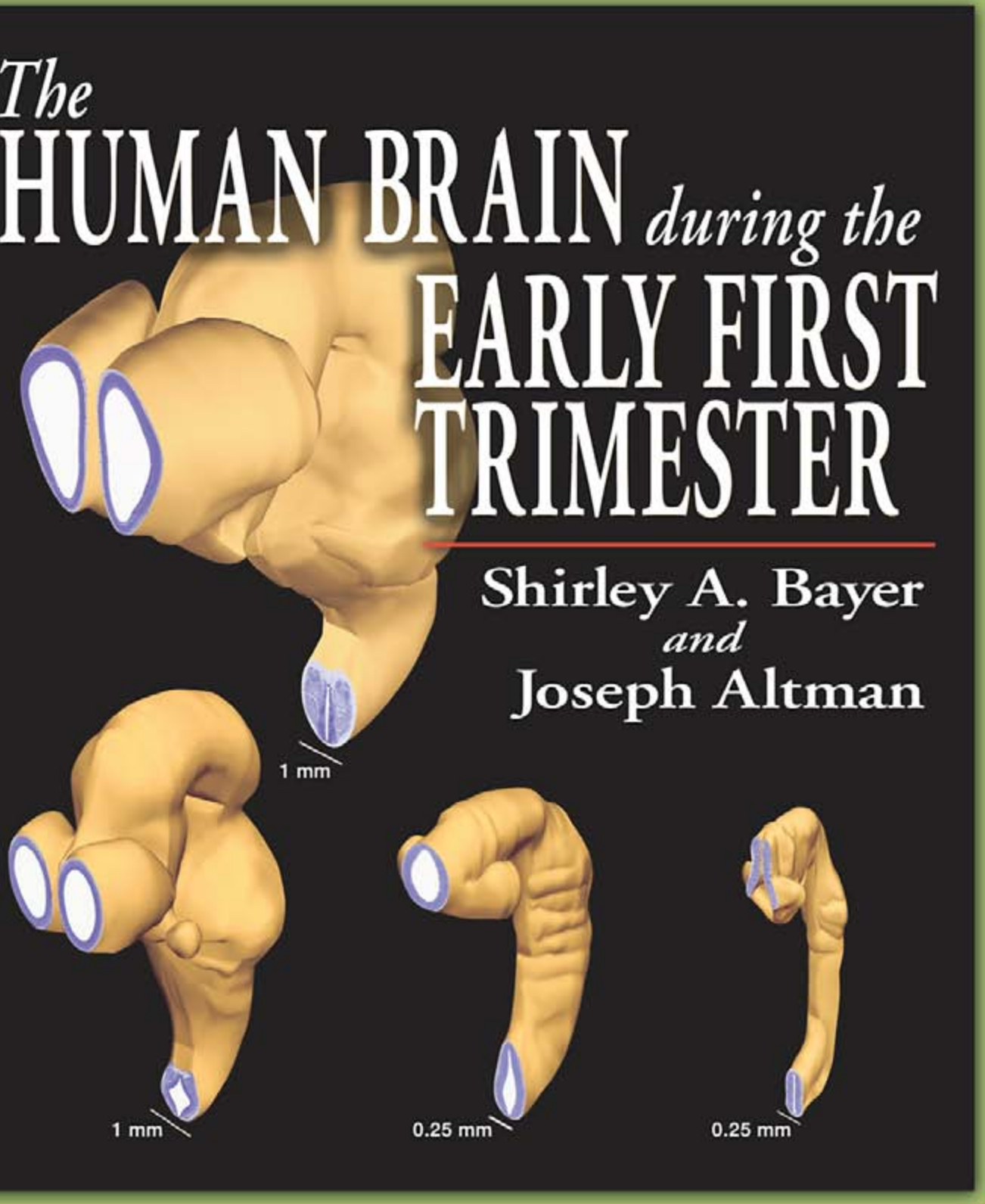
ATLAS OF
HUMAN CENTRAL NERVOUS SYSTEM DEVELOPMENT

VOLUME 5

The HUMAN BRAIN *during the* EARLY FIRST TRIMESTER

Shirley A. Bayer
and
Joseph Altman



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The HUMAN BRAIN *during the* EARLY FIRST TRIMESTER

ATLAS OF HUMAN CENTRAL NERVOUS SYSTEM DEVELOPMENT SERIES

Shirley A. Bayer *and* **Joseph Altman**

VOLUME 1

The Spinal Cord from Gestational Week 4 to the 4th Postnatal Month

VOLUME 2

The Human Brain during the Third Trimester

VOLUME 3

The Human Brain during the Second Trimester

VOLUME 4

The Human Brain during the Late First Trimester

VOLUME 5

The Human Brain during the Early First Trimester

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DEDICATION

We dedicate this volume to the new generation of neuroscientists: those who use powerful molecular techniques to study the mechanisms of central nervous system (CNS) development, and those who use advanced scanning techniques to monitor the development of the CNS under normal and abnormal conditions.

ACKNOWLEDGMENTS

We thank Dr. William DeMyer, pediatric neurologist at Indiana University Medical Center, for access to his personal library on human CNS development. We also thank the staff of the National Museum of Health and Medicine at the Armed Forces Institute of Pathology, Walter Reed Hospital, Washington, D.C.: Dr. Adrianne Noe, Director; Archibald J. Fobbs, Curator of the Yakovlev Collection; Elizabeth C. Lockett; and William Discher. We are most grateful to Dr. James M. Petras at the Walter Reed Institute of Research who made his darkroom facilities available so that we could develop all the photomicrographs on location rather than in our laboratory in Indiana. Finally, we thank Barbara Norwitz, Kari Budyk, and Suzanne Lassandro at CRC Press/Taylor & Francis for their personal attention to us and for expert help during production of the manuscript.

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PART I

INTRODUCTION

A. Organization of the Atlas

This is the last volume in the *Atlas of Human Central Nervous System Development* series. It deals with human brain development during the early first trimester from the 3rd through the 7th gestational weeks (GW3-GW7). Volume 1 (Bayer and Altman, 2002) records the development of the spinal cord from GW4 to the 4th postnatal month. Volumes 2 through 5 deal with prenatal brain development. The analysis procedes in reverse (older-to-younger) order: from more recognizable brain structures in the third trimester to progressively less familiar structures in the second trimester to often uncertain or hypothetical structures in the first trimester. Volume 2 (Bayer and Altman, 2004a) records brain development during the third trimester, with specimens ranging in age from GW37 to GW26; its major theme is the *maturation of the brain's settled and enduring neuron populations.* Volume 3 (Bayer and Altman, 2005) deals with brain development during the second trimester, with specimens ranging in age from GW24 to GW13.5; its major theme is the *migration, sojourning, and settling of the brain's diverse neuron populations.* Volume 4 (Bayer and Altman, 2006) presents brain development during the late first trimester, with specimens ranging in age from GW11 to GW7.5; its major theme is the *neuroepithelial mosaics that generate different populations of neurons and glia.* This volume presents brain development during the early first trimester, with specimens ranging in age from GW7.0 to GW3.2, and has four major themes: *(1) growth of the stockbuilding neuroepithelium along the expanding shorelines of the brain's superventricles, (2) early neurogenesis, (3) the onset of brain parenchymal development related to the expansion and decline of the superarachnoid reticulum, and (4) the inductive and signaling interactions between the brain and peripheral structures in the skull.*

The present volume features 14 normal specimens. Approximately two specimens near the same age were selected for analysis, one cut in the transverse (mainly coronal) plane, the other cut in the sagittal plane. For the oldest age group (GW7), there is a third specimen sectioned mainly in the horizontal plane. (Younger horizontally sectioned specimens are not in any of the collections we examined.) Each specimen is presented as a series of grayscale photographs of its Nissl-stained brain sections including the surrounding skull (**Parts II** through **XV**). The photographs are shown from anterior to posterior (coronal specimens), medial to lateral (sagittal specimens), and dorsal to ventral (horizontal GW7 specimen). Portrait orientation is used for the coronal specimens; the dorsal part of each section is toward the top of the page, the ventral part at the bottom, and the midline is in the vertical center of each section. Landscape orientation is used for the horizontal specimen; the anterior part of each section is facing to the left (bottom of page), posterior to the right (top of page), and the midline is in the horizontal center of each section. All coronal and horizontal specimes have computer-aided 3-dimensional reconstructions of their brains showing each section's location. That reconstruction clears up the ambiguity about the exact plane of sectioning through each brain; a problem we addressed in Volume 4. Portrait orientation is used for all sagittal specimens; the anterior part of each section is facing left, posterior right, dorsal top, and ventral bottom. **Parts II** through **XV** contain companion plates, designated as **A** and **B** on facing pages. **Part A** on the left page shows the full contrast photograph with labels of the skull and peripheral neural structures; **part B** on the right page shows low contrast copies of the same photograph with superimposed outlines of the labeled brain parts. The *low magnification plates* show entire sections to identify the large structures and subdivisions of the brain. The *high magnification plates* feature enlarged views of the brain core to identify smaller structures. For ease of interpretation in all plates, the ventricles are labeled in **CAPITALS**, the neuroepithelium and other germinal zones in **Helvetica bold**, transient structures in ***Times bold italic***, and permanent structures in Times Roman or **Times bold**. Fixation artifacts are usually outlined with dashed lines in **part B** of each plate, but few specimens in this volume have artifacts.

Since this is the final volume in the series, a **Concluding Essay (Part XVI)** links major themes of brain development at the cell and tissue level (described in the Atlas Series) with current neuro-developmental studies on gene expression and other molecular markers. **Figure 15** to **Figure 43** in the essay bring together photographs of individual brain structures at various ages so that the sequence of development is immediately apparent. An **Appendix** contains **tables** listing the estimated timespans of neurogenesis for the major populations in the human central ner-

vous system (CNS) based on experimentally determined data in rats. **References** follow the appendix, and the Atlas concludes with an alphabetized **Glossary** that defines the developmental structures labeled in the plates.

B. Specimens

All specimens are from the collections of human embryos and fetal brains currently kept at the National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, D.C. Nine specimens are from the Carnegie Collection and are designated by their respective numbers with the prefix C. The Carnegie Collection was started by Franklin P. Mall (1862-1917) and expanded at the Carnegie Institution of Washington under the direction of George L. Streeter (1873-1948) and George W. Corner (1889-1981). Five specimens are from the Minot Collection and are designated by their respective numbers with the prefix M. The Minot Collection is named after Charles S. Minot (1852-1914), who collected and prepared over 1900 embryos of different animal species, and approximately 100 human embryos, close to a century ago.

C. Photography and Computer Processing

All specimens were photographed using either an Olympus photomicroscope or a Wild photomakroskop. The magnification varied for each specimen according to the size of the head; the section with the largest area that could be accommodated within the field of view set the magnification for all sections of a particular specimen. All photographs were taken with a green filter to increase the contrast of the black and white film (Kodak technical pan #TP442). The film was developed at 20°C for 6 to 7 min in Kodak HC110 developer (dilution F), followed by Kodak stop bath for 30 s, Kodak fixer for 5 min, Kodak hypo clearing agent for 1 min, running water rinse for 10 min, and a brief rinse in Kodak photoflo before drying.

The negatives were scanned at 2700 dots-per-inch (dpi) with a Nikon Coolscan-1000 35-mm film scanner, which was interfaced to a PowerPC G3 Macintosh computer running Adobe Photoshop with a plug-in Nikon driver. To capture the subtle shades of gray, the negatives were scanned as color positives, inverted, and converted to grayscale. Using the enhancement features built into Adobe Photoshop and the additional features of Extensis Intellihance, adjustments were made to increase contrast and sharpness. When the image resolution was set to 300 dpi, a full-size photographic file printed at approximately 12 to 10 in. Most images are shown at slightly reduced full size on separate pages. Adobe Illustrator was used to superimpose labels and to outline structural details on low contrast copies of the Adobe Photoshop files. The plates were placed into a book-form layout using Adobe InDesign. Finally, camera-ready files were provided to Taylor & Francis in Adobe portable document format (pdf).

The entire brain and upper cervical spinal cord of each transversely cut specimen was three-dimensionally reconstructed in five steps. *First,* photographs of serial sections were made throughout the entire brain; the negatives were scanned and converted to computer files as described in the preceding paragraph. *Second,* all the files of sections selected for the reconstruction were placed into one large Photoshop file that contained a separate photograph in each layer. By altering the visibility and transparency of these layers the sections were aligned to each other as they were before sectioning. Then each layer was saved as a separate file. *Third,* Adobe Illustrator was used to outline the brain surface of each aligned section, and these contours were saved in separate Adobe Illustrator encapsulated postscript (eps) files. *Fourth,* the eps files were imported into 3D space (x, y, and z coordinates) using Cinema 4DXL (C4D, Maxon Computer, Inc.). For each section, points on the contours have unique x-y coordinates and the same z coordinate. By calculating the distance between sections, the entire array of contours was stretched out in the z axis. The C4D loft tool builds a "skin" of the brain as a spline mesh of polygons. The polygons start from the x-y points on the first contour with the most anterior z coordinate, to the x-y points on the next contour behind it, and finish with the x-y points on the last contour with the most posterior z coordinate. The spline meshes of the entire brain surface were rendered at various camera angles as completely opaque using the C4D ray-tracing engine. These reconstructions are shown in **Figure 1** to **Figure 14.** *Fifth,* spline meshes of the brain surface posterior to a specific section (coronal brains) or ventral to a specific section (horizontal brain) were rendered with a copy of the photograph of the particular section texture-mapped as a cap on the model. These reconstructions are shown as **insets in Part A** of each low magnification plate of the coronal and horizontal specimens.

D. Identification of Transient and Immature Brain Regions

With the exception of the rhombomeres in the pons and medulla that are visible prior to and including GW5.5, the identification of most structures in early first trimester human brain—in particular, the various neuroepithelial (NEP) compartments—have received little attention in the past. Most identifications are based on our previous ^{3}H-thymidine autoradiographic work with rats. There is a great similarity between the rat brain and human brain in the sequential order of neurogenesis and early neuronal differentiation, especially in the brainstem. Our experimental studies in the rat and the rationale for most of the proven or putative identifications we make are in the following publications.

Amygdala: Bayer (1980c).
Basal Ganglia: Bayer (1984, 1985b, 1987).
Cerebellum: Altman and Bayer (1978a, 1982a, 1985a,

1985b, 1985c, 1997).
Cerebral Cortex: Altman and Bayer (1990a, 1990b); Bayer and Altman (1990, 1991a).
Cranial Nerve Nuclei: Altman and Bayer (1980a, 1980b, 1980c, 1982b).
Hippocampus: Altman (1963); Altman and Das (1965a); Altman and Bayer (1975, 1990c, 1990d, 1990e); Bayer (1980a, 1980b).
Hypothalamus: Altman and Bayer (1978c, 1978d, 1978e, 1986).
Medulla: Altman and Bayer (1978b, 1980a, 1980b, 1980c, 1982b).
Midbrain: Altman and Bayer (1981a, 1981b, 1981c).
Olfactory Bulb: Altman (1969); Bayer (1983).
Pontine Area: Altman and Bayer (1978b, 1980d, 1987a, 1987b, 1987c, 1987d).
Precerebellar Nuclei: Altman and Bayer (1978b, 1987a, 1987b, 1987c, 1987d, 1997).
Preoptic Area: Altman and Bayer (1986); Bayer and Altman (1987).
Rhinencephalon: Bayer (1985a, 1986a, 1986b); Bayer and Altman (1991b).
Septal Area: Bayer (1979a, 1979b).
Spinal Cord: Altman and Bayer (1984, 2001).
Thalamus: Altman and Bayer (1979a, 1979b, 1979c, 1988a, 1988b, 1988c, 1989a, 1989b, 1989c).

E. Major Developmental Features of the First Trimester Brain

In **Part XVI**, **Concluding Essay**, we summarize the landmark events that characterize the development of the human CNS during the first trimester. Briefly reviewed, they are the following.

(i) For several weeks after closure of the neural tube (the future spinal cord) and the neural vesicles (the future rhombencephalon, mesencephalon, diencephalon, and telencephalon), the CNS consists of a single proliferative tissue, the *stockbuilding neuroepithelium* (NEP). These NEP cells do not produce neurons and neuroglia but rather the growing stock of pluripotent progenitor cells that will later give rise to the differentiating cells of the CNS.

(ii) The proliferating NEP cells undergo mitosis near the lumen of the ventricles, hence the growth of the stockbuilding NEP matrix is associated with the expansion of the narrow protoventricles to produce the large rhombencephalic, mesencephalic, diencephalic, and telencephalic *superventricles*.

(iii) The rate of stockbuilding cell mitosis varies in different components of the NEP matrix in relation to the sizes of the neuronal populations being generated for different brain structures. This results in a variegated ventricular shoreline (rhombomeres, evaginations, invaginations, eminences). We refer to these distinguishable NEP matrix shorelines as *NEP cell mosaics*.

(iv) When NEP cell proliferation shifts from stockbuilding progenitor cells to unloading postmitotic neurons and neuroglia, these cells migrate outward and accumulate in the brain parenchyma, the space situated between the NEP and the pia. We present evidence that the formation of a hitherto unidentified meningeal structure, the *superarachnoid reticulum*, is related to this parenchymal expansion. The superarachnoid reticulum is a broad, fluid-rich meningeal tissue sandwiched between the early-developing pia and the formative dura. The initial expansion of the superarachnoid reticulum antedates the appearance of the brain parenchyma. While the parenchyma continually expands as more and more neurons migrate into it and differentiate, the superarachnoid reticulum continually shrinks until it is a thin meninx. We postulate that the transient hypertophy of the superarachnoid reticulum serves as a *parenchymal expansion field* for the developing brain.

(v) The shrinkage of the NEP matrix is coupled with *cell migration*. A small complement of migrating cells produce fate-restricted *secondary germinal matrices* away from the ventricle, such as the external germinal layer of the cerebellum and the subgranular zone of the hippocampus. The bulk of migrating cells are young neurons that may sojourn in *transitional fields* but eventually settle in their final locations throughout the parenchyma.

(vi) Peripheral and central inductive and signaling mechanisms play a major role in producing fate-restricted NEP cell mosaics, guiding migrating neurons, and directing axons to grow to their targets. Interactions between the NEP and the cephalic and branchial placodes (peripherocentral signaling) influence the diversification of NEP mosaics. Centro-central signaling between CNS structures is responsible for the coordinated development of different brain regions not directly connected with the periphery.

(vii) An attempt is made to relate the morphological evidence for NEP matrix diversification, cell-fate restriction, neuronal migration, and axonal guidance in the human CNS with the underlying genetic and molecular mechanisms revealed by current research in animals.

PART II: GW7 CORONAL

This specimen is embryo #2155 in the Minot Collection, designated here as M2155. The crown-rump length (CR) is 17.5 mm estimated to be at gestational week (GW) 7. Most of M2155's brain sections are cut (10 μm) in the coronal plane, but the plane shifts to predominantly horizontal in the posterior medulla. We photographed 71 sections at low magnification from the frontal prominence to the posterior tips of the mesencephalon and cerebellum. Seventeen of these sections are illustrated in **Plates 1AB to 17AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of M2155's brain (**Figure 1**), and to show each illustrated section *in situ* (*insets,* **Plates 1A-17A**). A prominent developmental strategy during the early first trimester is that **many developing brain structures interact with primordial structures in the head and neck**. Consequently, each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 18-20** show high-magnification views of the cerebral cortex, diencephalon, and mesencephalon. Some high-magnification plates are rotated 90˚ (landscape orientation) to more efficiently use page space. The brain of M2155 has considerable variation in the thickness of the neuroepithelium and in the number of migrating neurons in various parts of the brain parenchyma.

Throughout the telencephalon, the neuroepithelium is the most prominent structure surrounding the enlarging telencephalic superventricle. A cell-sparse primordial plexiform layer is adjacent to the cerebral cortical neuroepithelium. A few pioneer Cajal-Retzius neurons have migrated into this layer, but most cortical neurons have not yet been generated. The cerebral cortical neuroepithelium is growing by adding more neuonal stem cells that will produce neurons during the late first trimester (**Volume 4**, Bayer and Altman, 2006) and early second trimester (**Volume 3**, Bayer and Altman, 2005). In contrast to the cerebral cortical neuroepithelium, the basal ganglionic and basal telencephalic neuroepithelia do have adjacent migrating neurons. In some areas, these neurons appear to migrate together in early (outermost and less dense) to late (innermost and most dense) waves. In accordance with the peripheral interaction theme, there is only the slightest indication of an olfactory bulb evagination in spite of the fact that a fully invaginated olfactory epithelium is in the nasal cavity and olfactory nerve fibers already contact the brain just anterior to the basal telencephalon. We hypothesize that olfactory nerve fibers have the capacity to induce the cortical neuroepithelium to proliferate and evaginate into an olfactory bulb later on. There is an olfactory evagination by GW7.5 (*See* **Volume 4**, Bayer and Altman, 2006, **Plates 188A and B**, pp. 464-465).

The diencephalic neuroepithelium surrounds a slit-like superventricle. It is thinnest in the hypothalamic and subthalamic areas, where it is surrounded by densely packed waves of migrating neurons. It is postulated that these areas of the superventricle have shrinking shorelines as the neuroepithelia "unload" their stock of neuronal precursors. In contrast, the superventricle shoreline is still expanding as the thalamic neuroepithelium continues to add more neuronal precursors than to unload postmitotic neurons. The few neurons outside the thalamic neuroepithelium are postulated to be the oldest neurons in the ventral complex, posterior complex, and the reticular nucleus.

The mesencephalon contains a stockbuilding neuroepithelium in the pretectum and tectum (relatively few adjacent migrating neurons). On the other hand, the tegmental and isthmal neuroepithelia are much thinner because most of their neuronal progeny has migrated out. These cells accumulate as inner dense clumps and outer sparse arrays interspersed among the thick accumulations of subpial fiber bands in the tegmental and isthmal parenchyma.

Both the pons and medulla have neuroepithelia that are shrinking as they have already unloaded their neuronal precursors into an expanding parenchyma. Cells are migrating and settling in longitudinal arrays at the pontine flexure. A few cells are settling in the superior olive complex and many are settling in the reticular formation throughout the pons and medulla. Facial motor neurons are migrating from medial to lateral, leaving behind their axons in the genu of the facial nerve. Migrating cochlear nuclear neurons are outside the neuroepithelium in the anterior part of the lower rhombic lip, while migrating inferior olive neurons are in the posterior intramural migratory stream outside the precerebellar neuroepithelium in the posterior lower rhombic lip; some neurons have already settled in the inferior olive. Many neurons have settled in the solitary nucleus, surrounding a definite solitary tract. The hypoglossal nucleus is also distinguishable in the lower medulla.

The cerebellar neuroepithelium is exceptional in the rhombencephalon because it is the only neuroepithelium still in the stockbuilding phase, mainly adding precursors of Purkinje cells. Many deep nuclear neurons have already been generated and are migrating in the cellular layers of the cerebellar transitional field. The fibrous layers probably contain afferents from the spinal cord and the vestibular ganglion.

M2155 Computer-aided 3-D Brain Reconstructions

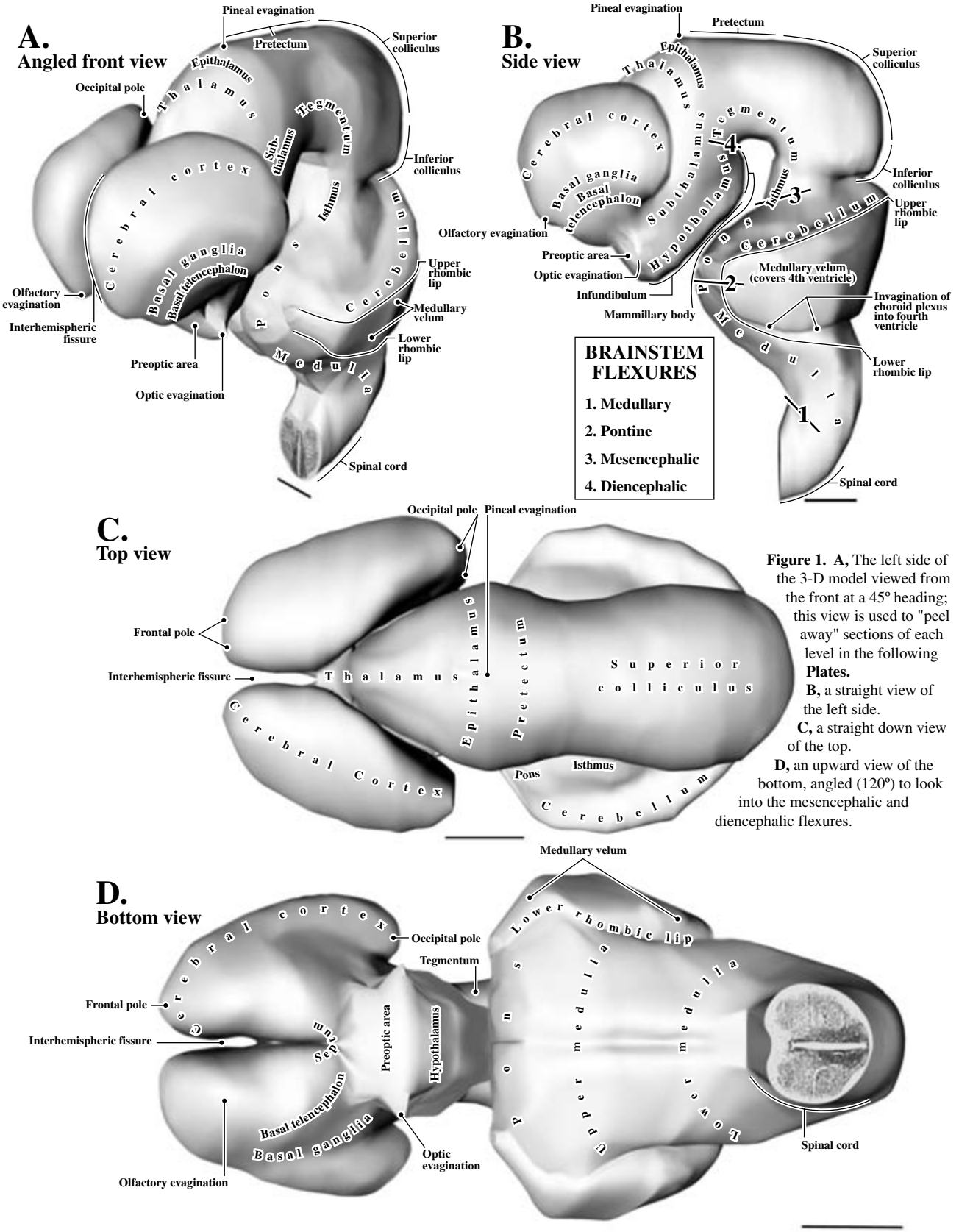


Figure 1. A, The left side of the 3-D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.**

B, a straight view of the left side.

C, a straight down view of the top.

D, an upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures.

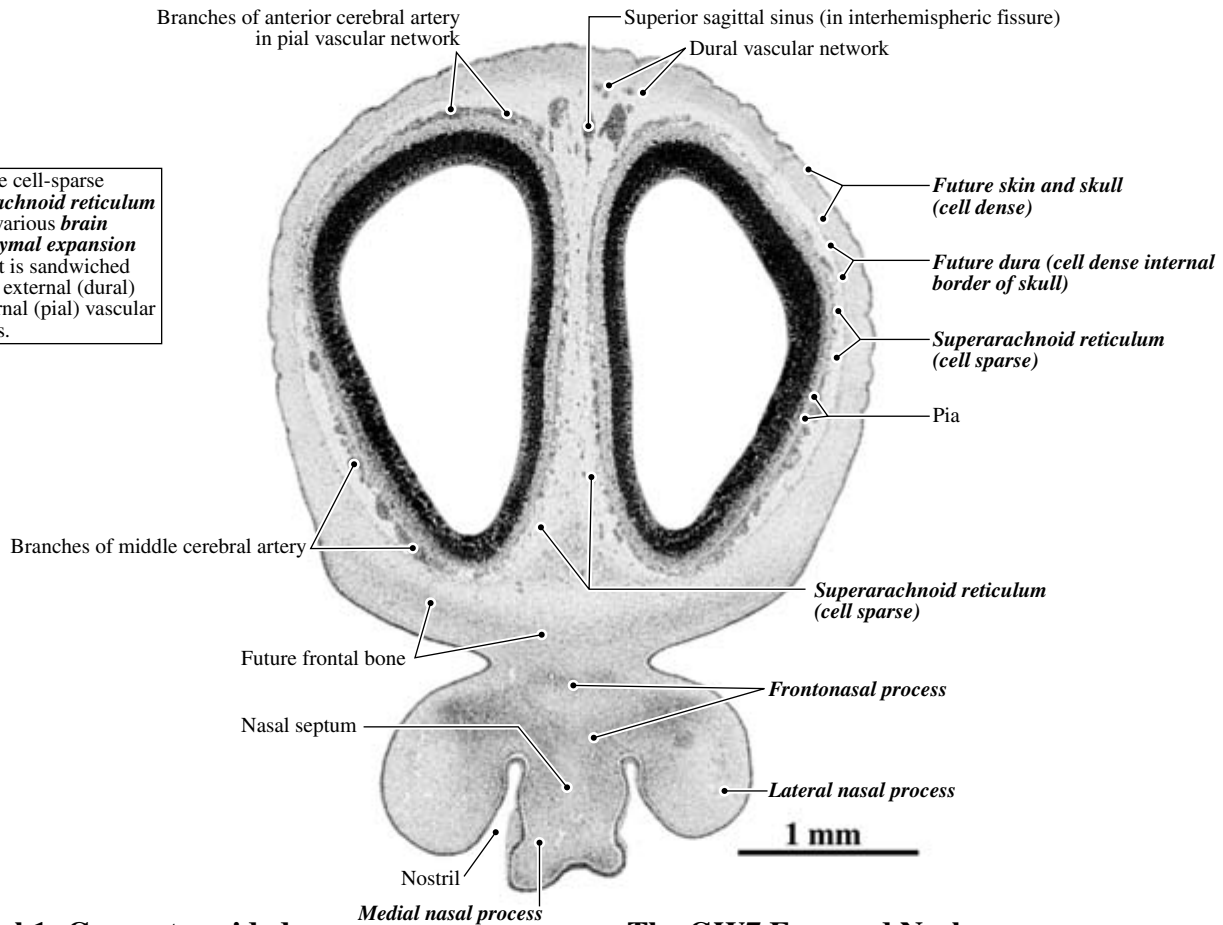
Scale bars = 1 mm

PLATE 1A

GW7 Coronal
CR 17.5 mm
M2155
Level 1: Section 50

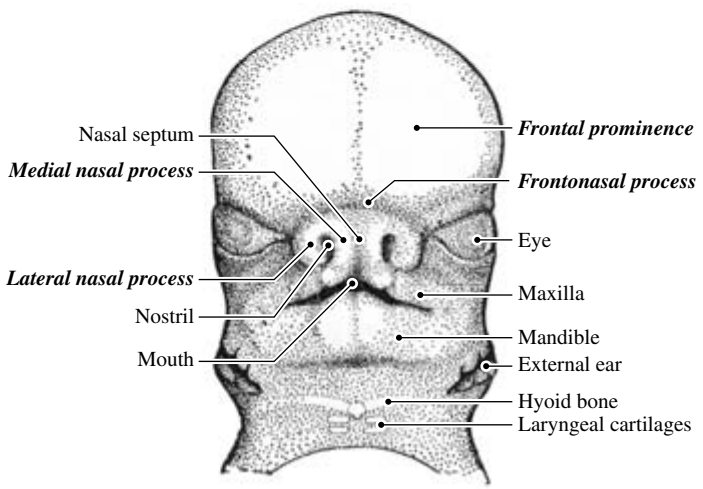
Non-neural structures labeled

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.



↓ Level 1: Computer-aided 3-D Brain Reconstruction

The GW7 Face and Neck
Figure 247E modified (Patten, 1953, p. 429.)

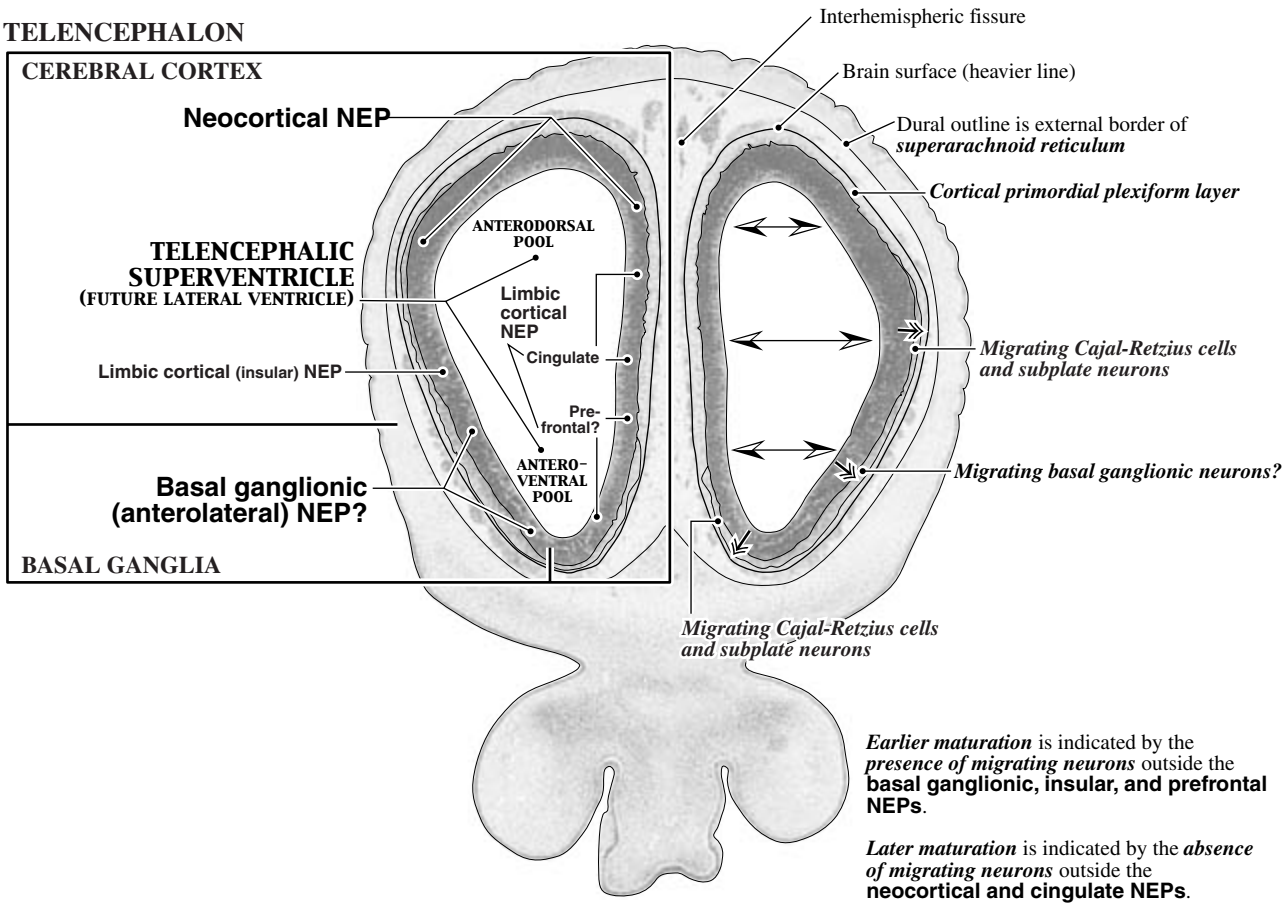


FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 1B

NEP - Neuroepithelium

Neural structures labeled

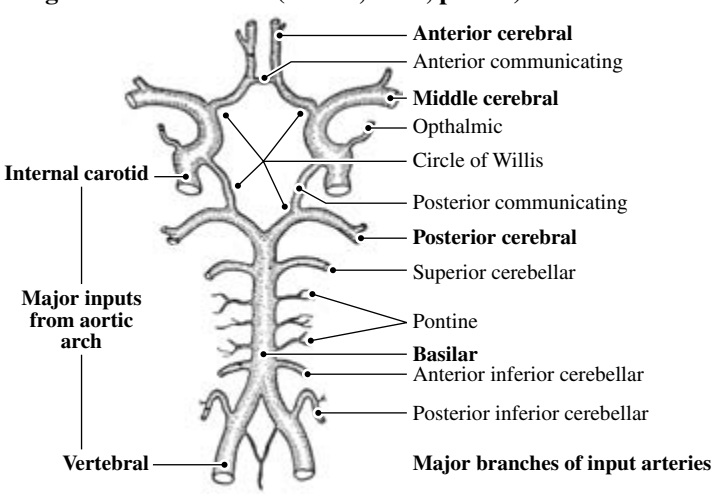


Earlier maturation is indicated by the ***presence of migrating neurons*** outside the **basal ganglionic, insular, and prefrontal NEPs**.

Later maturation is indicated by the ***absence of migrating neurons*** outside the **neocortical and cingulate NEPs**.

Major Arteries at Base of Brain

Figure 394D modified (Patten, 1953, p. 625.)



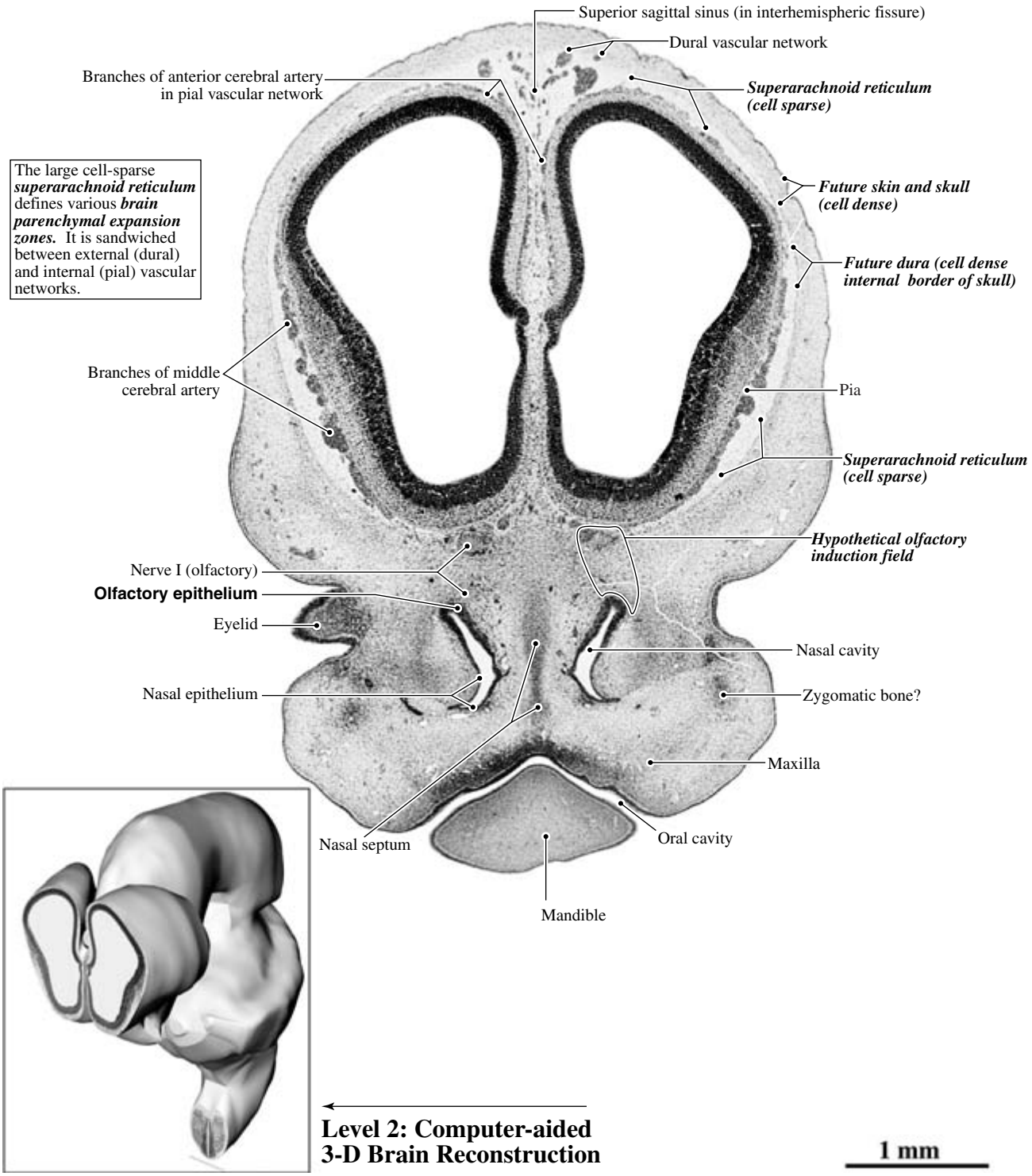
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 2A

GW7 Coronal
CR 17.5 mm
M2155
Level 2: Section 116

Peripheral neural and non-neural structures labeled



Level 2: Computer-aided 3-D Brain Reconstruction

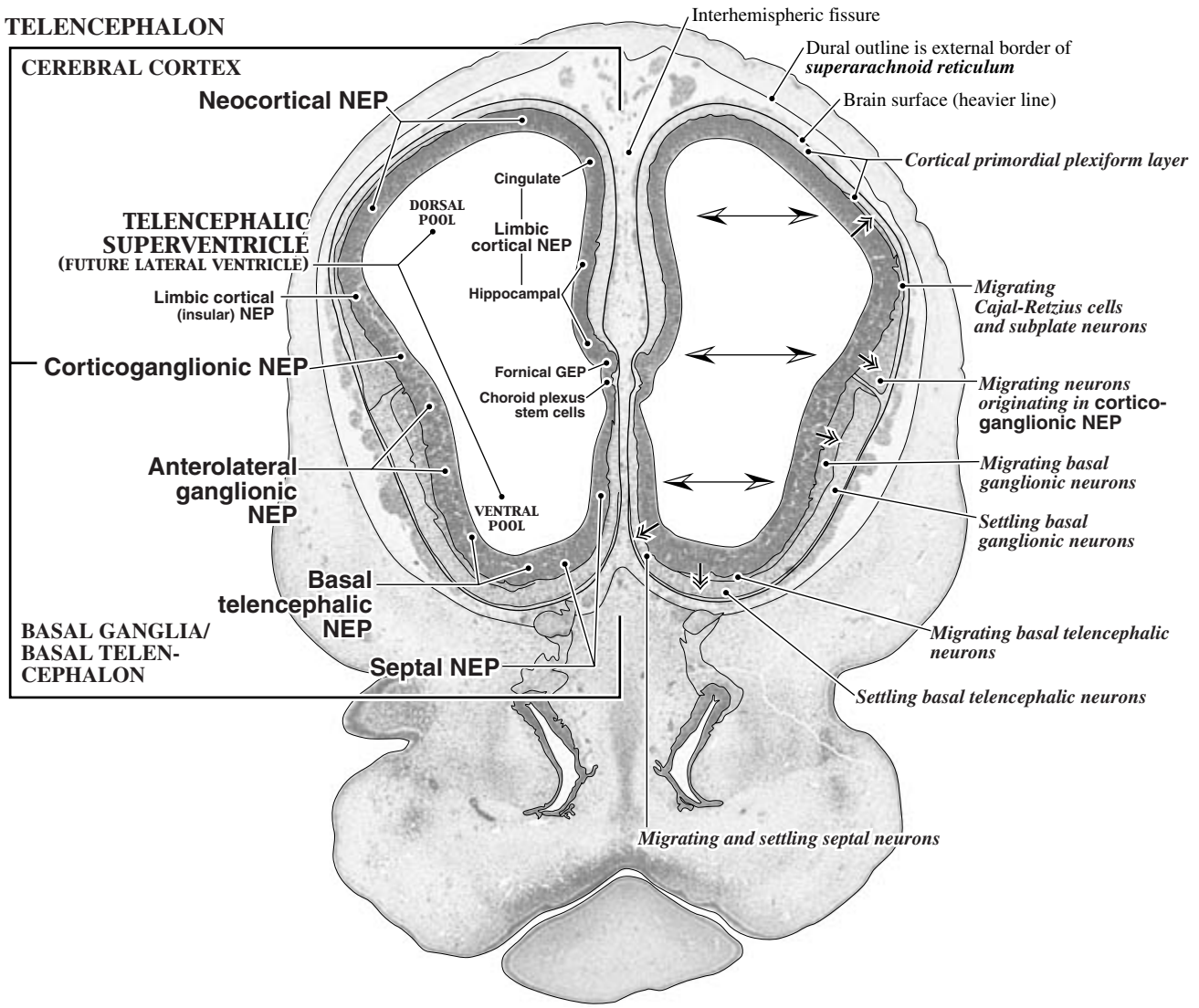
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 2B

Central neural structures labeled



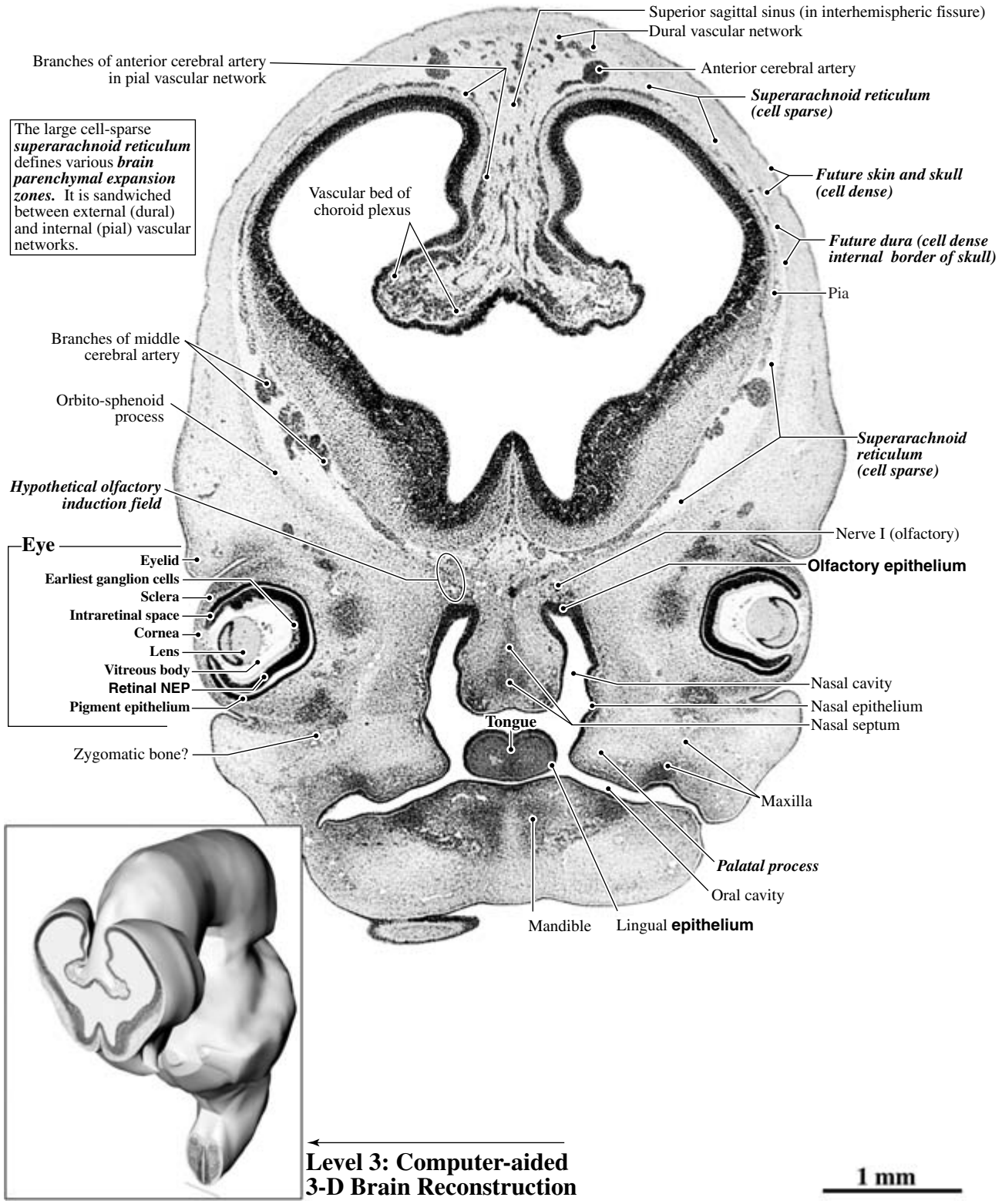
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 3A

GW7 Coronal
CR 17.5 mm
M2155
Level 3:
Section 164

Peripheral neural and non-neural structures labeled



Level 3: Computer-aided 3-D Brain Reconstruction

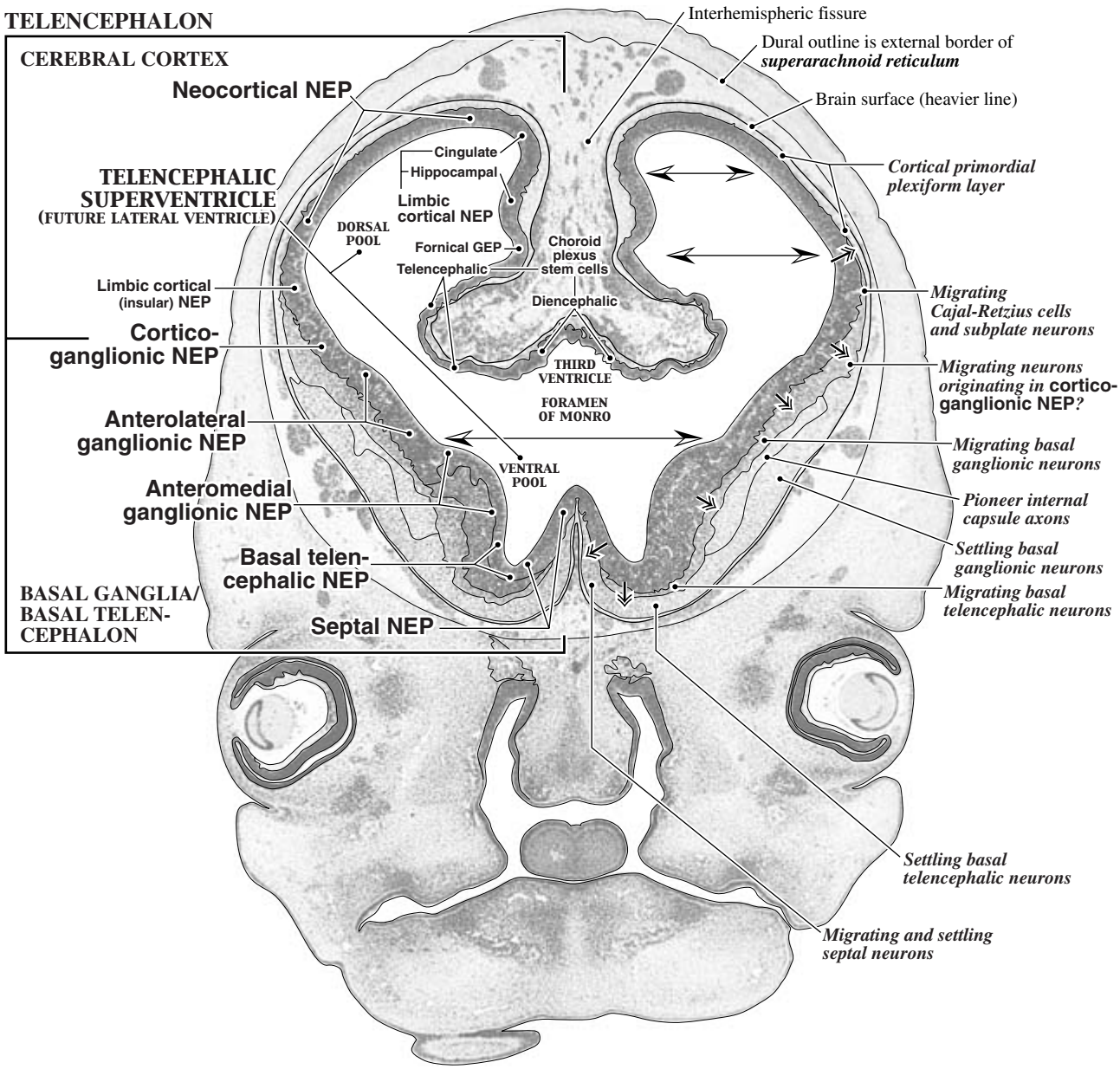
1 mm

PLATE 3B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

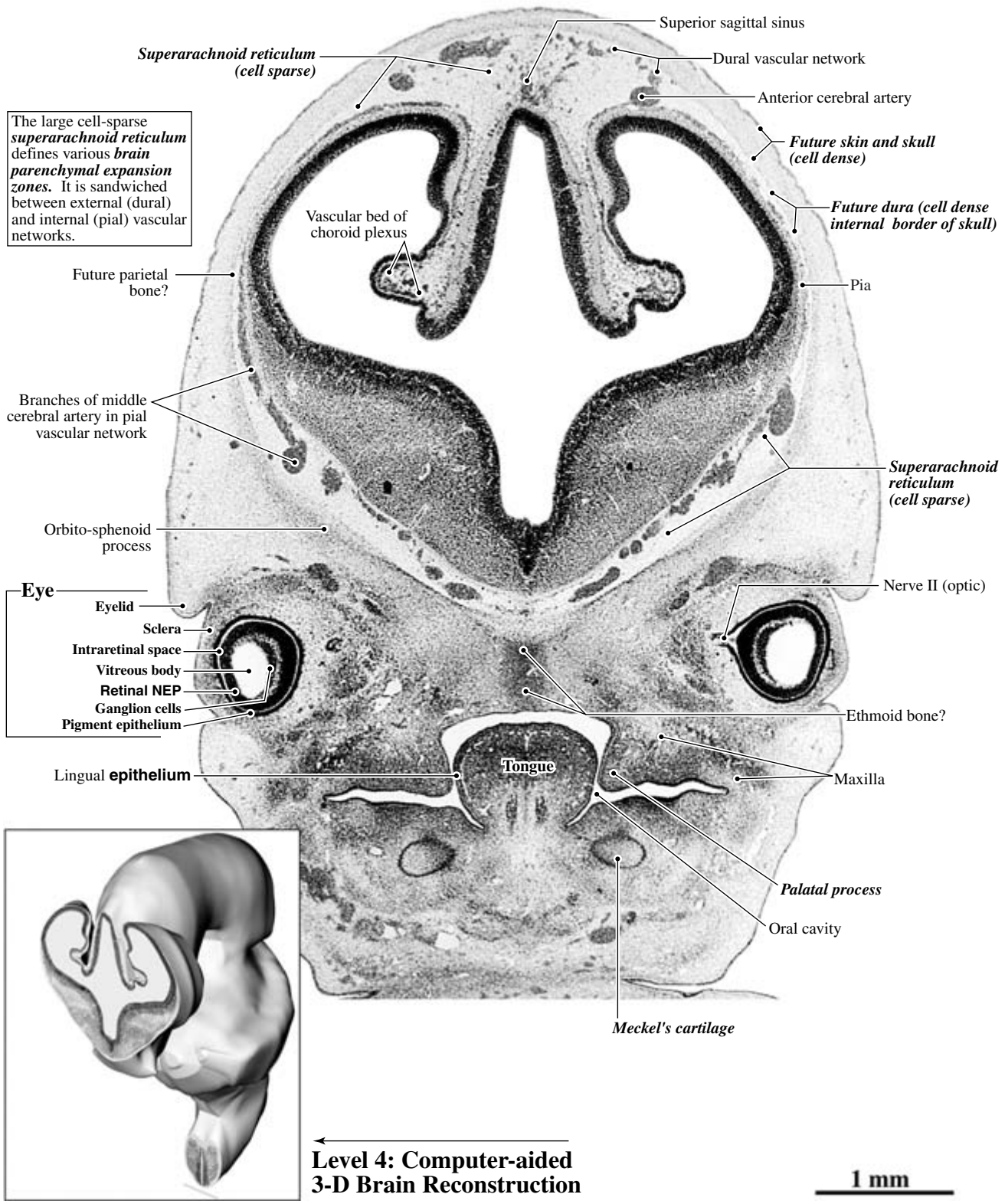
PLATE 4A

See a high magnification view of the thalamus and cerebral cortex in Plates 18A and B.

GW7 Coronal
CR 17.5 mm
M2155
Level 4:
Section 201

Peripheral neural and non-neural structures labeled

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.



Level 4: Computer-aided 3-D Brain Reconstruction

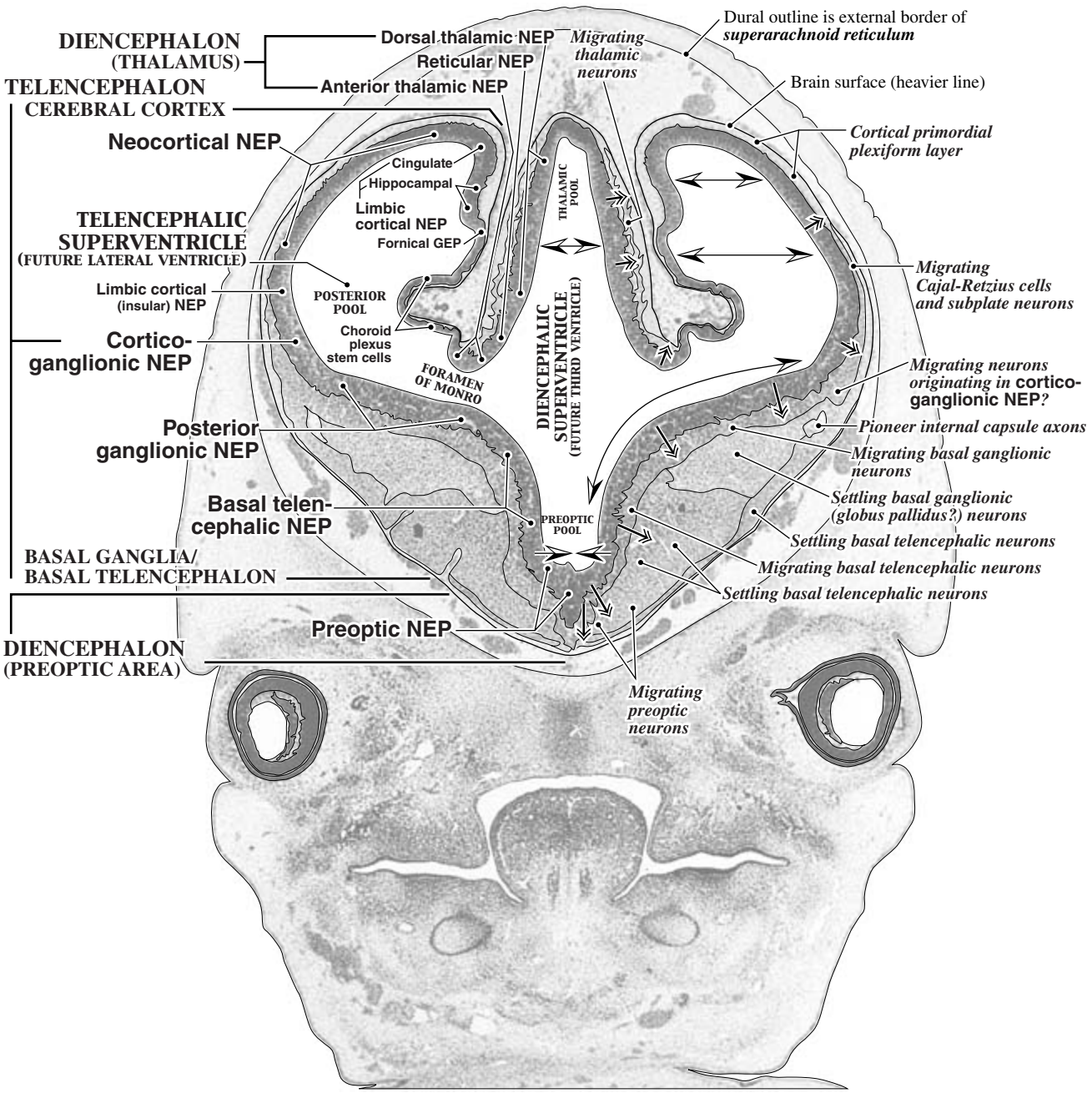
1 mm

PLATE 4B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

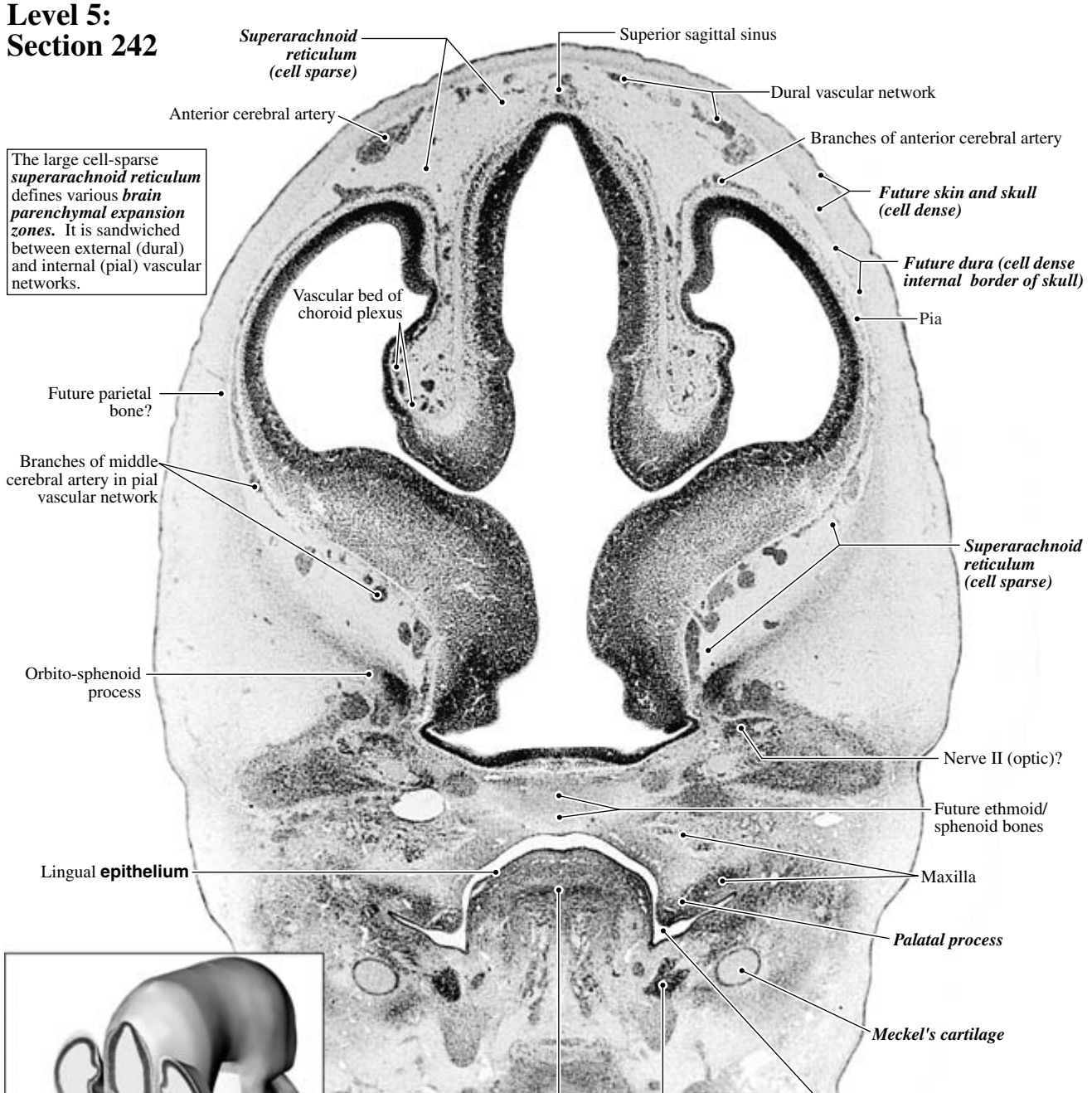
PLATE 5A

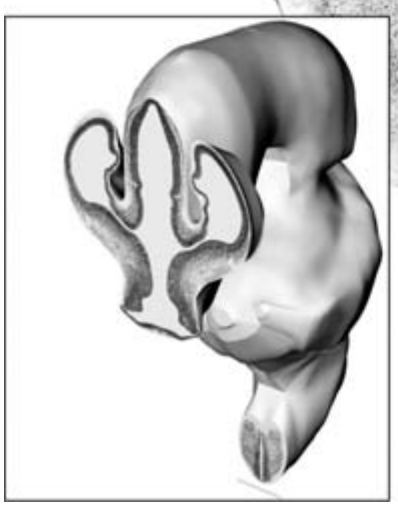
See a high magnification view of the thalamus and cerebral cortex from Section 236 in Plates 19A and B.

GW7 Coronal
CR 17.5 mm
M2155
Level 5:
Section 242

Peripheral neural and non-neural structures labeled

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.





Level 5: Computer-aided 3-D Brain Reconstruction

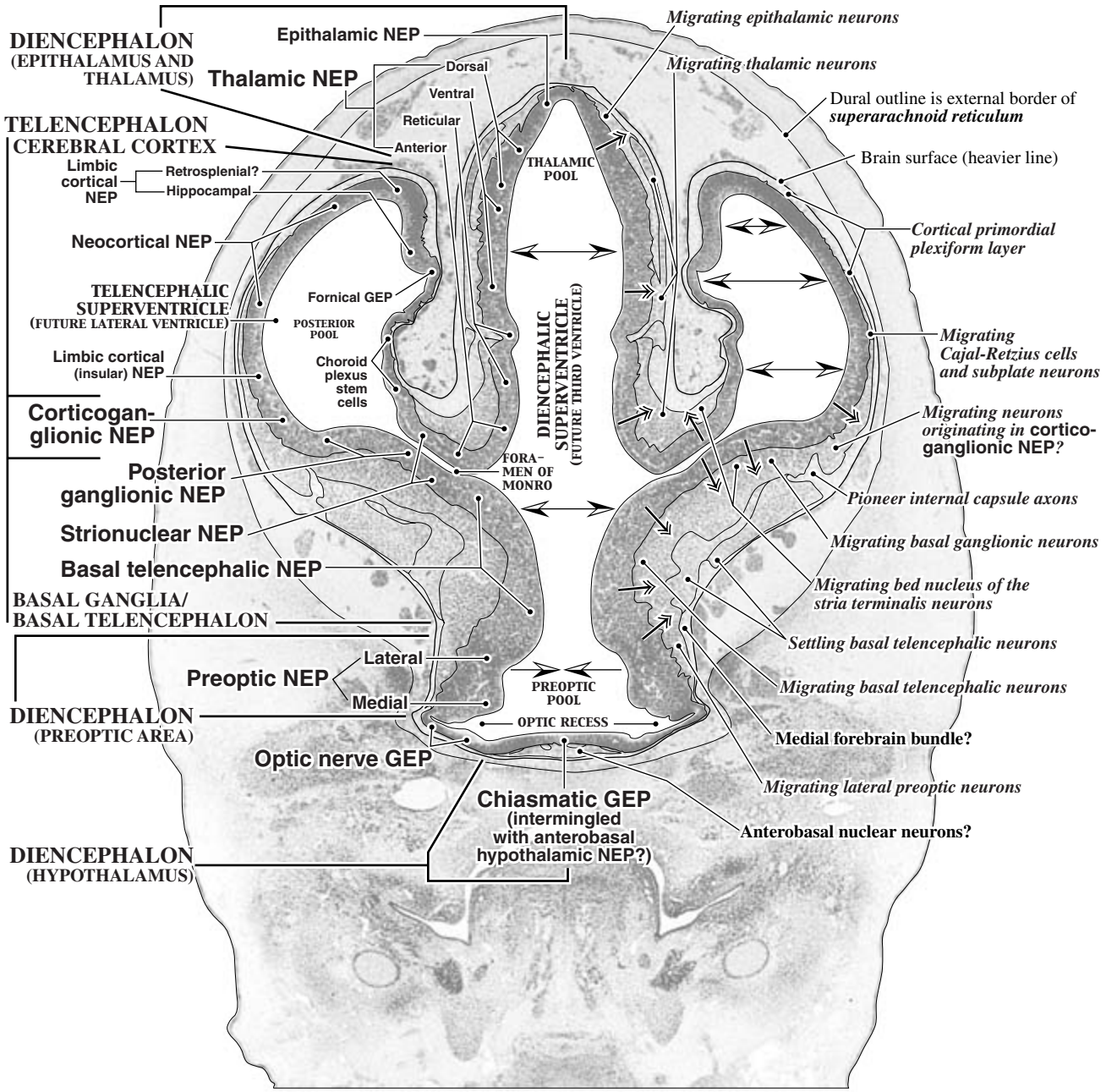
1 mm

PLATE 5B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

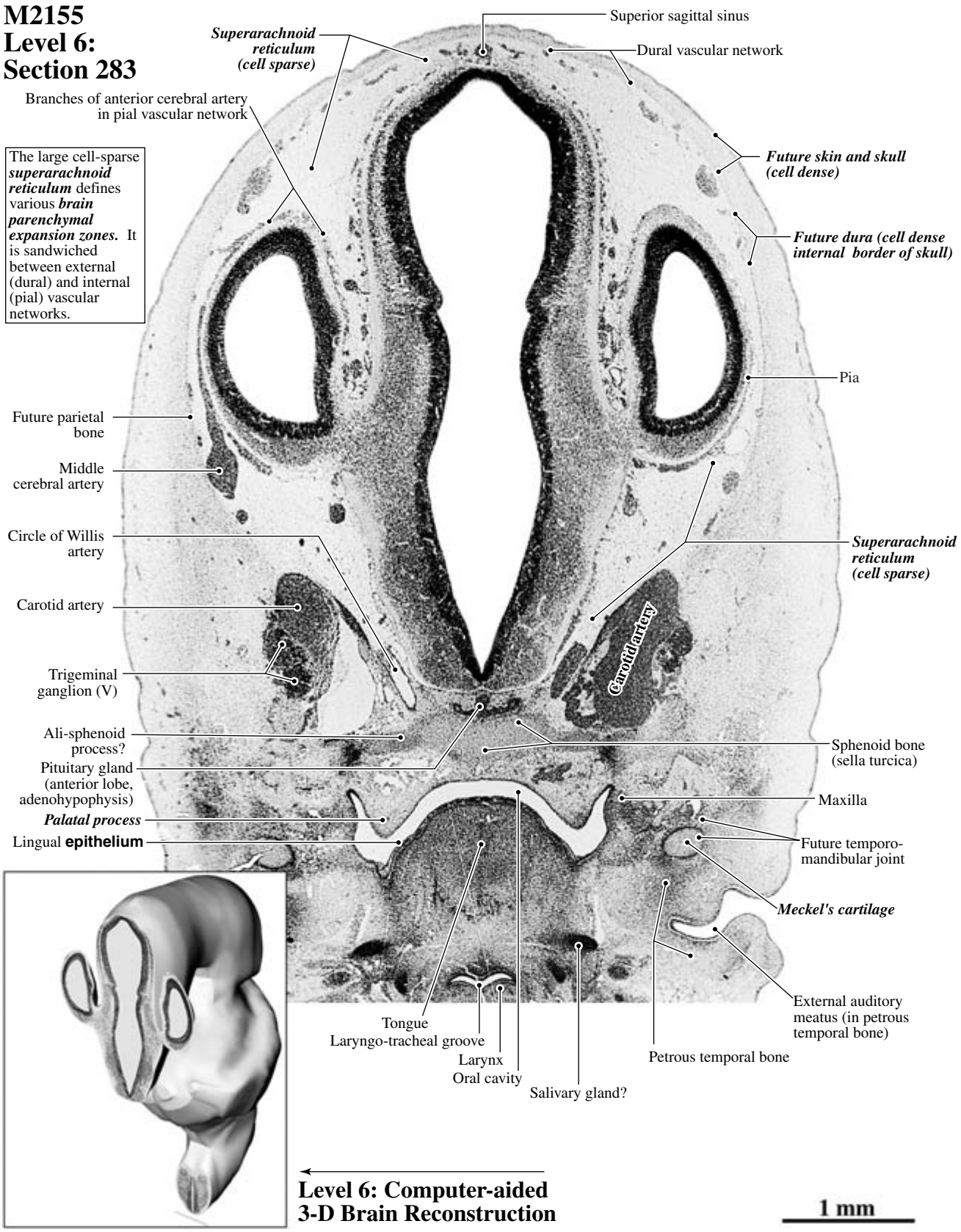
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 6A

GW7 Coronal
CR 17.5 mm
M2155
Level 6:
Section 283

Peripheral neural and non-neural structures labeled



The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

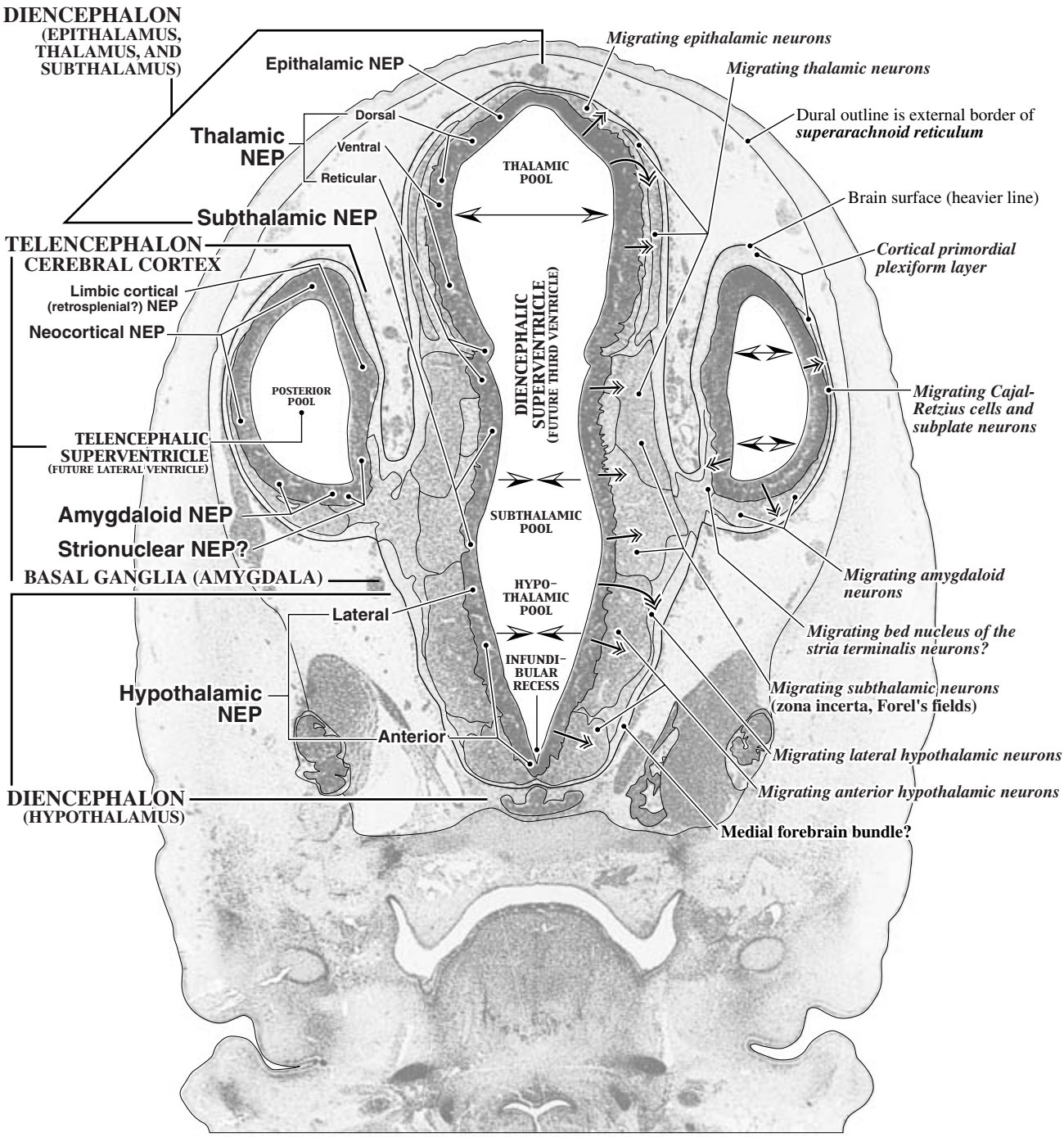
Level 6: Computer-aided 3-D Brain Reconstruction

1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 6B
NEP - Neuroepithelium

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

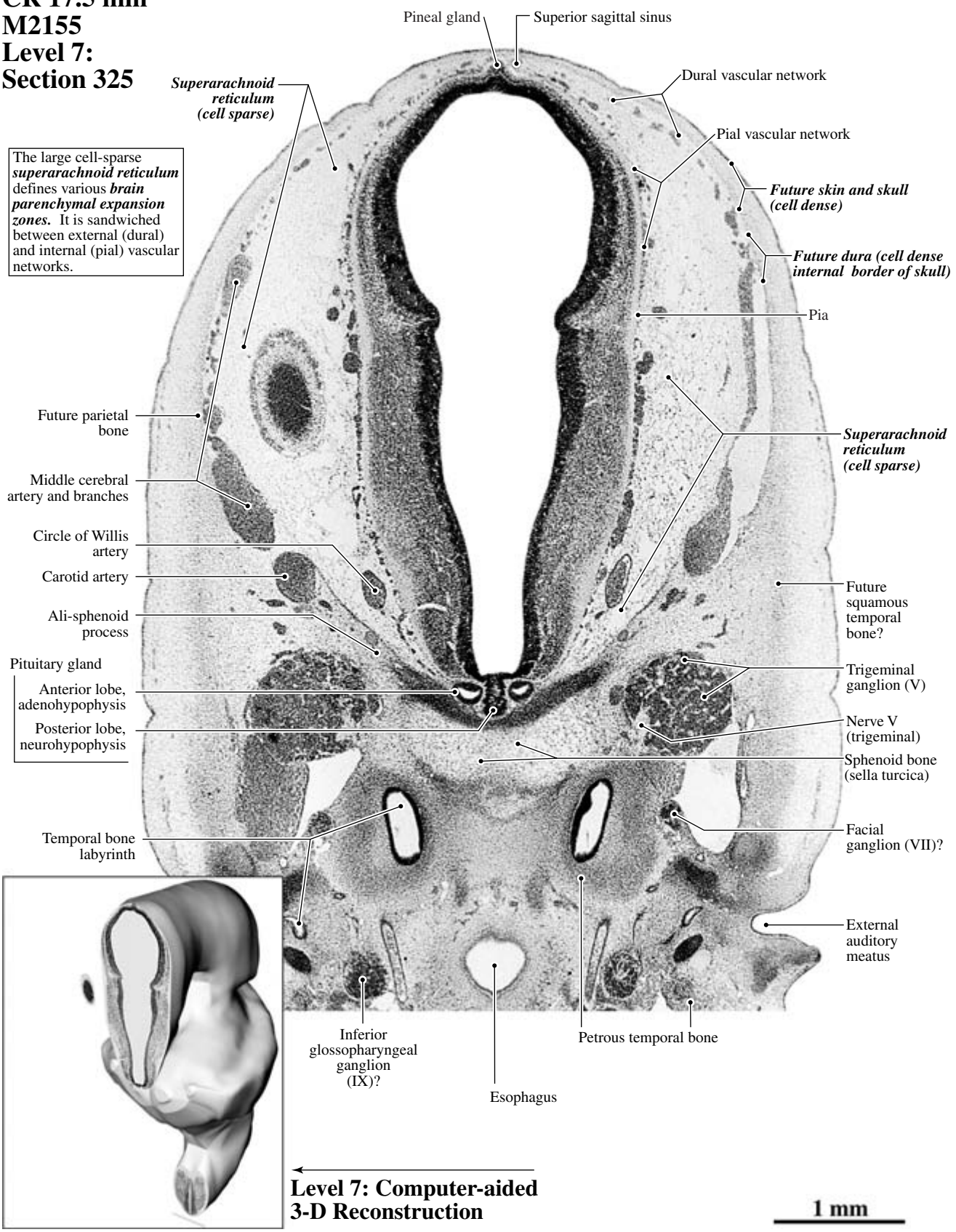
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 7A

GW7 Coronal
CR 17.5 mm
M2155
Level 7:
Section 325

Peripheral neural and non-neural structures labeled



The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

Level 7: Computer-aided 3-D Reconstruction

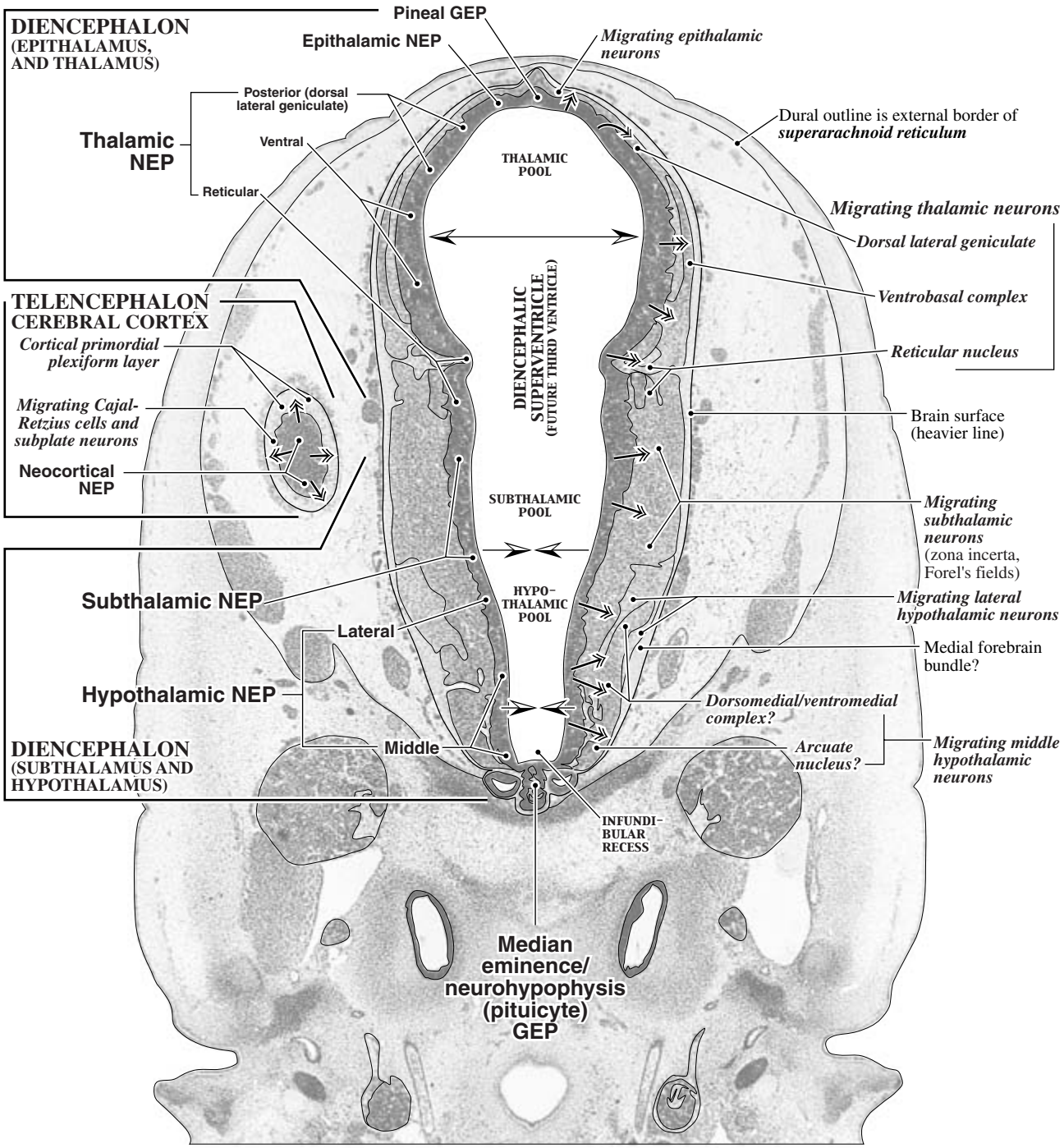
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 7B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

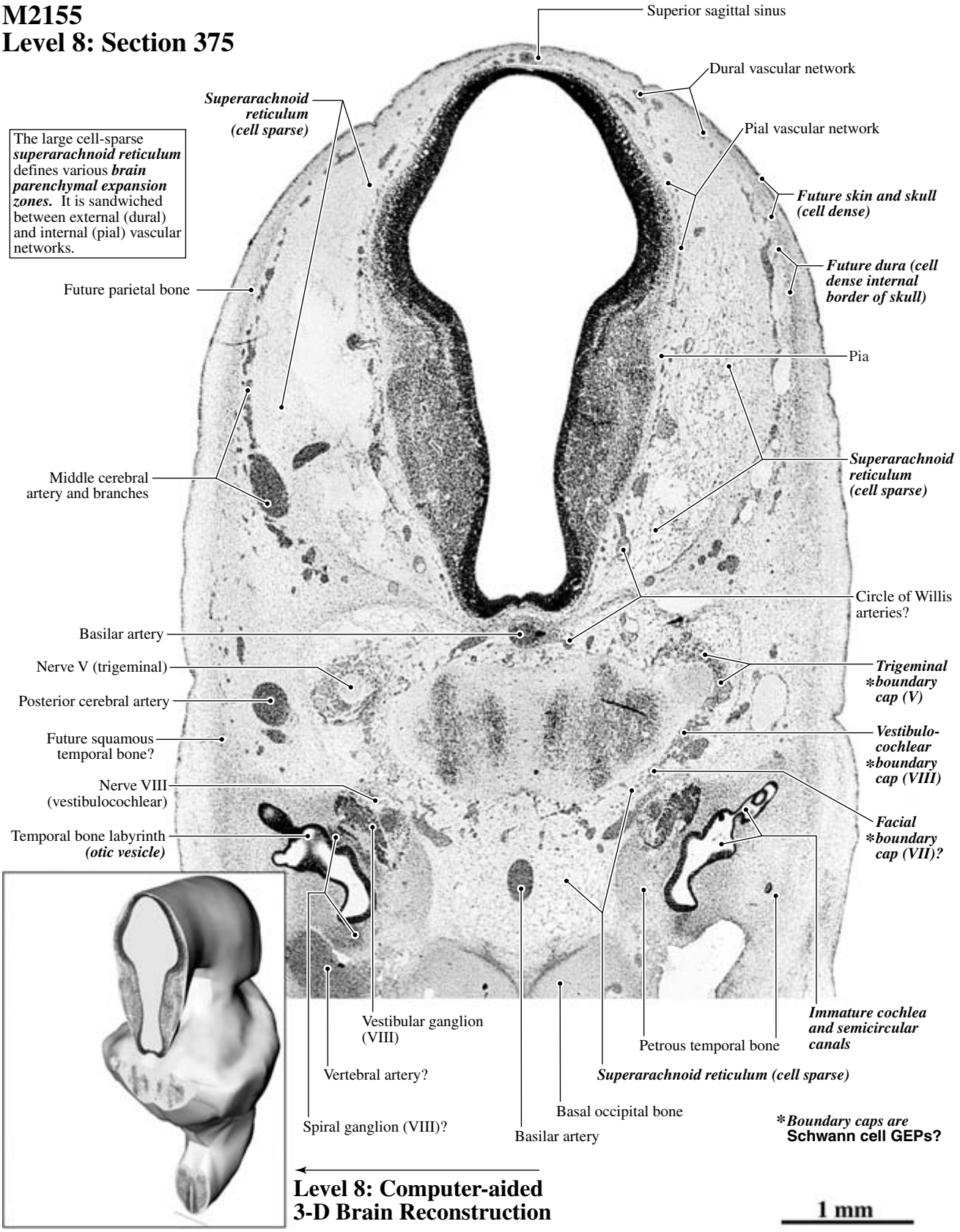
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 8A

GW7 Coronal
CR 17.5 mm
M2155
Level 8: Section 375

Peripheral neural and non-neural structures labeled



The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

Boundary caps are** **Schwann cell GEPs?

Level 8: Computer-aided 3-D Brain Reconstruction

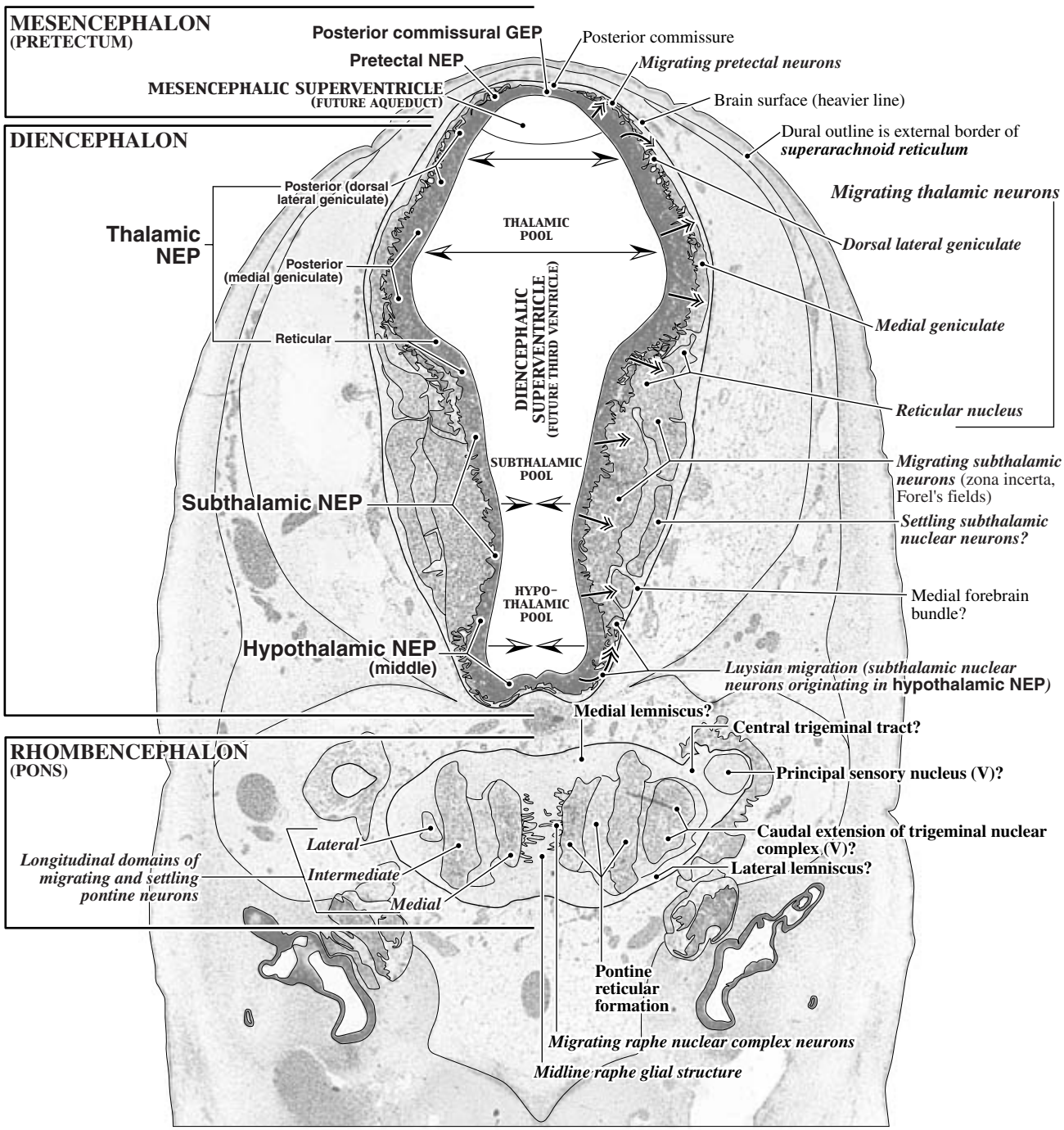
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 8B

Central neural structures labeled

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

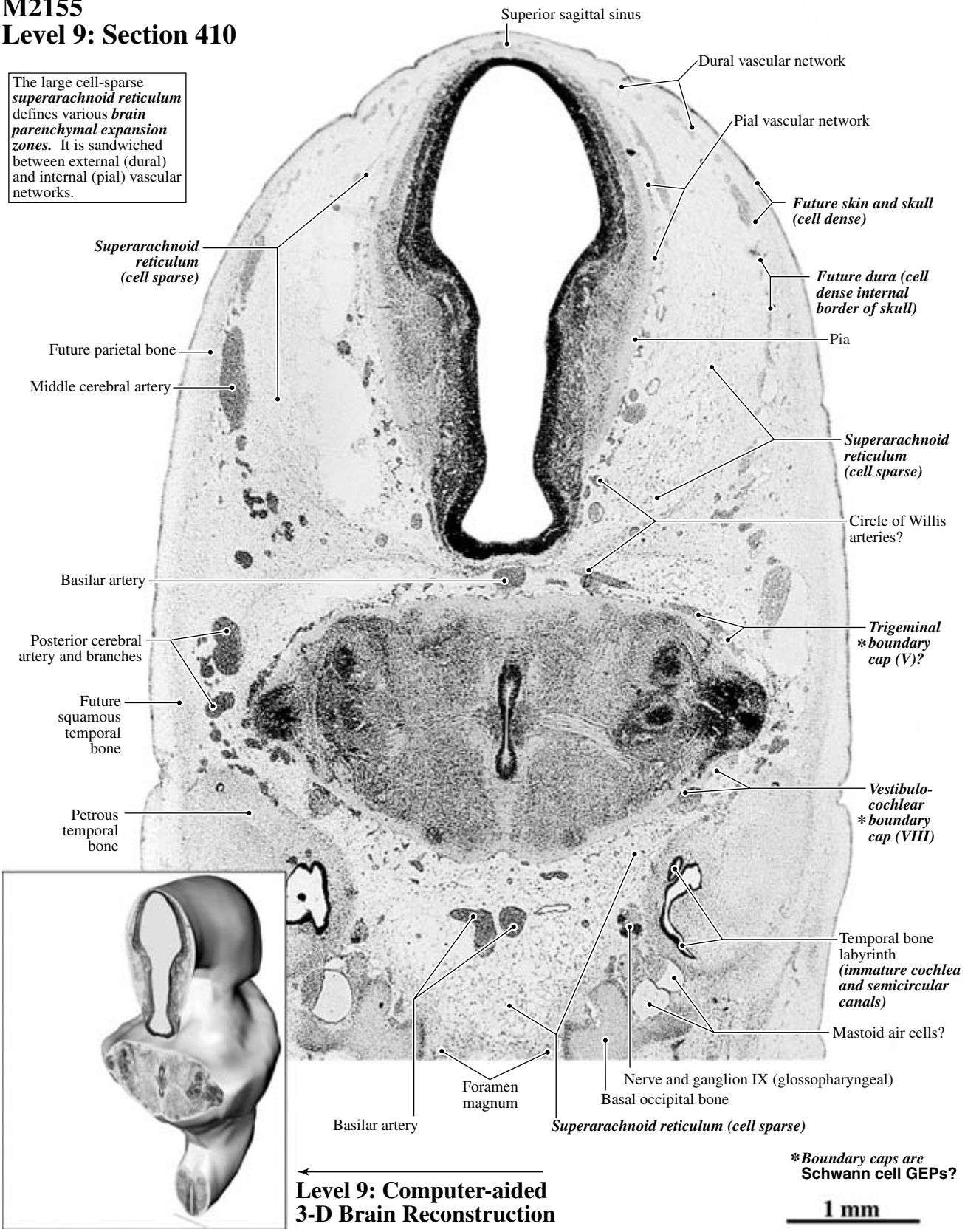
PLATE 9A

GW7 Coronal
CR 17.5 mm
M2155
Level 9: Section 410

Peripheral neural and non-neural structures labeled

See a high magnification view of the mesencephalon and diencephalon from Section 390 in Plates 20A and B.

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.



Level 9: Computer-aided 3-D Brain Reconstruction

*Boundary caps are Schwann cell GEPs?

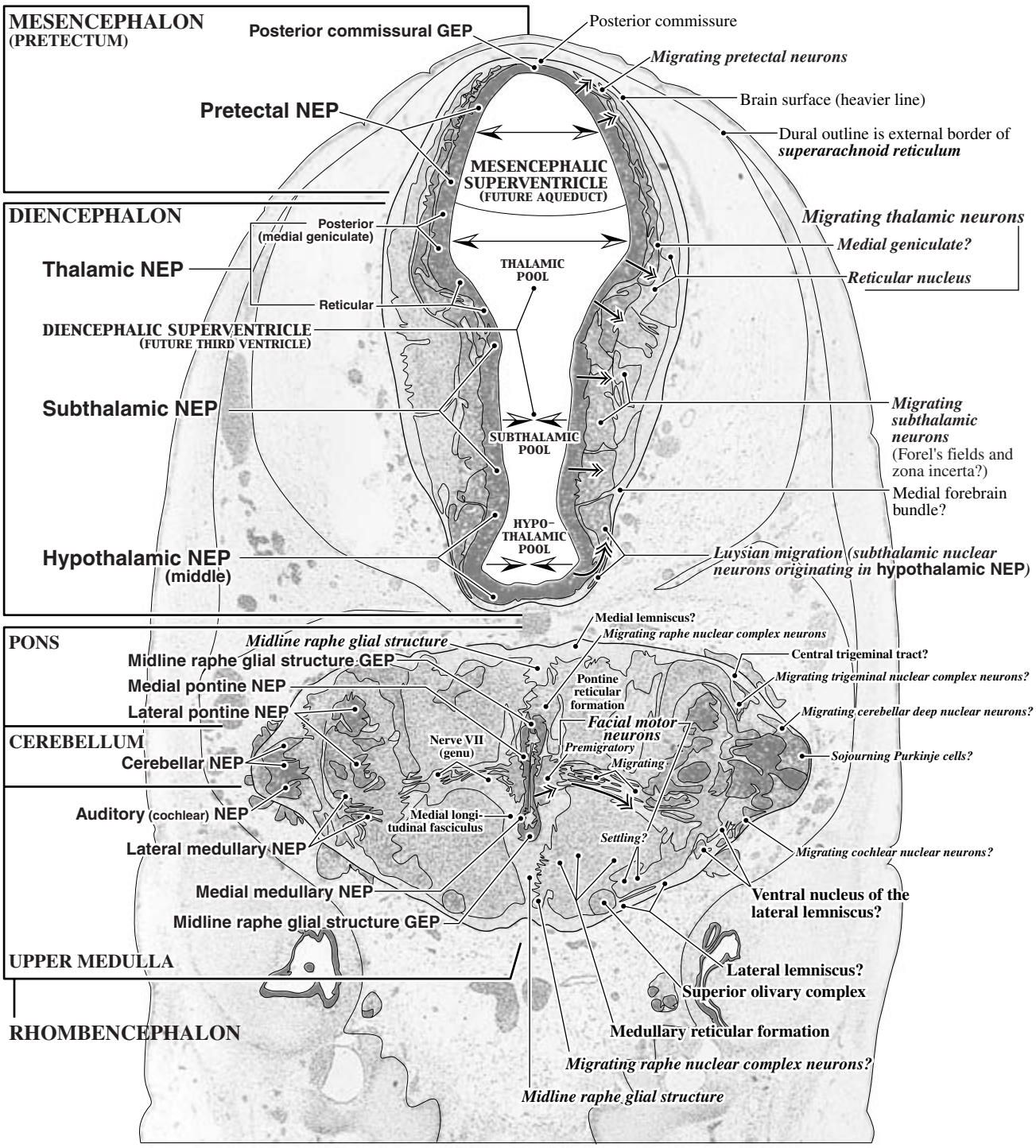
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 9B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

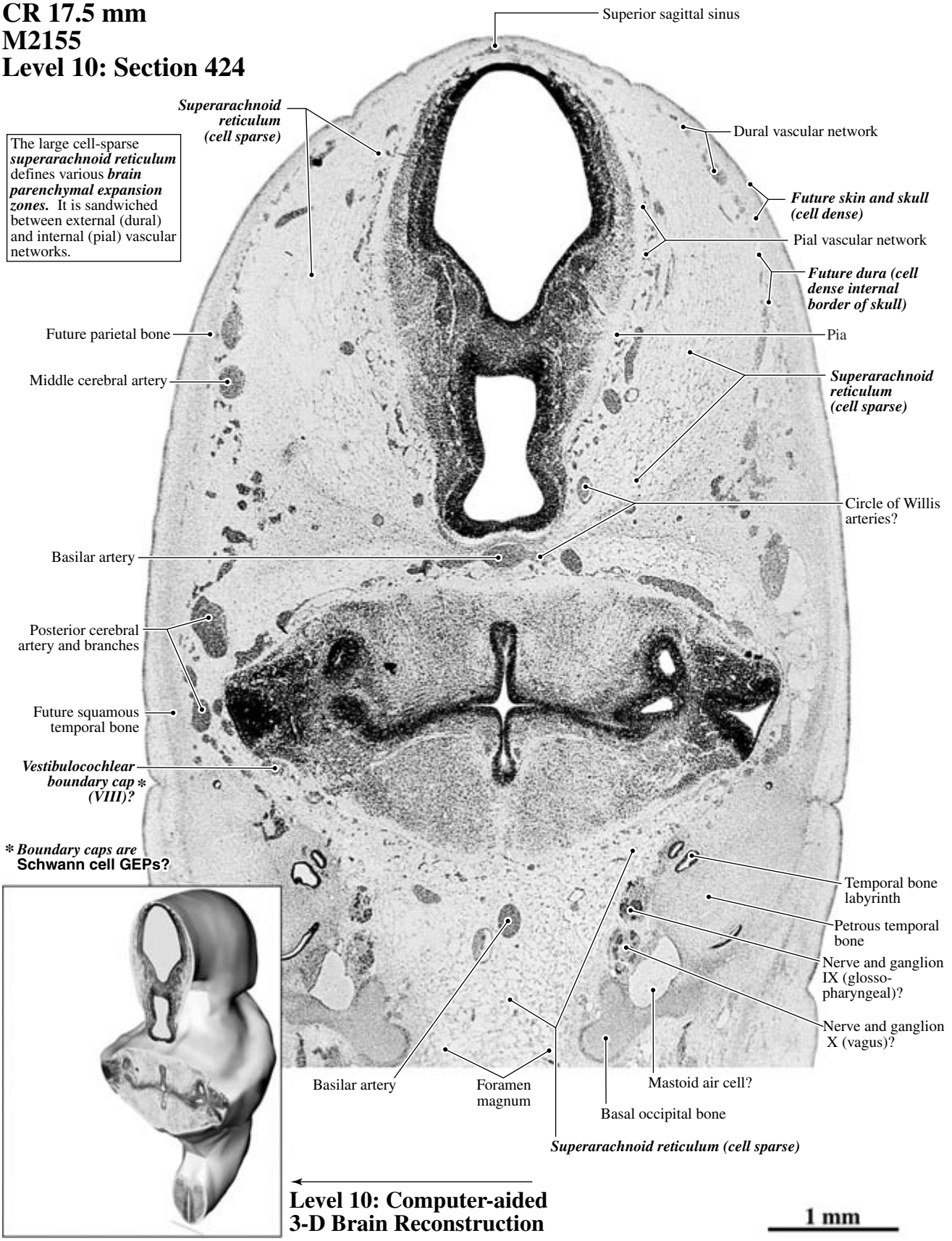
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 10A

GW7 Coronal
CR 17.5 mm
M2155
Level 10: Section 424

Peripheral neural and non-neural structures labeled



The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

* ***Boundary caps are*** **Schwann cell GEPs?**

Level 10: Computer-aided 3-D Brain Reconstruction

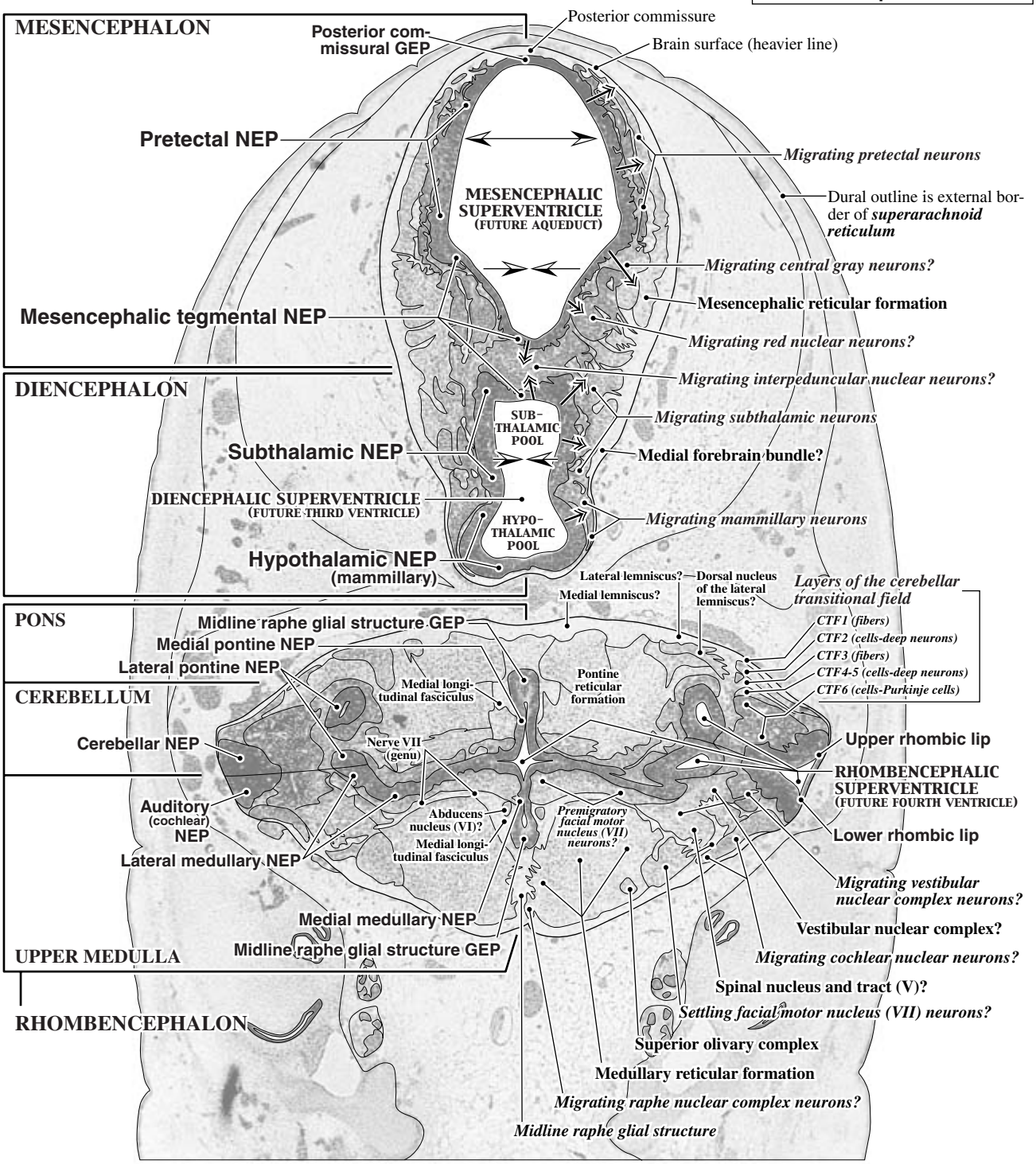
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 10B

Central neural structures labeled

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 11A

GW7 Coronal
CR 17.5 mm
M2155
Level 11: Section 444

Peripheral neural and non-neural structures labeled

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

Superior sagittal sinus
Superarachnoid reticulum (cell sparse)
Dural vascular network
Future skin and skull (cell dense)
Pial vascular network
Future dura (cell dense internal border of skull)
Future parietal bone
Pia
Middle cerebral artery
Circle of Willis arteries?
Superarachnoid reticulum (cell sparse)
Basilar artery
Posterior cerebral artery and branches
Future squamous temporal bone
Temporal bone labyrinth
Petrous temporal bone
Superarachnoid reticulum (cell sparse)
Foramen magnum
Basilar artery
Basal occipital bone
Vagal ganglion (X)?
Mastoid air cells?

Level 11: Computer-aided 3-D Brain Reconstruction

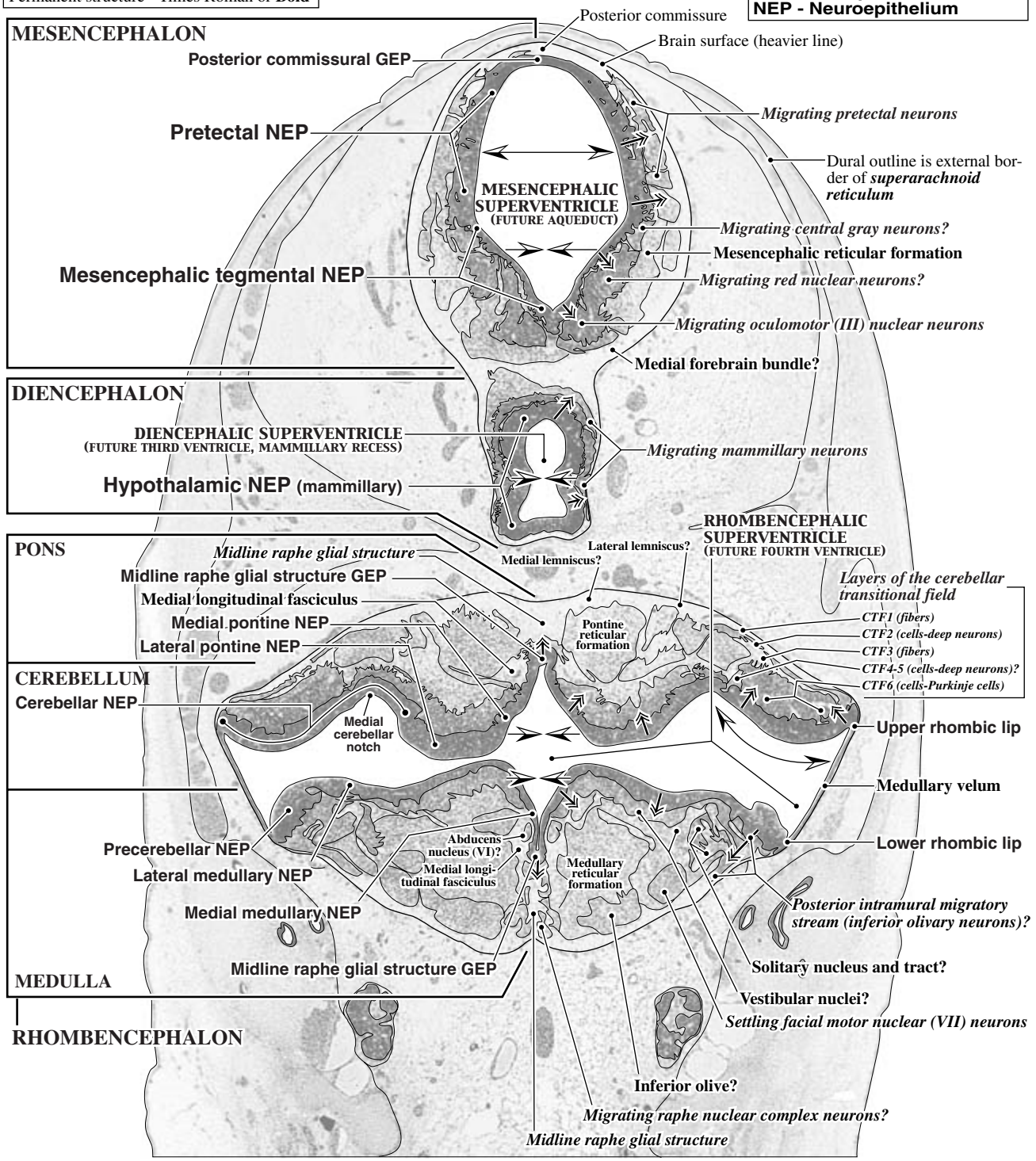
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Central neural structures labeled

PLATE 11B

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

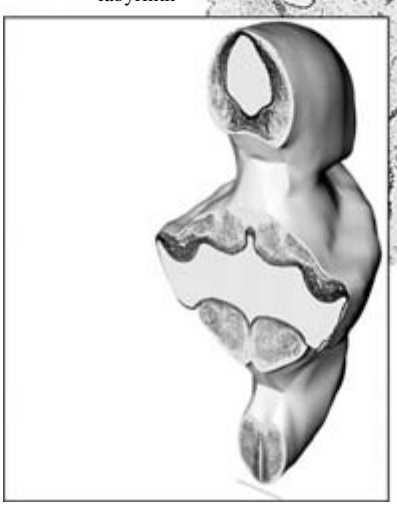
Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 12A

GW7 Coronal
CR 17.5 mm
M2155
Level 12: Section 500

Peripheral neural and non-neural structures labeled

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.



Superior sagittal sinus

Dural vascular network

Pial vascular network

Pia

Superarachnoid reticulum (cell sparse)

Future skin and skull (cell dense)

Nerve III (oculomotor)

Posterior cerebral artery

Future dura (cell dense internal border of skull)

Future squamous temporal bone

Temporal bone labyrinth

Glossopharyngeal ∗ boundary cap (IX)?

Vagal boundary ∗ cap (X)?

Vertebral artery?

Future squamous occipital bone

Superarachnoid reticulum (cell sparse)

Traces of the vagal (X) and glossopharyngeal (IX) nerve sheaths?

∗Boundary caps are **Schwann cell GEPs?**

Level 12: Computer-aided 3-D Brain Reconstruction

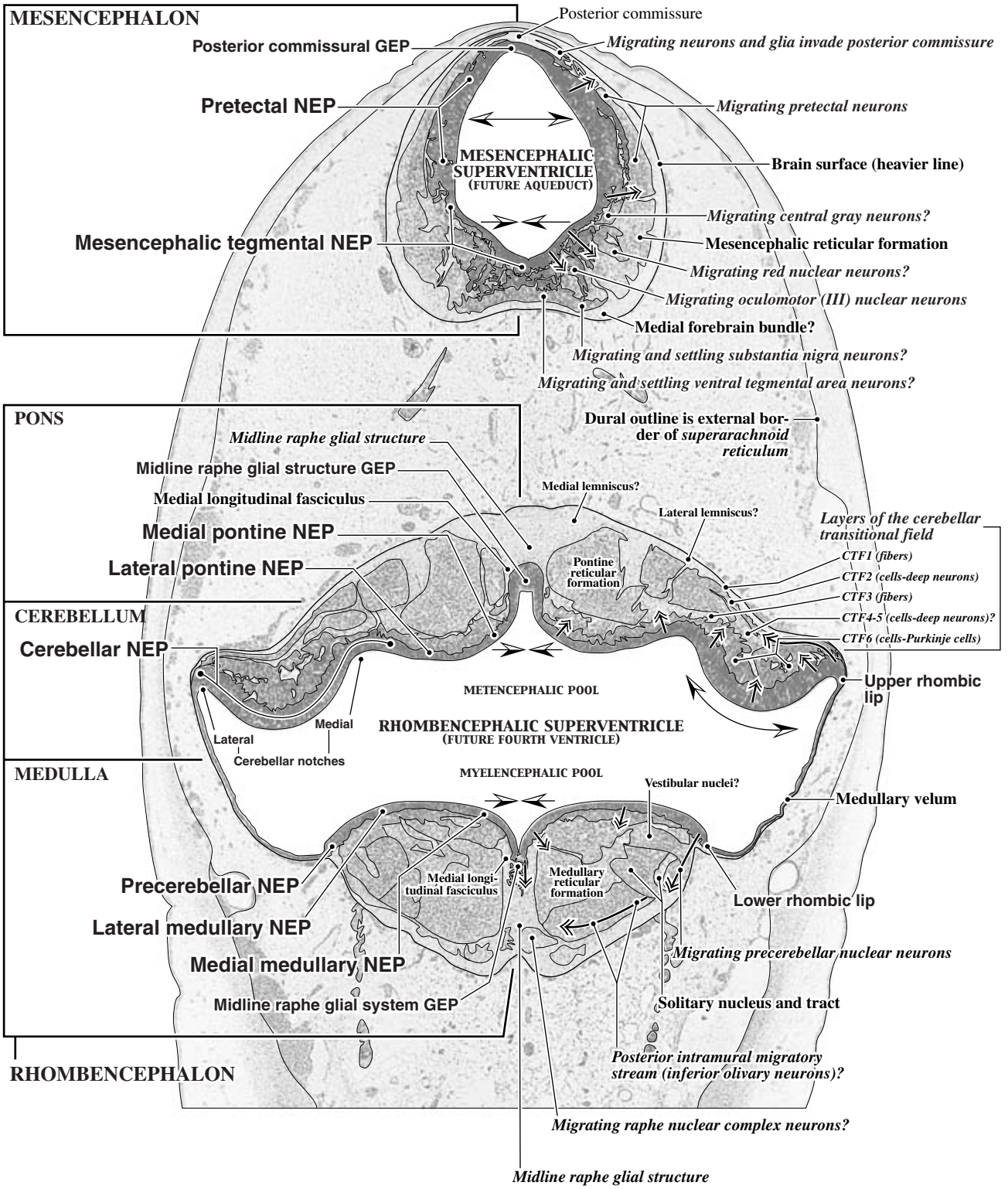
1 mm

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Central neural structures labeled

PLATE 12B

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

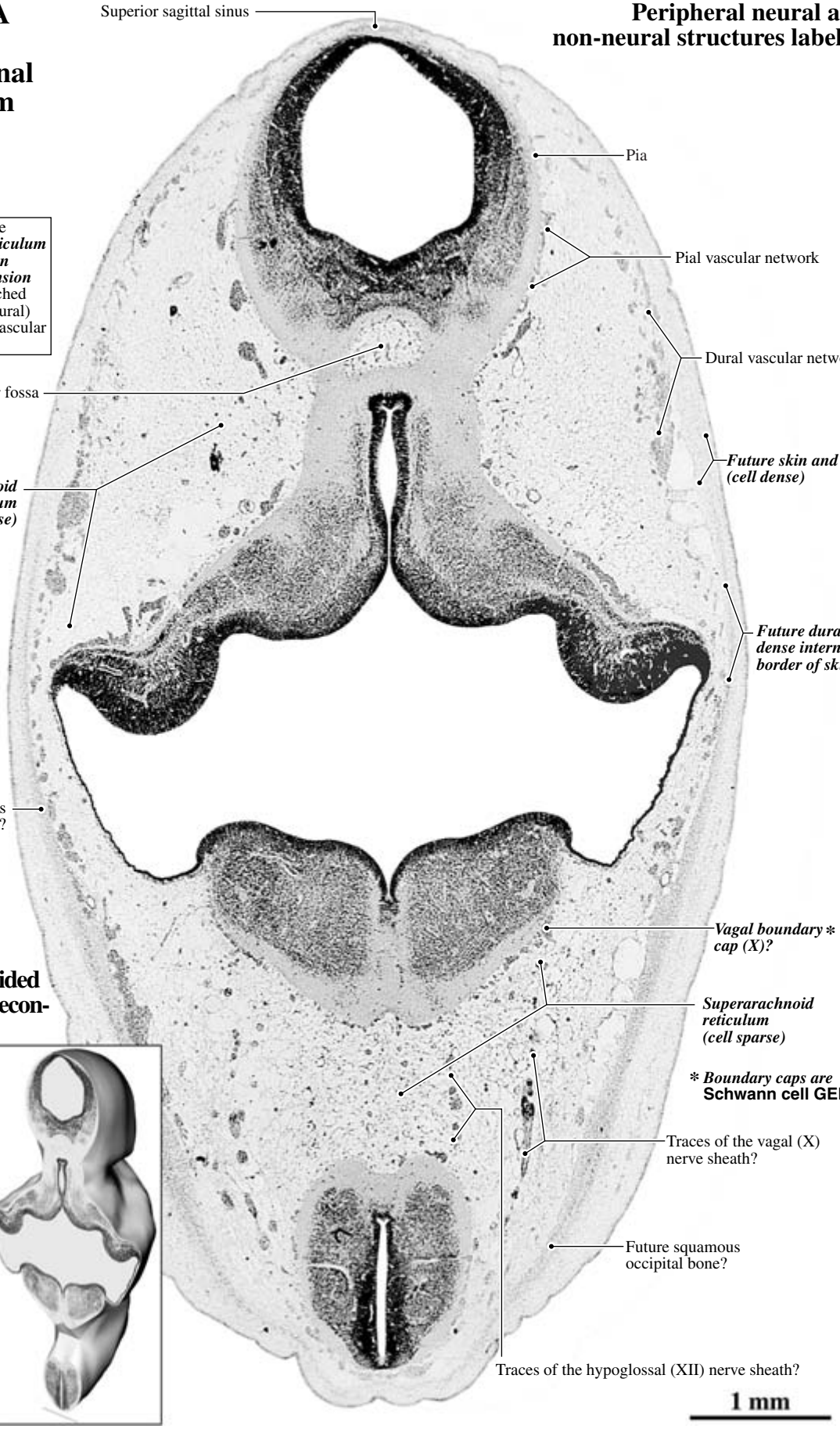
Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 13A

GW7 Coronal
CR 17.5 mm
M2155
Level 13:
Section 533

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

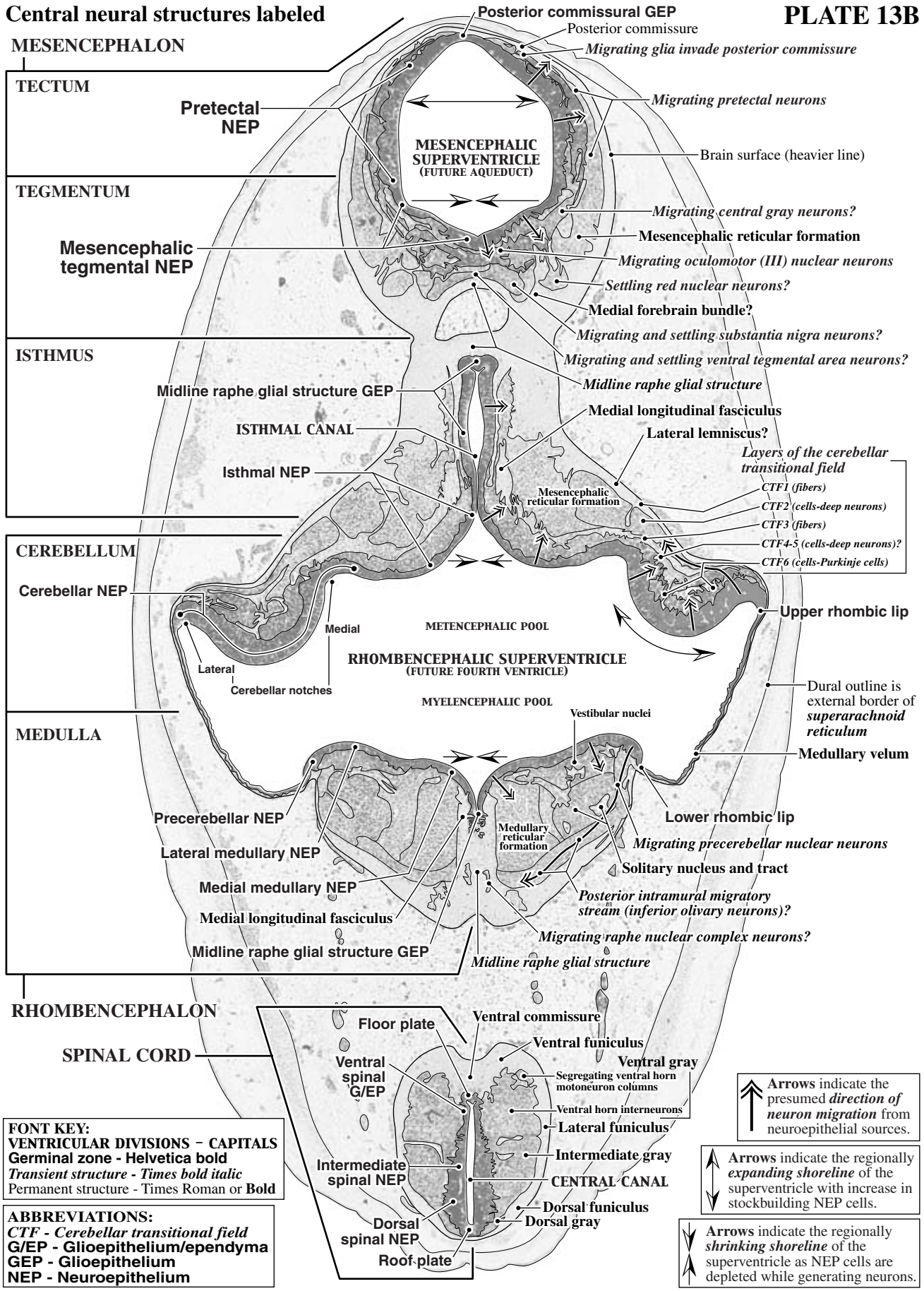
Peripheral neural and non-neural structures labeled



Level 13: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 13B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
G/EP - Glioepithelium/ependyma
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

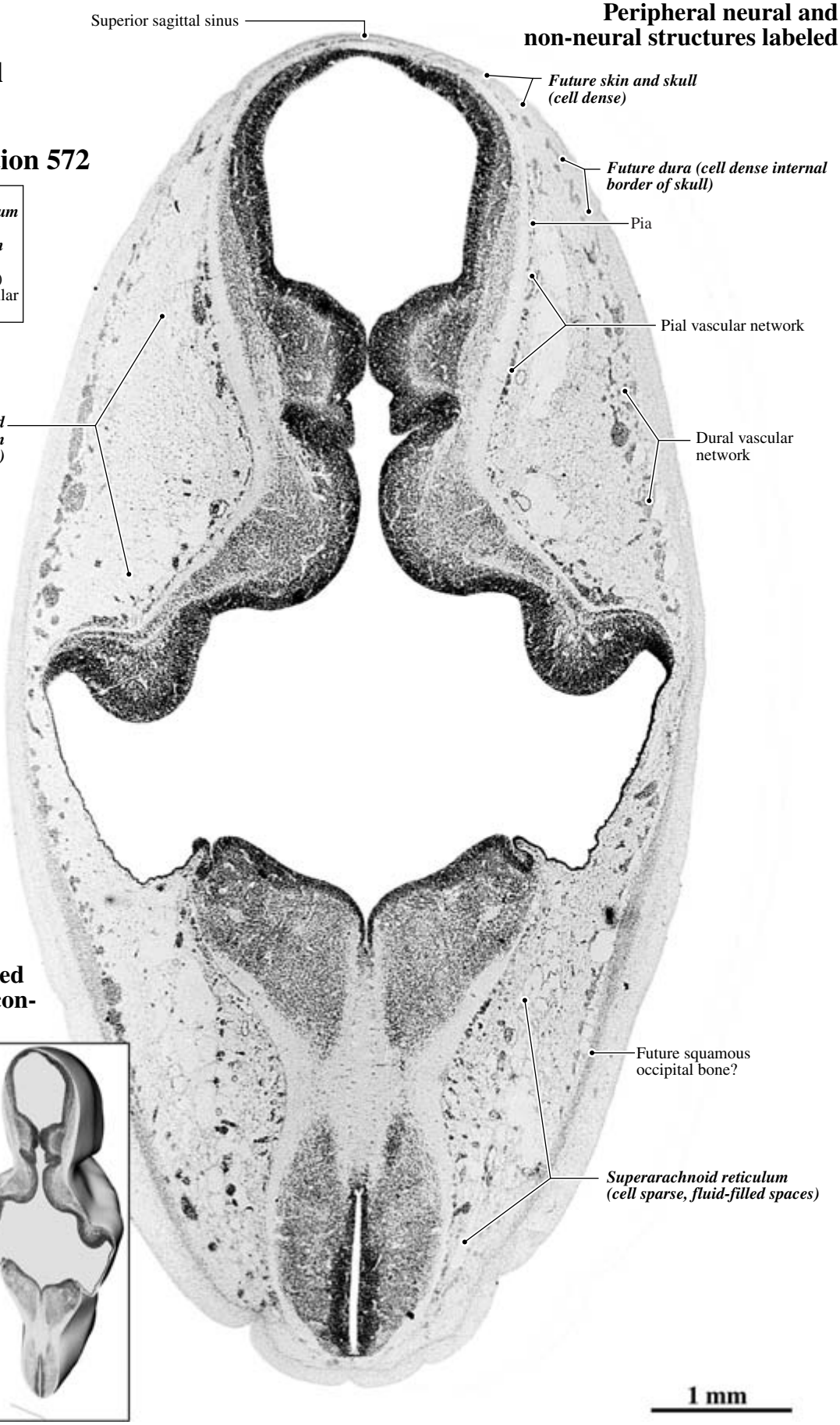
Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 14A

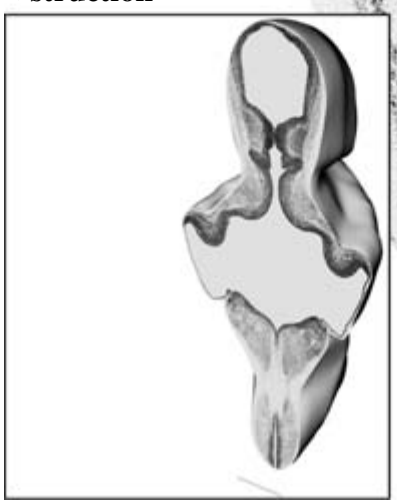
GW7 Coronal
CR 17.5 mm
M2155
Level 14: Section 572

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

Peripheral neural and non-neural structures labeled



Level 14: Computer-aided 3-D Brain Reconstruction



Central neural structures labeled

PLATE 14B

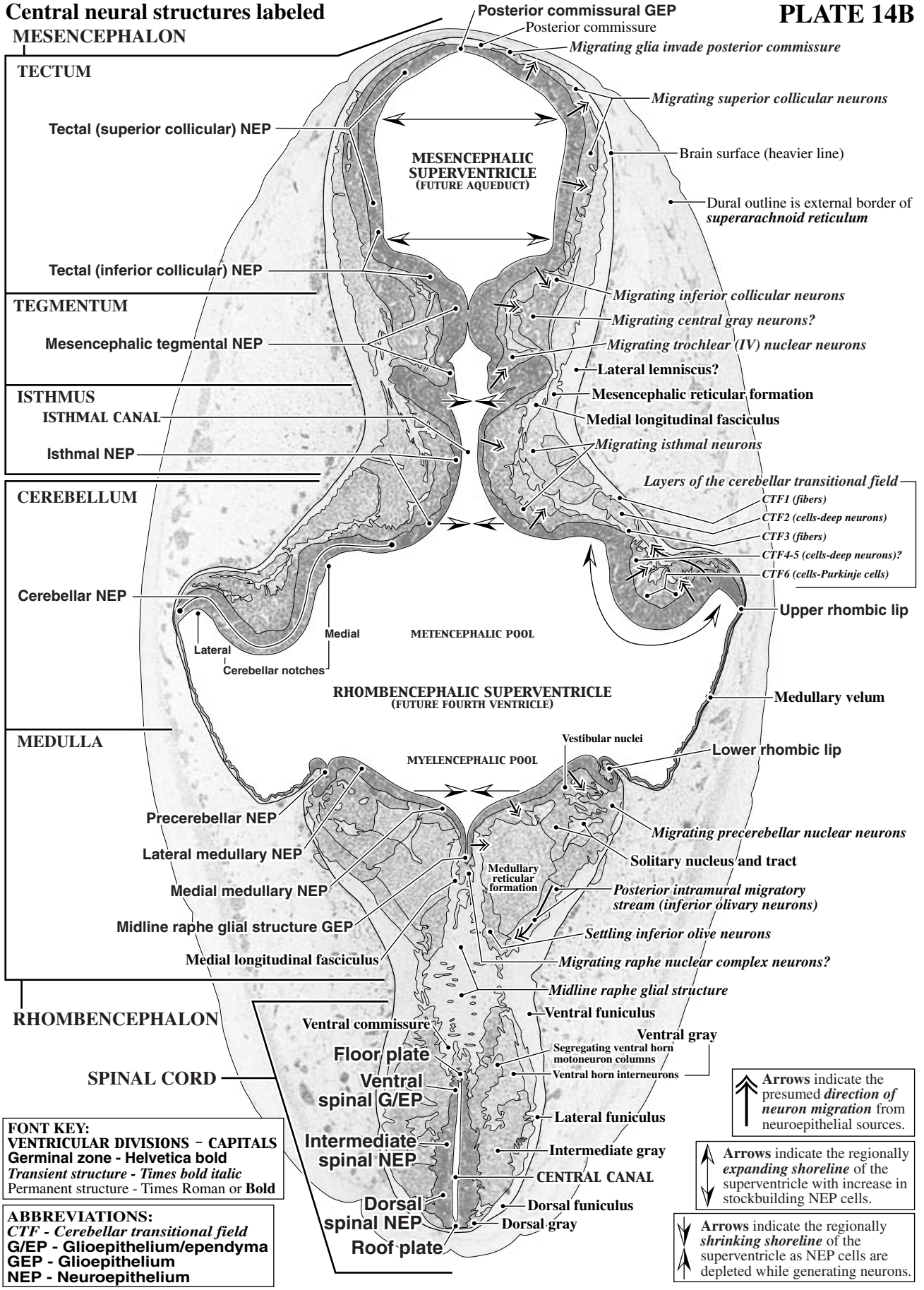
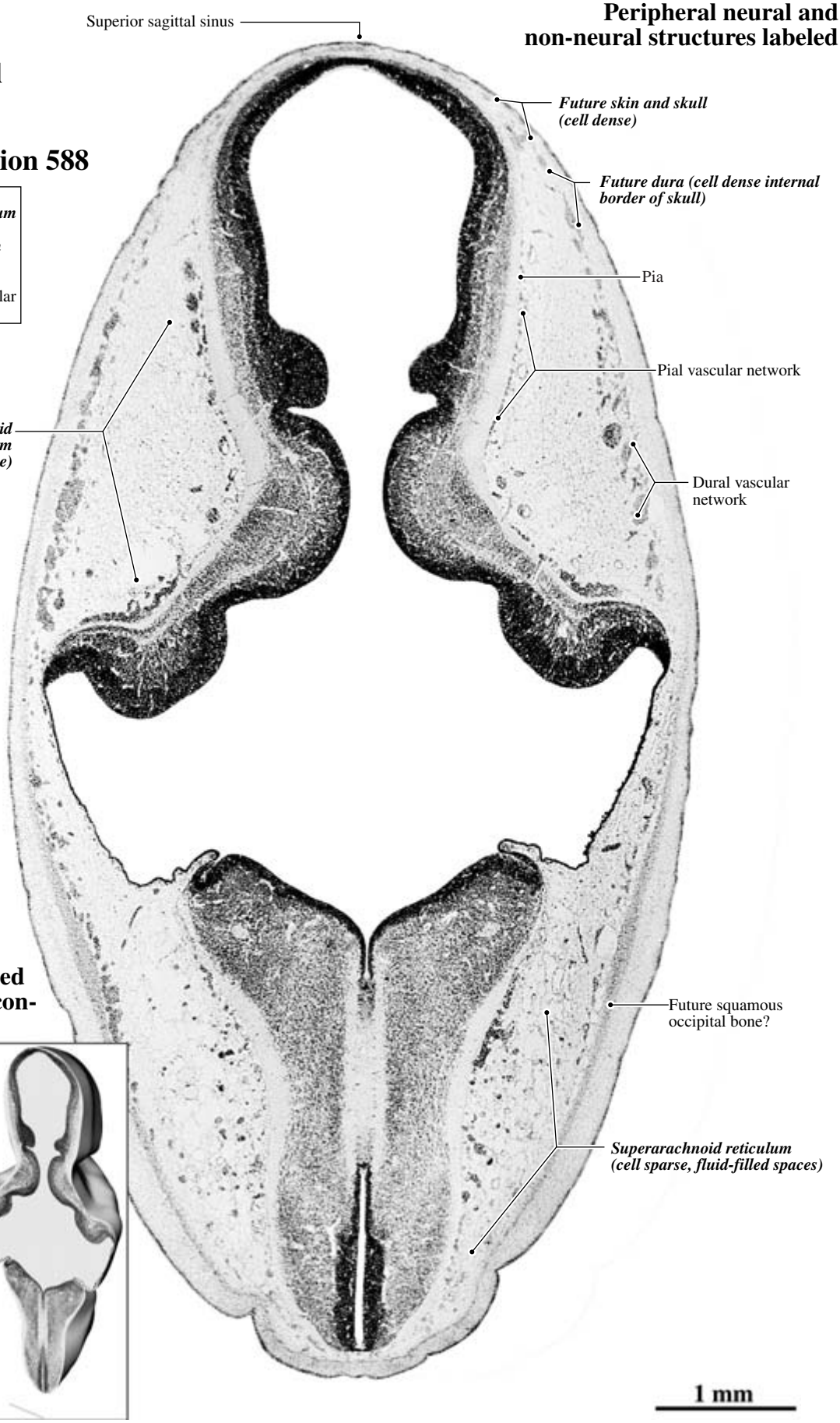


PLATE 15A

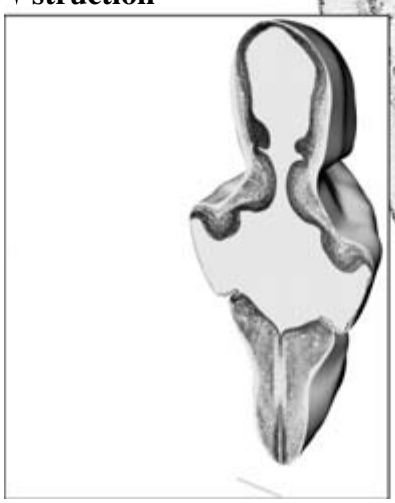
GW7 Coronal
CR 17.5 mm
M2155
Level 15: Section 588

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

Peripheral neural and non-neural structures labeled

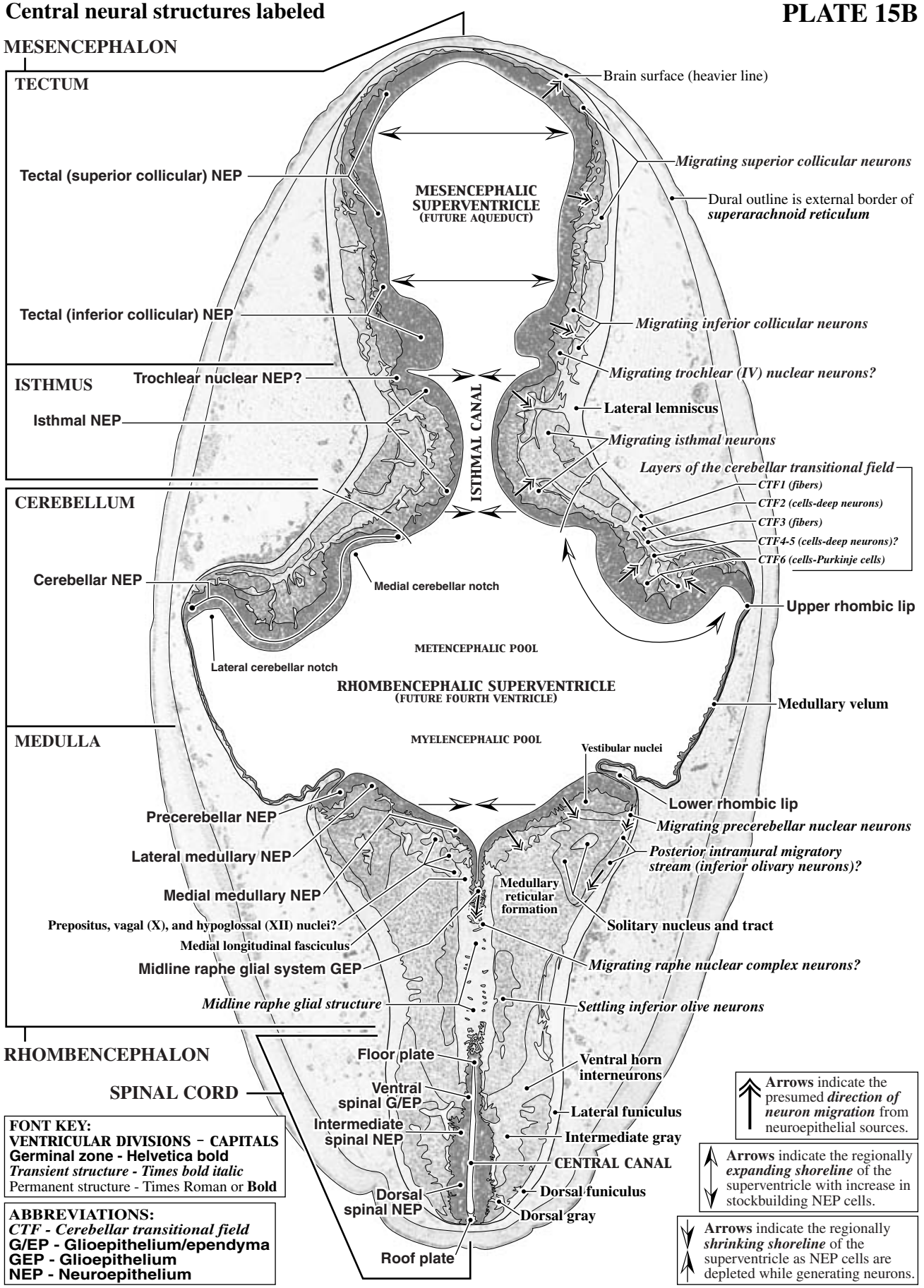


Level 15: Computer-aided 3-D Brain Reconstruction



Central neural structures labeled

PLATE 15B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
G/EP - Glioepithelium/ependyma
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

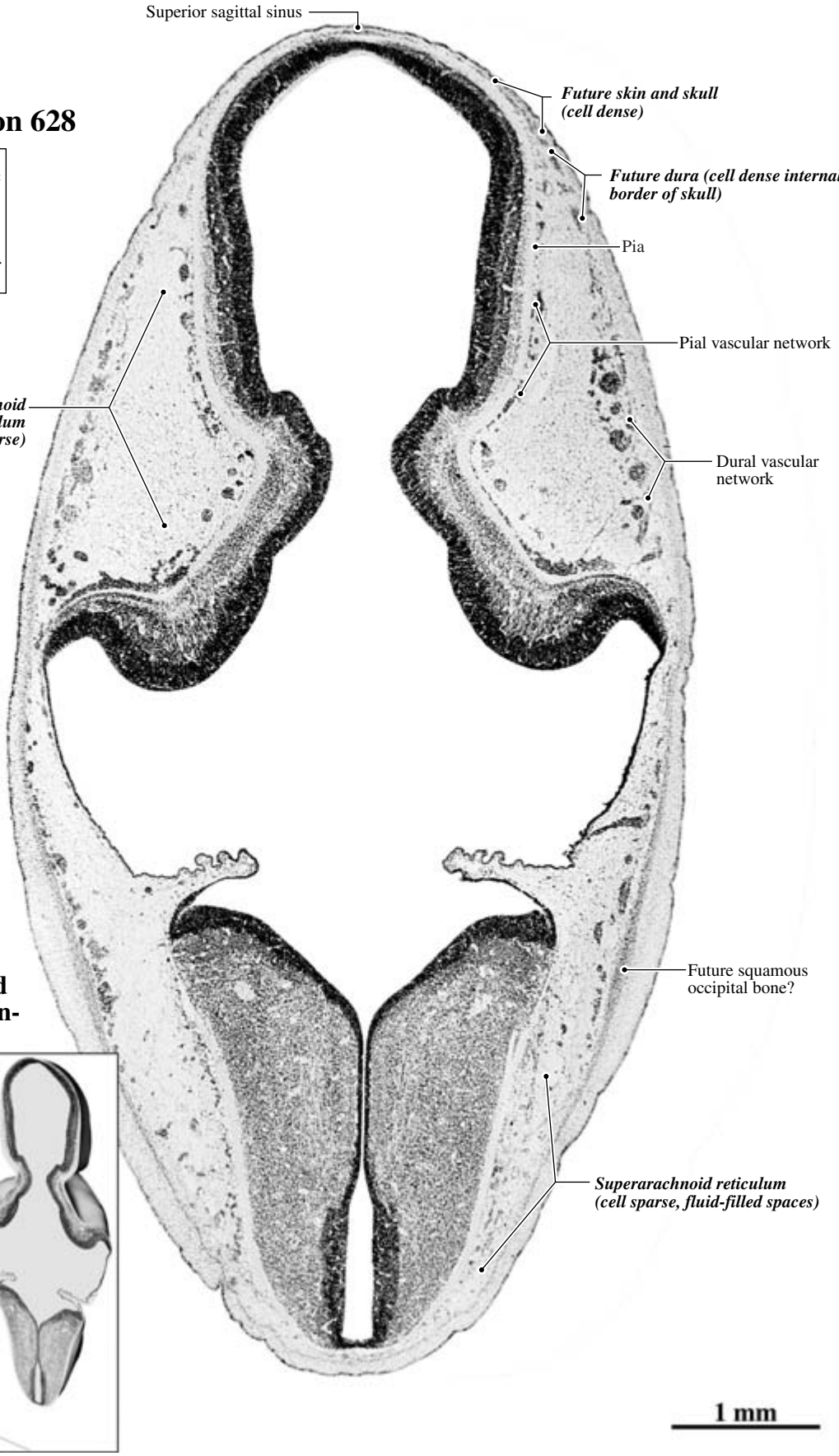
Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 16A

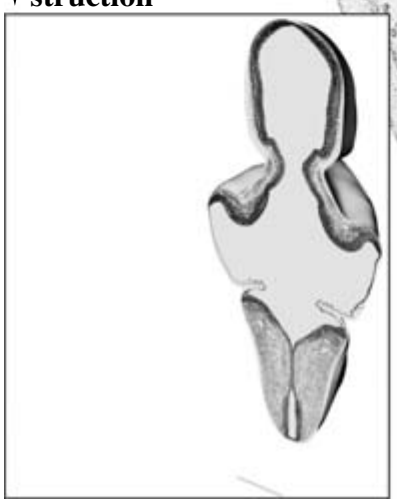
Peripheral neural and non-neural structures labeled

GW7 Coronal
CR 17.5 mm
M2155
Level 16: Section 628

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.



Level 16: Computer-aided 3-D Brain Reconstruction



Central neural structures labeled

PLATE 16B

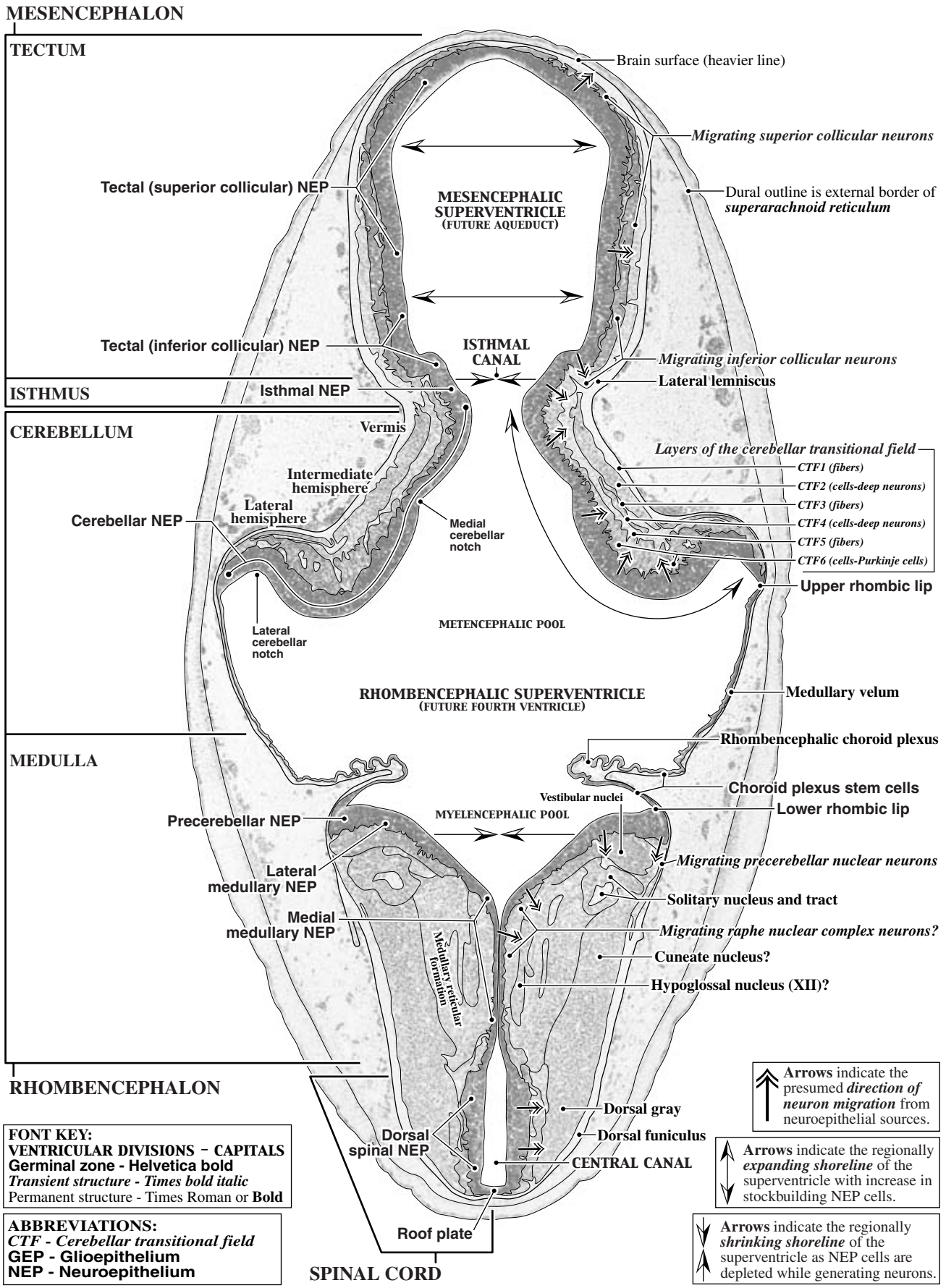
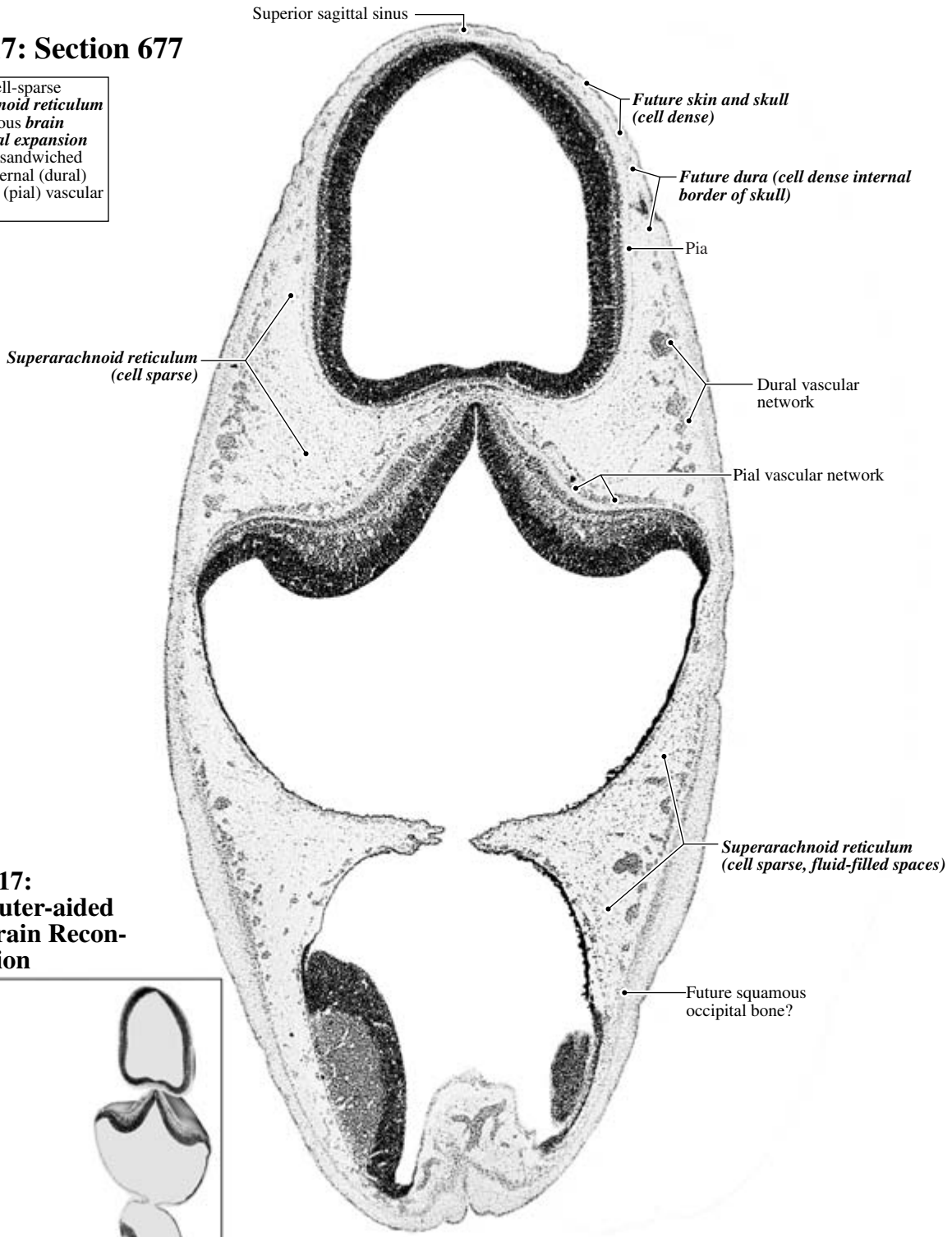


PLATE 17A

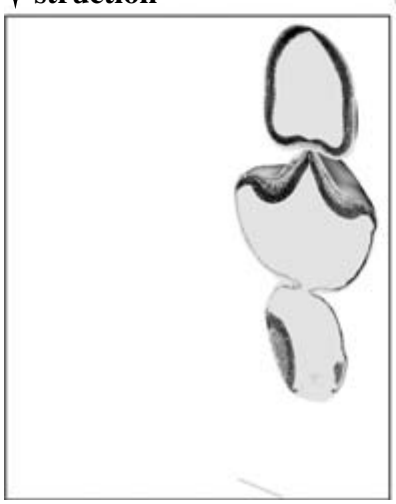
Peripheral neural and non-neural structures labeled

GW7 Coronal
CR 17.5 mm
M2155
Level 17: Section 677

The large cell-sparse ***superarachnoid reticulum*** defines various ***brain parenchymal expansion zones.*** It is sandwiched between external (dural) and internal (pial) vascular networks.

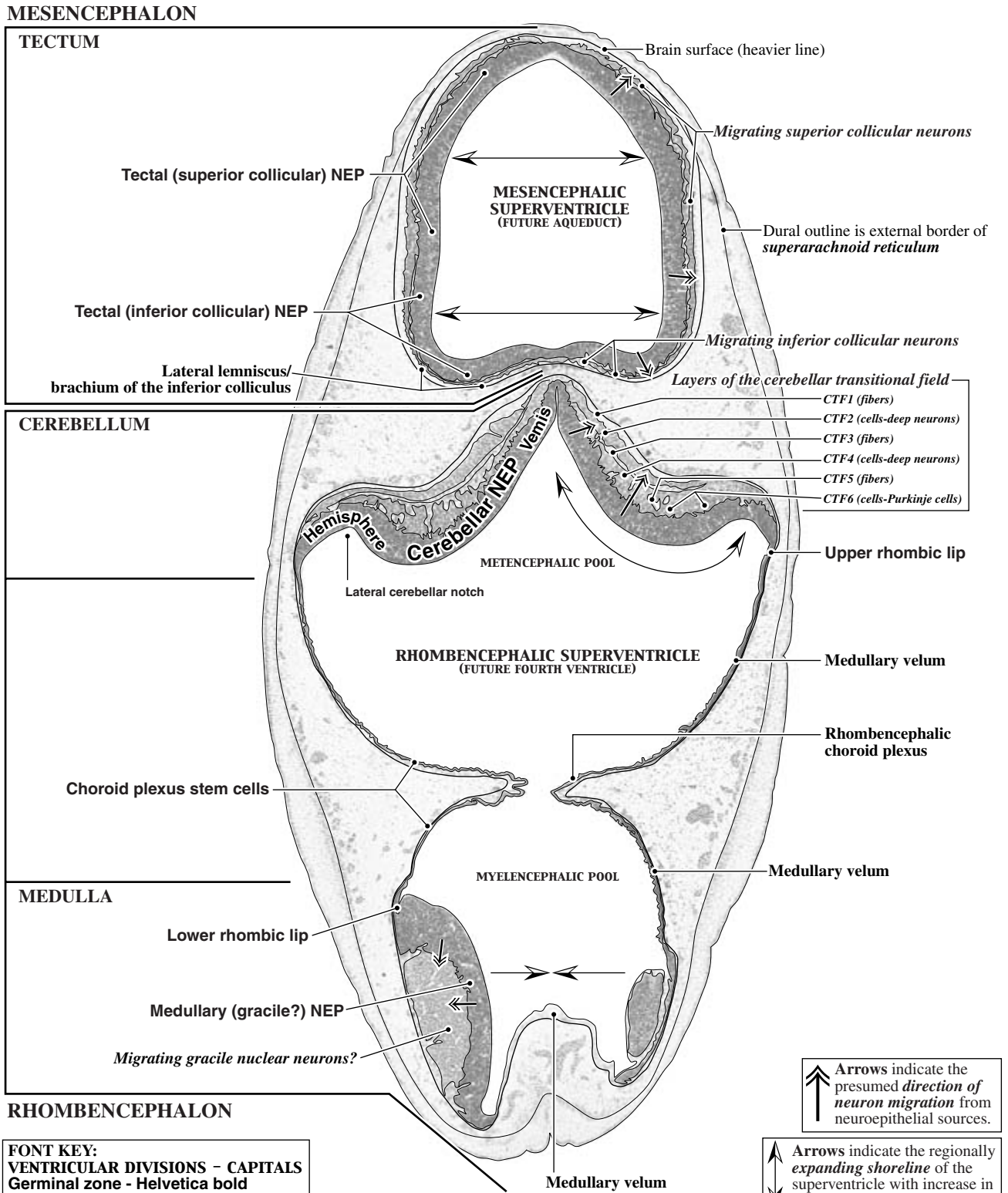


Level 17: Computer-aided 3-D Brain Reconstruction



Central neural structures labeled

PLATE 17B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
NEP - Neuroepithelium

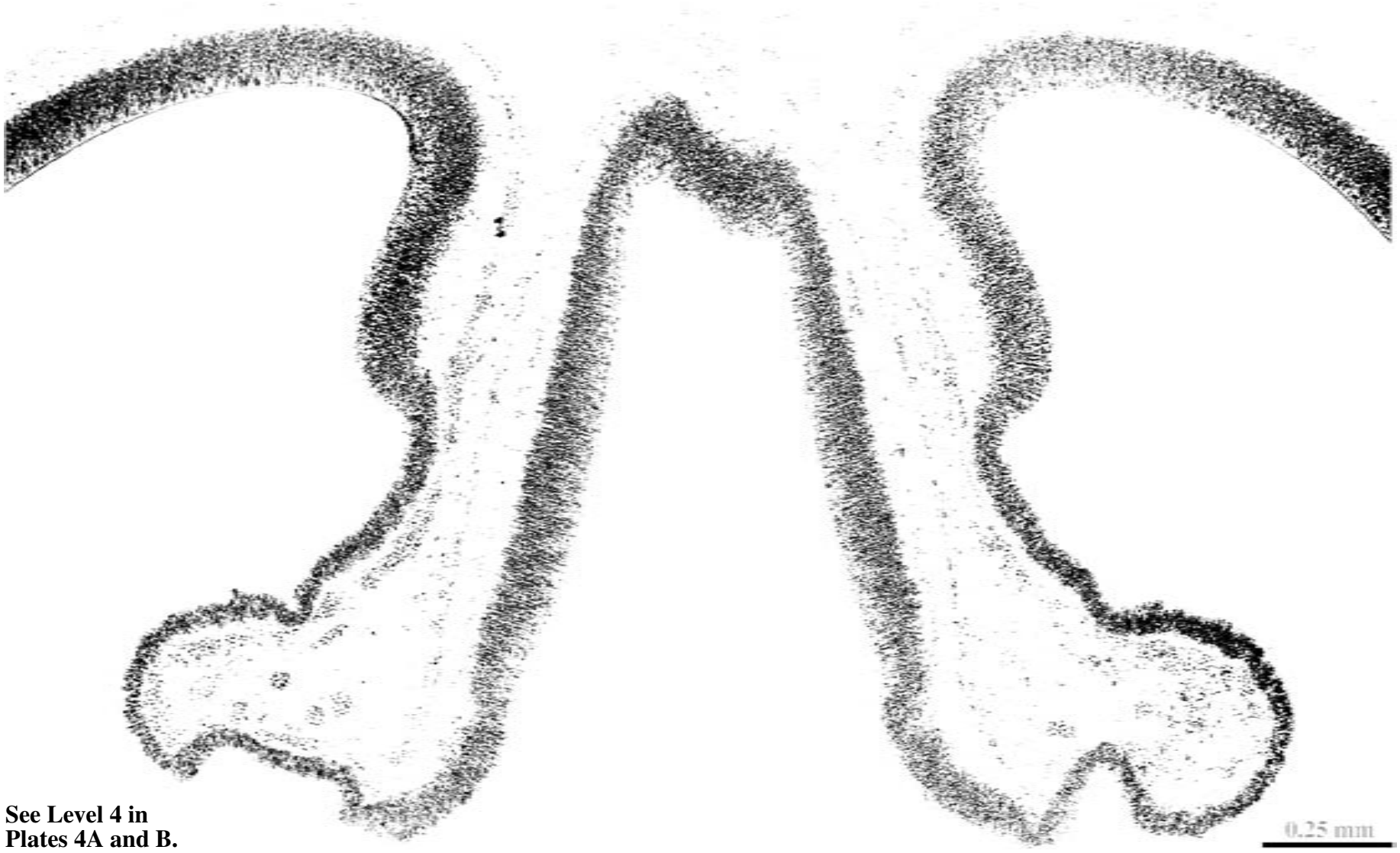
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 18A

GW7 Coronal, CR 17.5 mm, M2155
Near Level 4: Section 203



See Level 4 in Plates 4A and B.

PLATE 18B

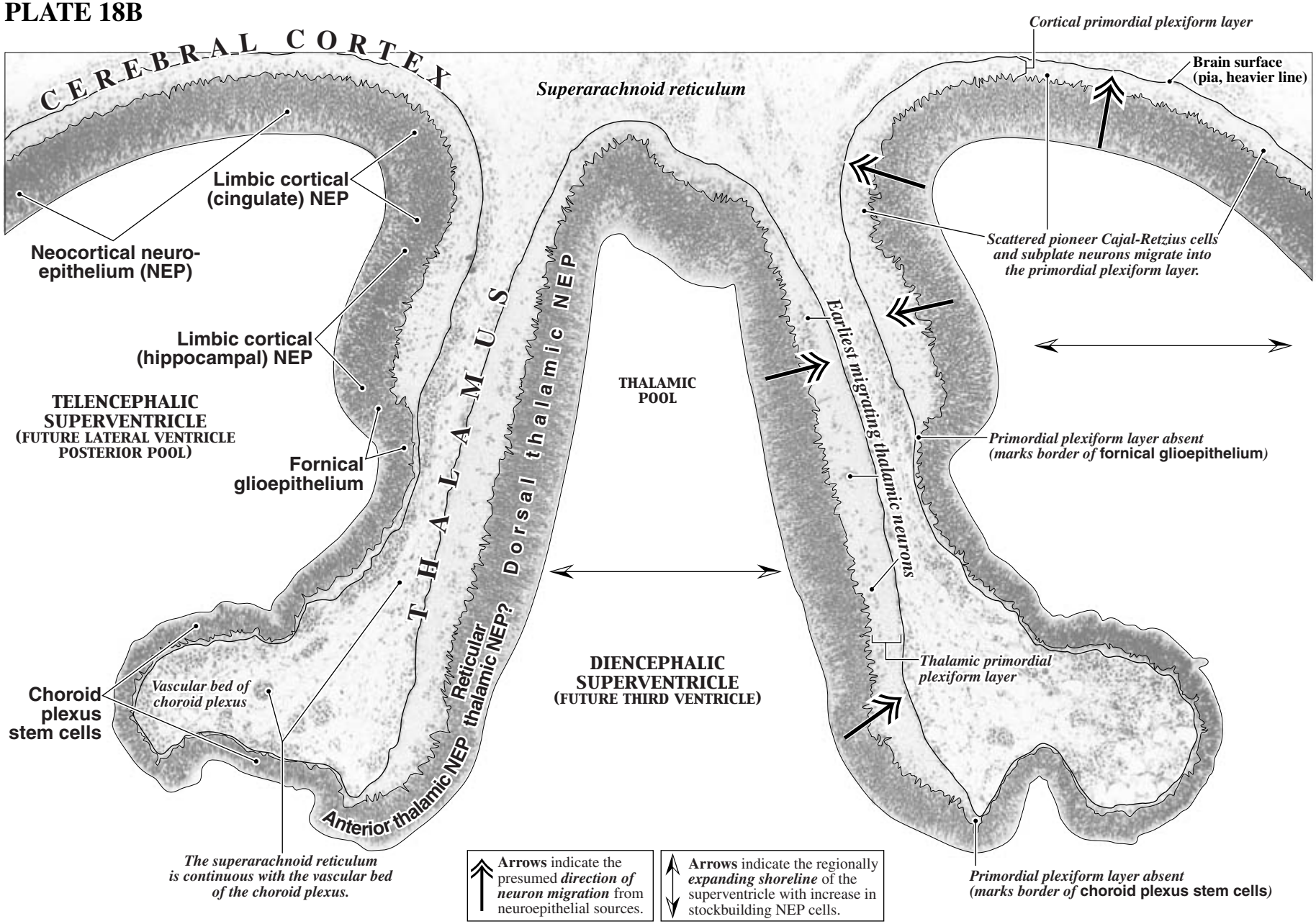
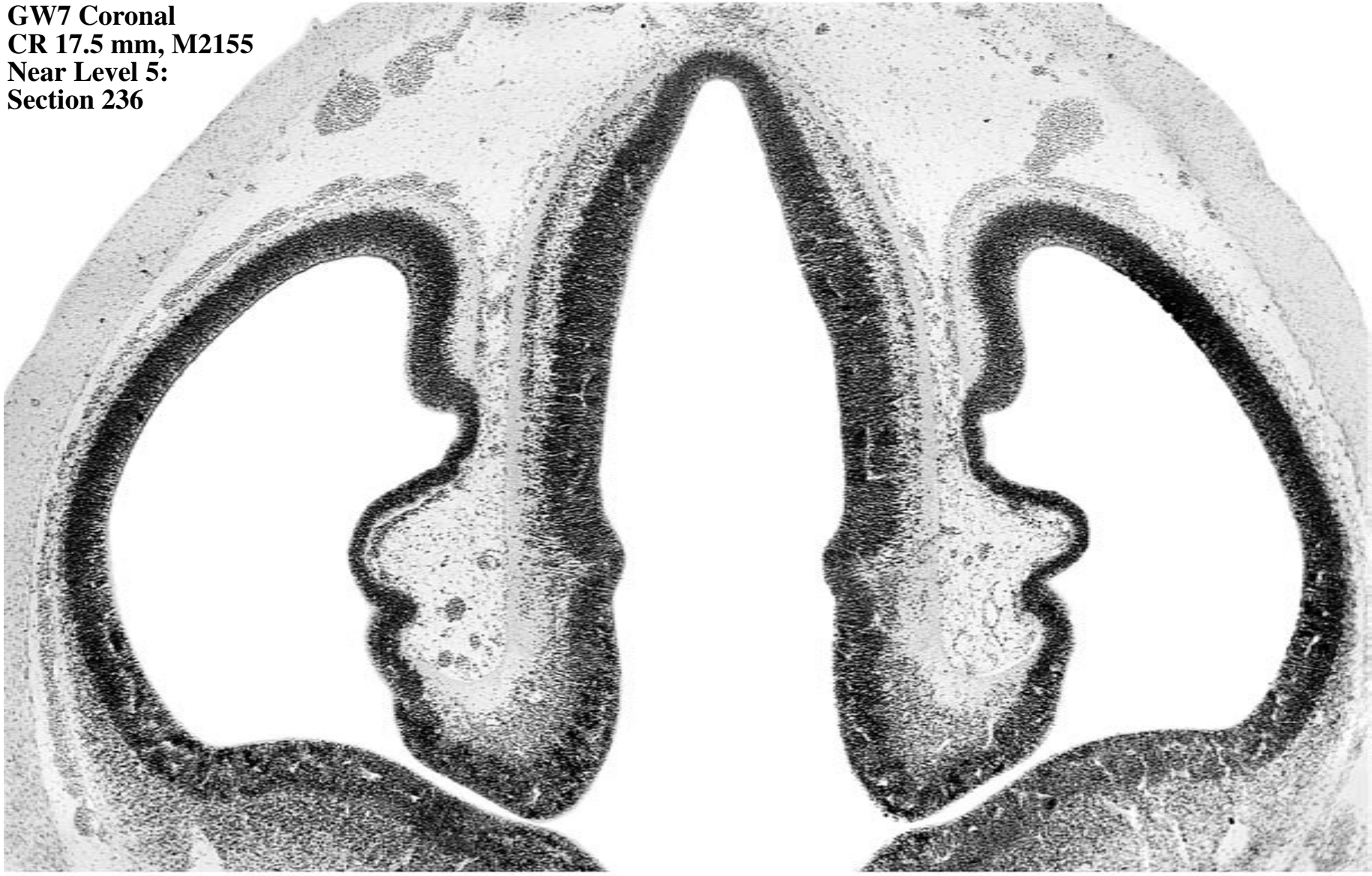

CEREBRAL CORTEX
Cortical primordial plexiform layer
Brain surface (pia, heavier line)
Superarachnoid reticulum
Limbic cortical (cingulate) NEP
Neocortical neuro-epithelium (NEP)
Limbic cortical (hippocampal) NEP
TELENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL VENTRICLE POSTERIOR POOL)
Fornical glioepithelium
THALAMUS
Dorsal thalamic NEP
Reticular thalamic NEP?
Anterior thalamic NEP
THALAMIC POOL
Earliest migrating thalamic neurons
Scattered pioneer Cajal-Retzius cells and subplate neurons migrate into the primordial plexiform layer.
Primordial plexiform layer absent (marks border of fornical glioepithelium)
Thalamic primordial plexiform layer
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE)
Choroid plexus stem cells
Vascular bed of choroid plexus
The superarachnoid reticulum is continuous with the vascular bed of the choroid plexus.
Primordial plexiform layer absent (marks border of choroid plexus stem cells)
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.

PLATE 19A

GW7 Coronal
CR 17.5 mm, M2155
Near Level 5:
Section 236



See Level 5 in Plates 5A and B.

PLATE 19B

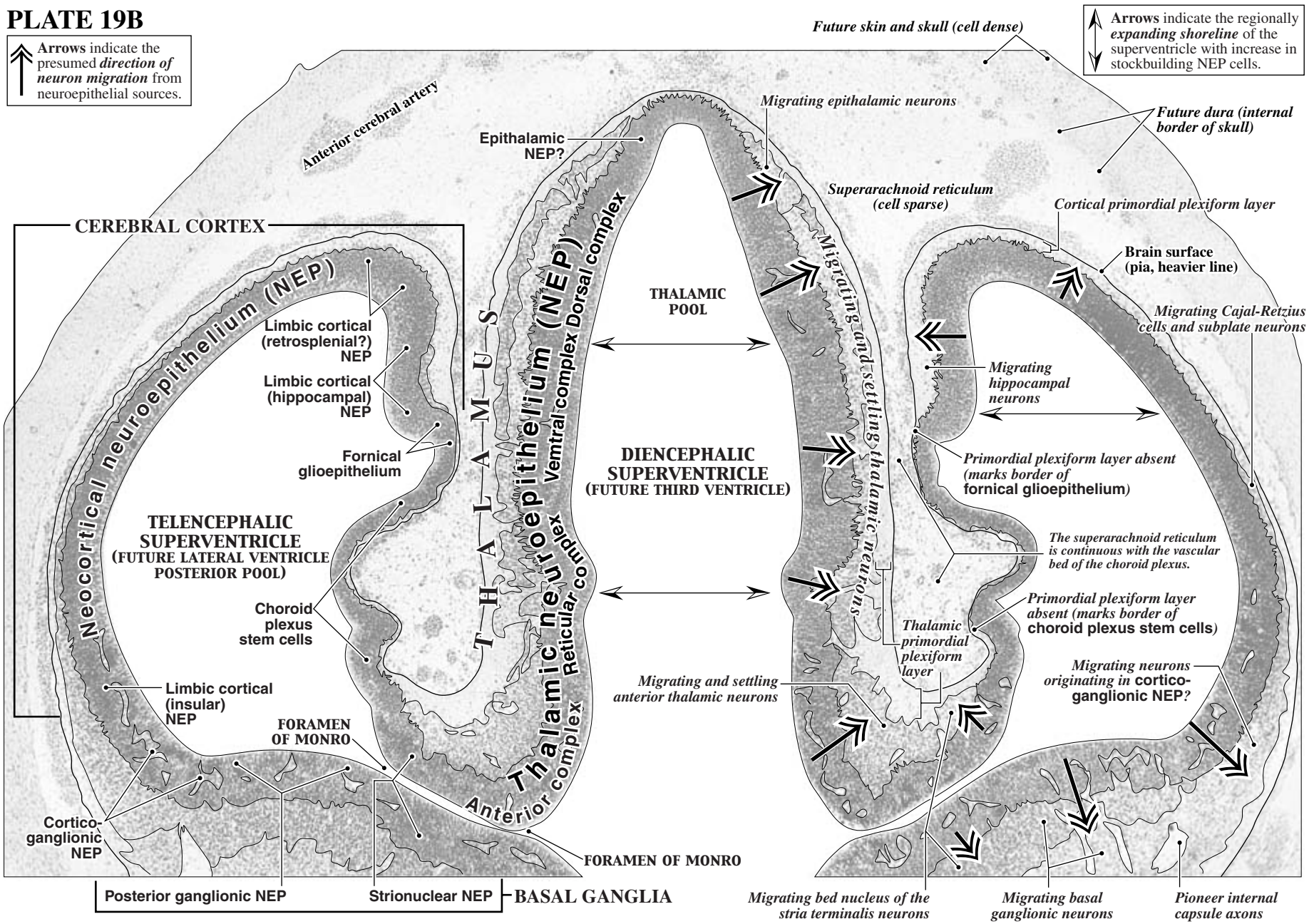
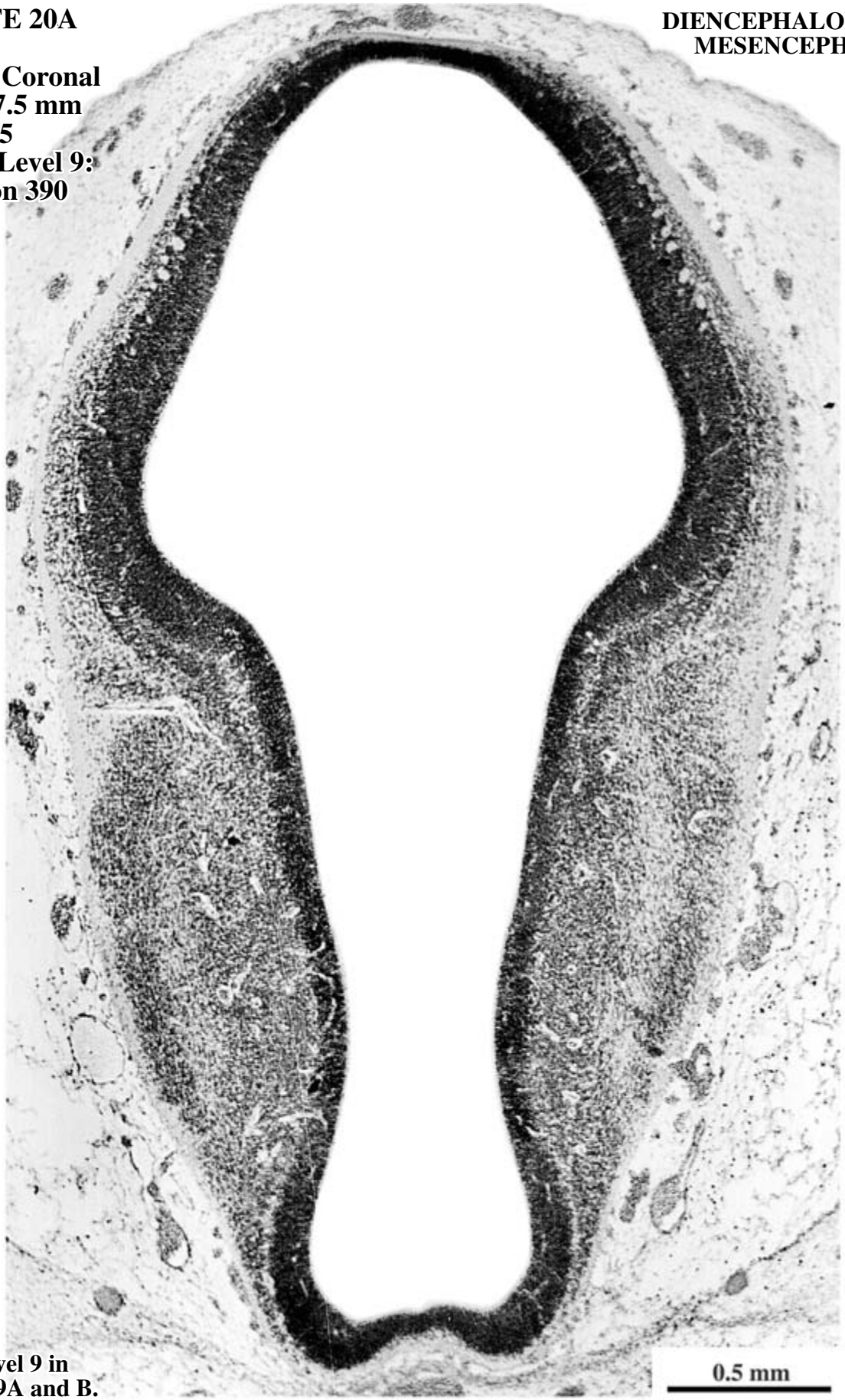

Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.
Future skin and skull (cell dense)
Anterior cerebral artery
Migrating epithalamic neurons
Future dura (internal border of skull)
Epithalamic NEP?
Superarachnoid reticulum (cell sparse)
Cortical primordial plexiform layer
CEREBRAL CORTEX
Neocortical neuroepithelium (NEP)
Limbic cortical (retrosplenial?) NEP
Limbic cortical (hippocampal) NEP
Fornical glioepithelium
TELENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL VENTRICLE POSTERIOR POOL)
Choroid plexus stem cells
Limbic cortical (insular) NEP
FORAMEN OF MONRO
Cortico-ganglionic NEP
Posterior ganglionic NEP
Strionuclear NEP
BASAL GANGLIA
THALAMUS
Thalamic neuroepithelium (NEP)
Ventral complex
Dorsal complex
Reticular complex
Anterior complex
THALAMIC POOL
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE)
FORAMEN OF MONRO
Migrating and settling thalamic neurons
Migrating and settling anterior thalamic neurons
Brain surface (pia, heavier line)
Migrating Cajal-Retzius cells and subplate neurons
Migrating hippocampal neurons
Primordial plexiform layer absent (marks border of fornical glioepithelium)
The superarachnoid reticulum is continuous with the vascular bed of the choroid plexus.
Primordial plexiform layer absent (marks border of choroid plexus stem cells)
Thalamic primordial plexiform layer
Migrating neurons originating in cortico-ganglionic NEP?
Migrating bed nucleus of the stria terminalis neurons
Migrating basal ganglionic neurons
Pioneer internal capsule axons

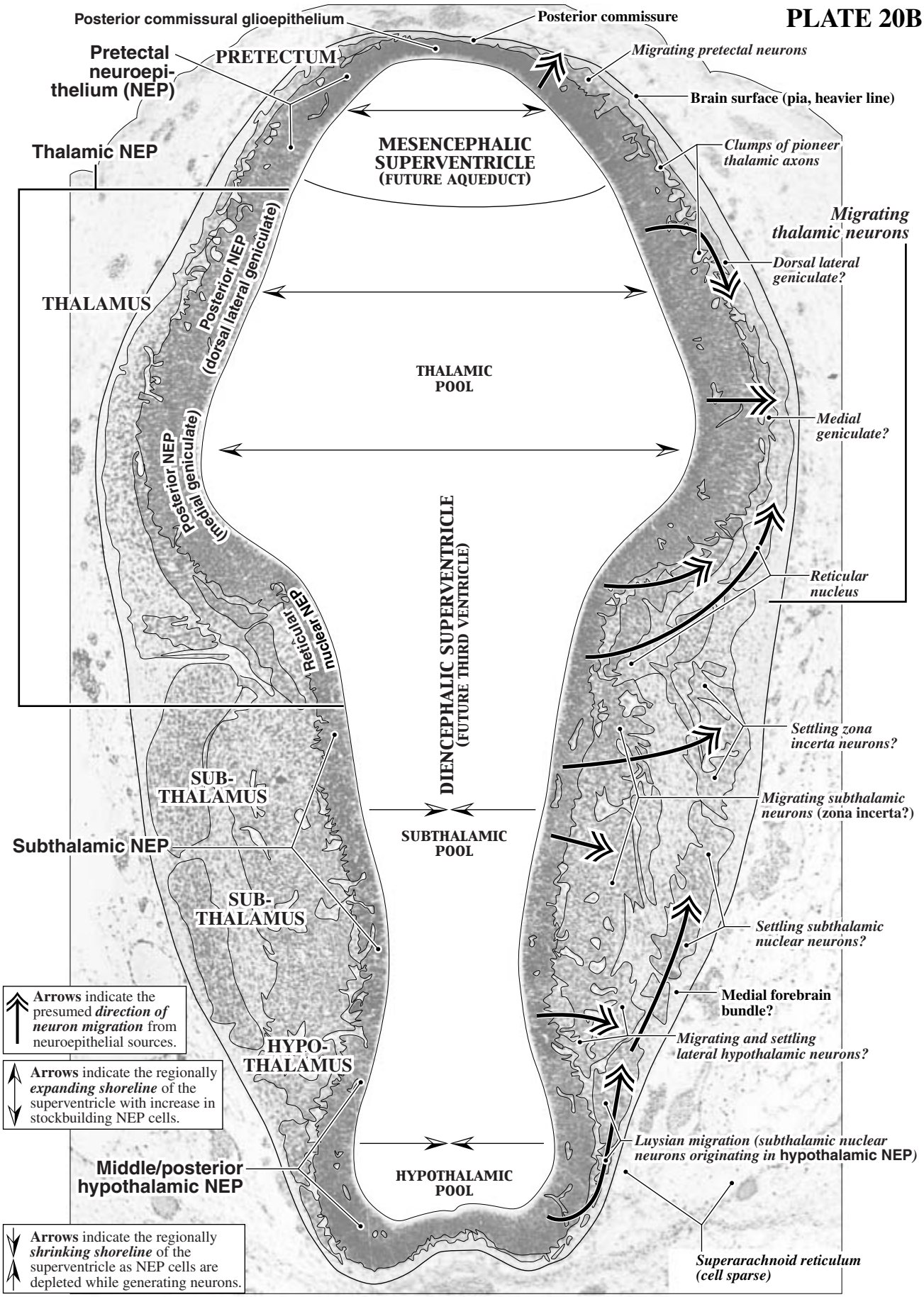
PLATE 20A

GW7 Coronal
CR 17.5 mm
M2155
Near Level 9:
Section 390



See Level 9 in Plates 9A and B.

PLATE 20B


Posterior commissural glioepithelium
Posterior commissure
Pretectal neuroepithelium (NEP)
PRETECTUM
Migrating pretectal neurons
Brain surface (pia, heavier line)
Thalamic NEP
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Clumps of pioneer thalamic axons
Migrating thalamic neurons
Dorsal lateral geniculate?
THALAMUS
Posterior NEP (dorsal lateral geniculate)
THALAMIC POOL
Medial geniculate?
Posterior NEP (medial geniculate)
Reticular NEP
Reticular nucleus
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE)
Settling zona incerta neurons?
SUB-THALAMUS
Migrating subthalamic neurons (zona incerta?)
SUBTHALAMIC POOL
Subthalamic NEP
SUB-THALAMUS
Settling subthalamic nuclear neurons?
Medial forebrain bundle?
HYPO-THALAMUS
Migrating and settling lateral hypothalamic neurons?
Luysian migration (subthalamic nuclear neurons originating in hypothalamic NEP)
Middle/posterior hypothalamic NEP
HYPOTHALAMIC POOL
Superarachnoid reticulum (cell sparse)
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.
Arrows indicate the regionally shrinking shoreline of the superventricle as NEP cells are depleted while generating neurons.

PART III: GW7 SAGITTAL

Carnegie Collection specimen #1390 (designated here as C1390) was collected in 1916 from a tubal pregnancy. The crown-rump length (CR) is 18 mm estimated to be at gestational week (GW) 7. C1390 was fixed in formalin, embedded in paraffin, and was cut in 20-μm sagittal sections that were stained with aluminum cochineal. Various orientations of the computer-aided 3-D reconstruction of M2155's brain is used to show the gross external features of a GW7 brain (**Figure 2**). Like most sagittally cut specimens, C1390's sections are not parallel to the midline; **Figure 2** shows the approximate rotations in top (**B**) and back views (**C**). We photographed 62 sections at low magnification from the left to right sides of the brain. Seven of the sections, mainly from the left side of the brain, are illustrated in **Plates 21AB to 27AB**. Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) indicate the approximate location of the midline and identify non-neural structures, peripheral neural structures, and brain ventricular divisions; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 28AB** show three high-magnification sections in the region of the facial nerve genu. The brain of C1390 is at a similar stage of development as M2155, the previous GW7 specimen.

Throughout the telencephalon, the neuroepithelium is the most prominent structure surrounding the enlarging telencephalic superventricle. All parts of the neuroepithelium are in "stockbuilding" stage, increasing the shorelines of the expanding telencephalic superventricles as more neuronal stem cells are added. Very few pioneer Cajal-Retzius neurons have migrated into the primordial plexiform layer adjacent to the cortical neuroepithelium. In contrast, the basal ganglionic and basal telencephalic neuroepithelia are adjacent to migrating neurons that form distinctive mounds in the floor of the telencephalon. The sagittal plane is ideal to show the slight evagination of the olfactory neuroepithelium in exactly the same region that is contacted by olfactory nerve fibers.

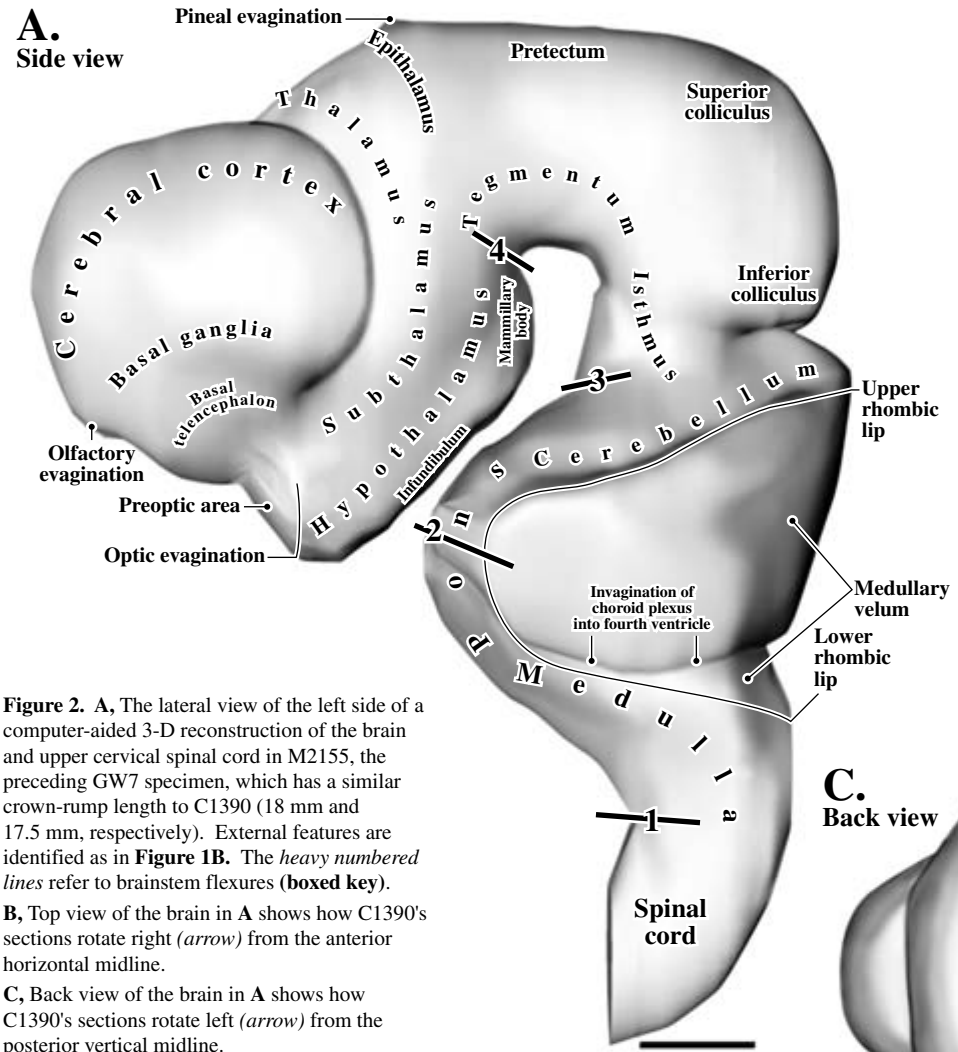
The diencephalic neuroepithelium surrounds a large superventricle. It is shrinking in the hypothalamic and subthalamic areas where stem cells are depleted as they generate neurons. Many migrating and settling young neurons are in the parenchyma surrounding these neuroepithelia. In contrast, the superventricular shoreline is expanding in thalamic areas as the thalamic neuroepithelium continues to add more neuronal precursors than to unload postmitotic neurons. The few neurons outside the thalamic neuroepithelium are best seen in sections grazing the dorsolateral part of the diencephalon.

The roof (tectum and pretectum) of the mesencephalon contains a stockbuilding neuroepithelium adjacent to a very thin layer of pioneer migrating neurons. However, bundles of fibers in the posterior commissure are very distinct, and spike-like arrays of cells extend between these bundles. Possibly premigratory neurons produce axons while they are sequestered in the pretectal neuroepithelium. The tegmental and isthmal neuroepithelia are much thinner because most of their neuronal progeny has migrated out. These cells accumulate as inner dense clumps and outer sparse arrays interspersed among the thick subpial fiber band in the tegmental and isthmal parenchyma.

Both the pons and medulla have neuroepithelia that are shrinking as stem cells unload their neuronal and glial progeny into an expanding parenchyma. The longitudinal arrays at the pontine flexure are easy to see in the sagittal plane. The genu of the facial motor nerve forms fascicles adjacent to the neuroepithelium in medial sections; these fascicles are adjacent to the pial surface in lateral sections. What is presumed to be the solitary tract is the most prominent internal fiber tract in the medulla. Both the pons and medulla have a thick subpial fibrous layer. Lateral sections show large peripheral sensory nerves contacting the brain. No doubt, many of the superficial fibers are the afferent axons of these ganglia along with ascending fiber tracts from the the spinal cord. All of the peripheral nerves (most clearly shown in the trigeminal nerve) have dense glia (Schwann cells), while central fiber tracts are clear. Thus, peripheral gliogenesis precedes the generation of oligodendrocytes in central fiber tracts.

The exceptionally thick cerebellar neuroepithelium, in comparison with the thin adjacent pontine neuroepithelium, is most easily seen in lateral sections where it sharply juts into the rhombencephalic superventricle at the medial cerebellar notch. All parts of the cerebellar neuroepithelium are stockbuilding Purkinje stem cells. Most deep nuclear neurons are migrating in the cellular layers of the cerebellar transitional field.

EXTERNAL FEATURES OF THE GW7 BRAIN



A perfect sagittal cut through the brain is parallel to the entire midline.

Based on Level 1, the sections of C1390's brain rotate an estimated 8.1º from the midine, 4.3º counter-clockwise from the anterior horizontal midline (B, top view), and 3.8º clockwise from the posterior vertical midline (C, back view).

In the sections illustrated on the following pages, the anterior brain (top and left) is tilted away from the observer, while the posterior brain (bottom and right) is tilted toward the observer.

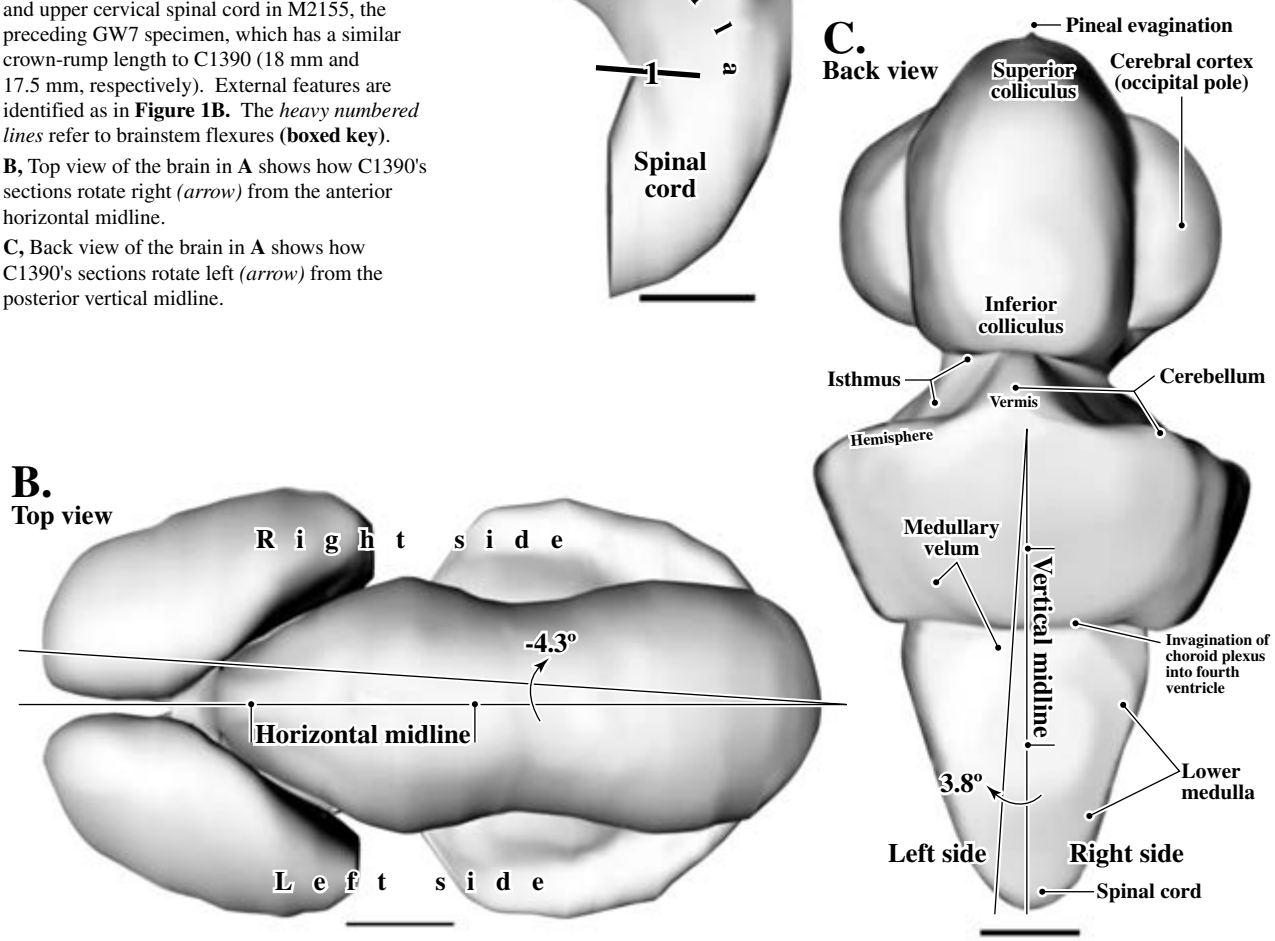
BRAINSTEM FLEXURES

1. Medullary
2. Pontine
3. Mesencephalic
4. Diencephalic

Figure 2. A, The lateral view of the left side of a computer-aided 3-D reconstruction of the brain and upper cervical spinal cord in M2155, the preceding GW7 specimen, which has a similar crown-rump length to C1390 (18 mm and 17.5 mm, respectively). External features are identified as in **Figure 1B.** The *heavy numbered lines* refer to brainstem flexures **(boxed key)**.

B, Top view of the brain in **A** shows how C1390's sections rotate right *(arrow)* from the anterior horizontal midline.

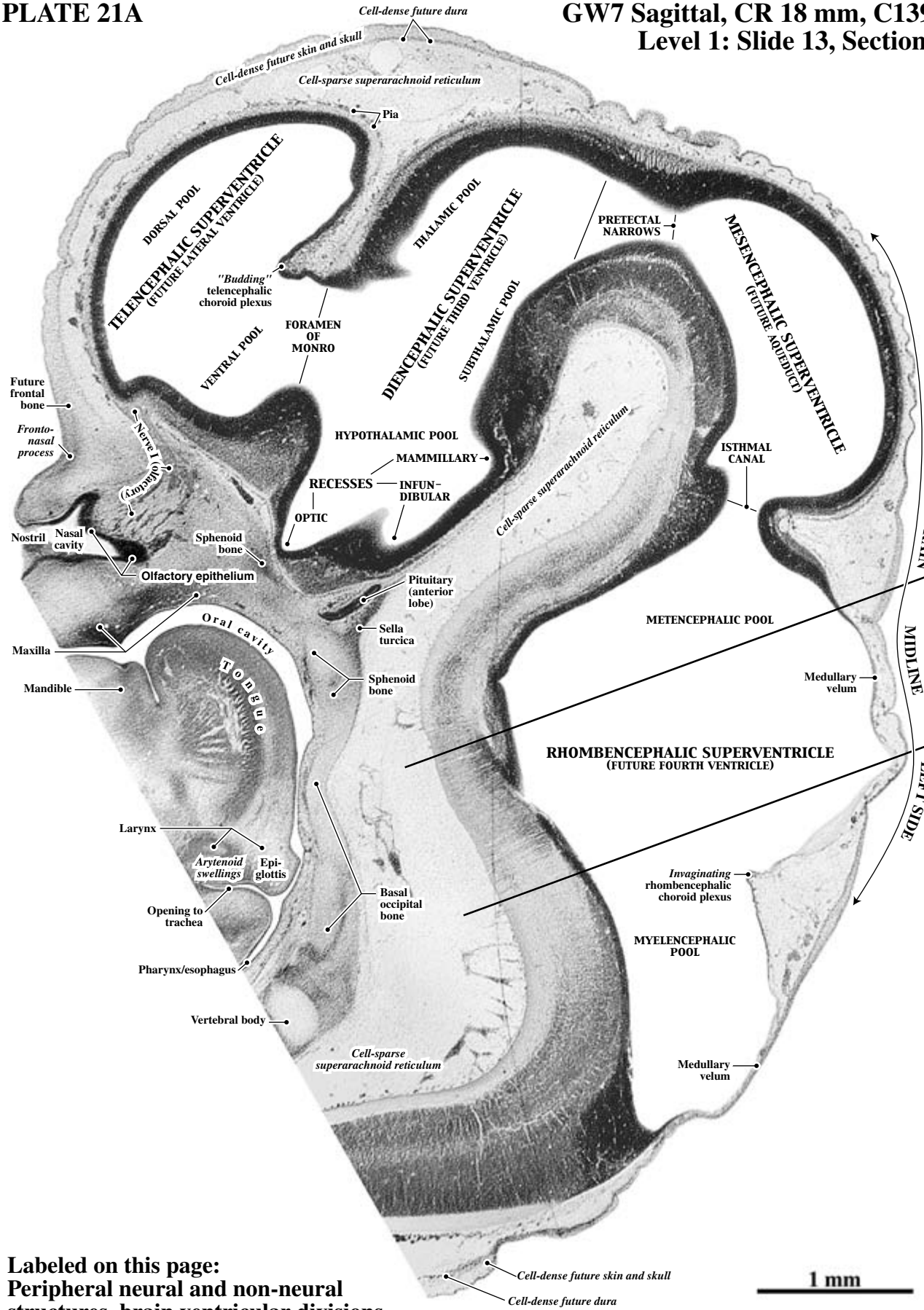
C, Back view of the brain in **A** shows how C1390's sections rotate left *(arrow)* from the posterior vertical midline.



Scale bars = 1 mm

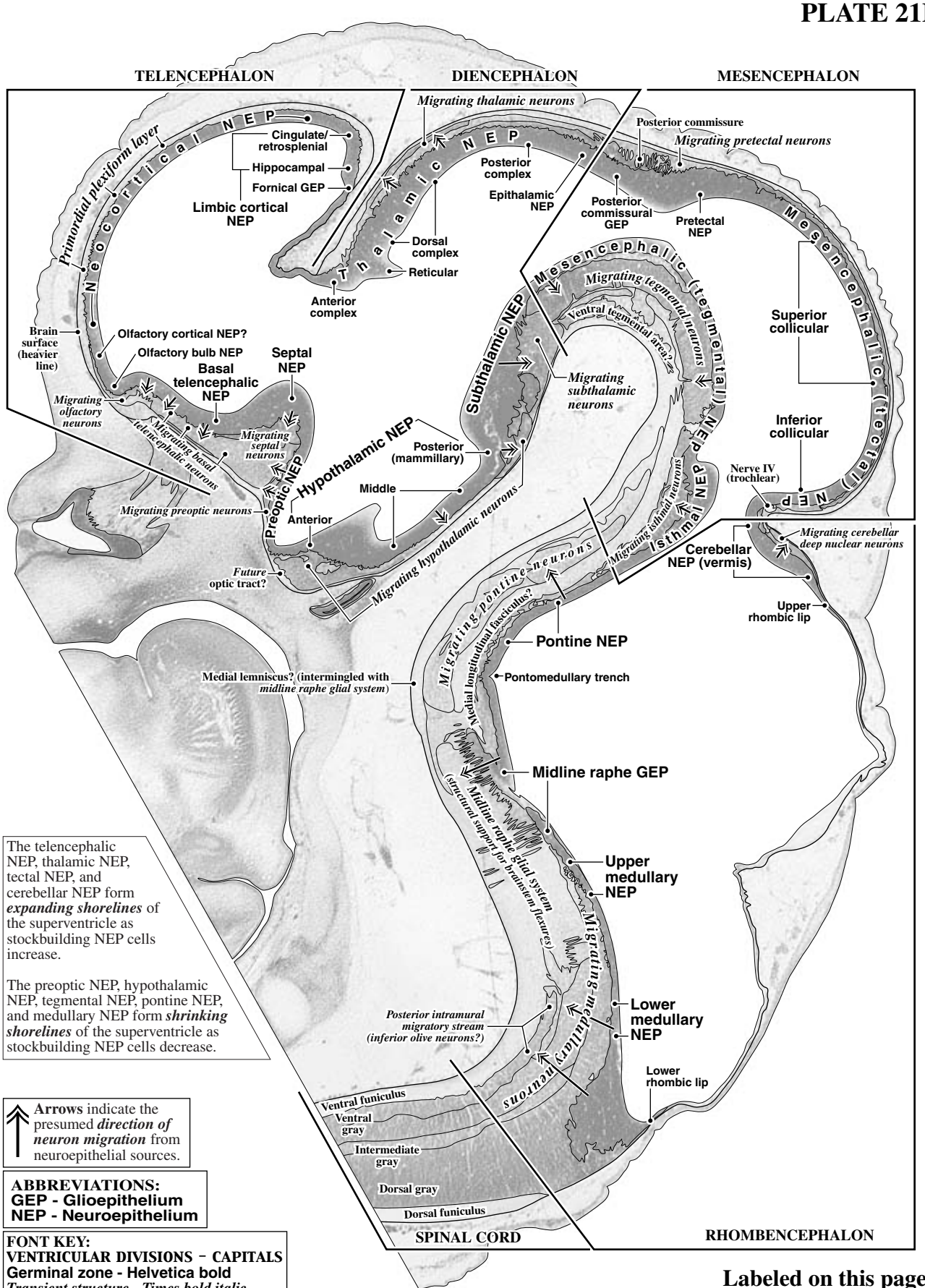
PLATE 21A

GW7 Sagittal, CR 18 mm, C1390
Level 1: Slide 13, Section 5



Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 21B



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

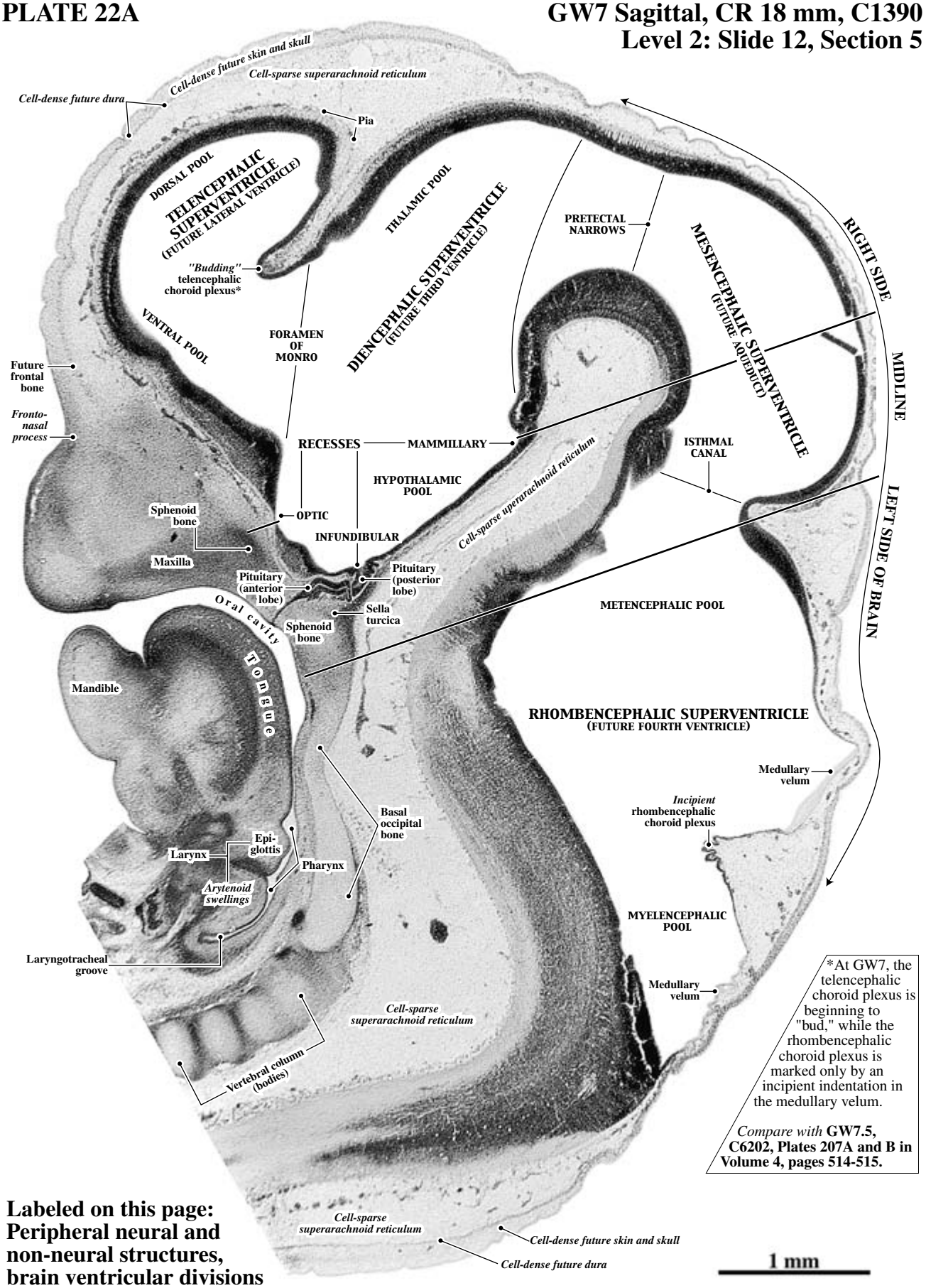
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Labeled on this page:
Central neural structures

PLATE 22A

GW7 Sagittal, CR 18 mm, C1390
Level 2: Slide 12, Section 5

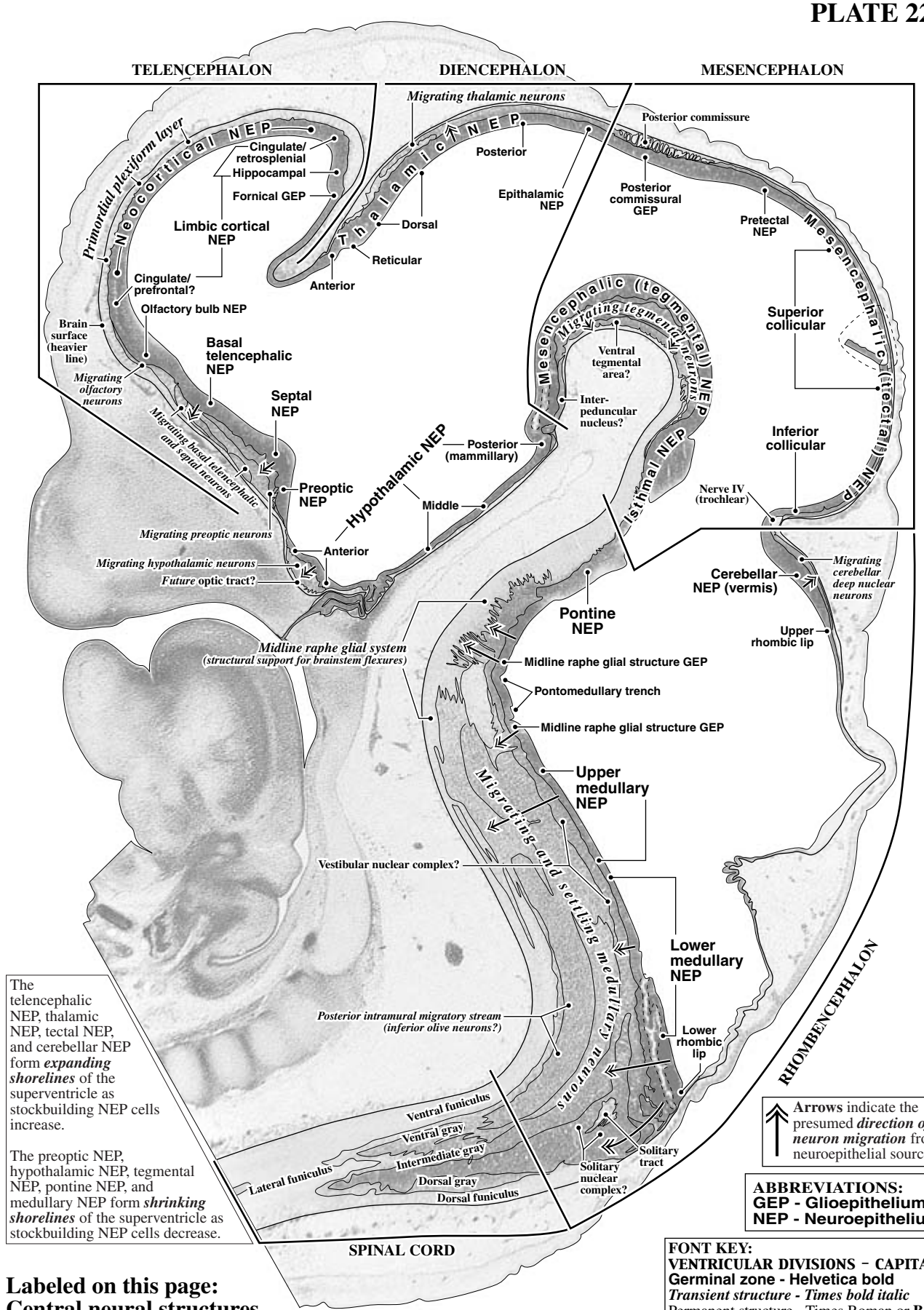


*At GW7, the telencephalic choroid plexus is beginning to "bud," while the rhombencephalic choroid plexus is marked only by an incipient indentation in the medullary velum.

Compare with **GW7.5, C6202, Plates 207A and B in Volume 4, pages 514-515.**

Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 22B



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

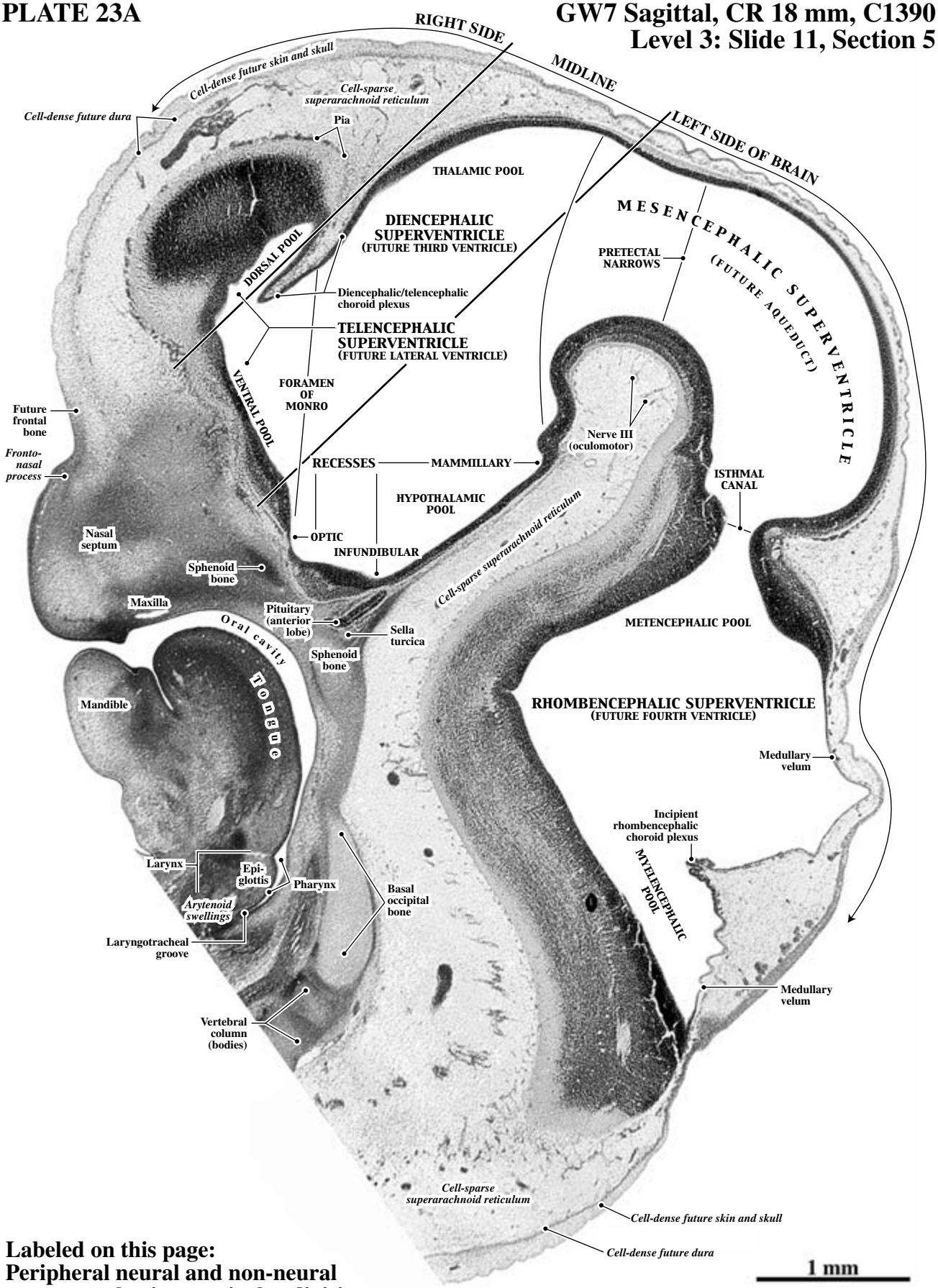
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Labeled on this page:
Central neural structures

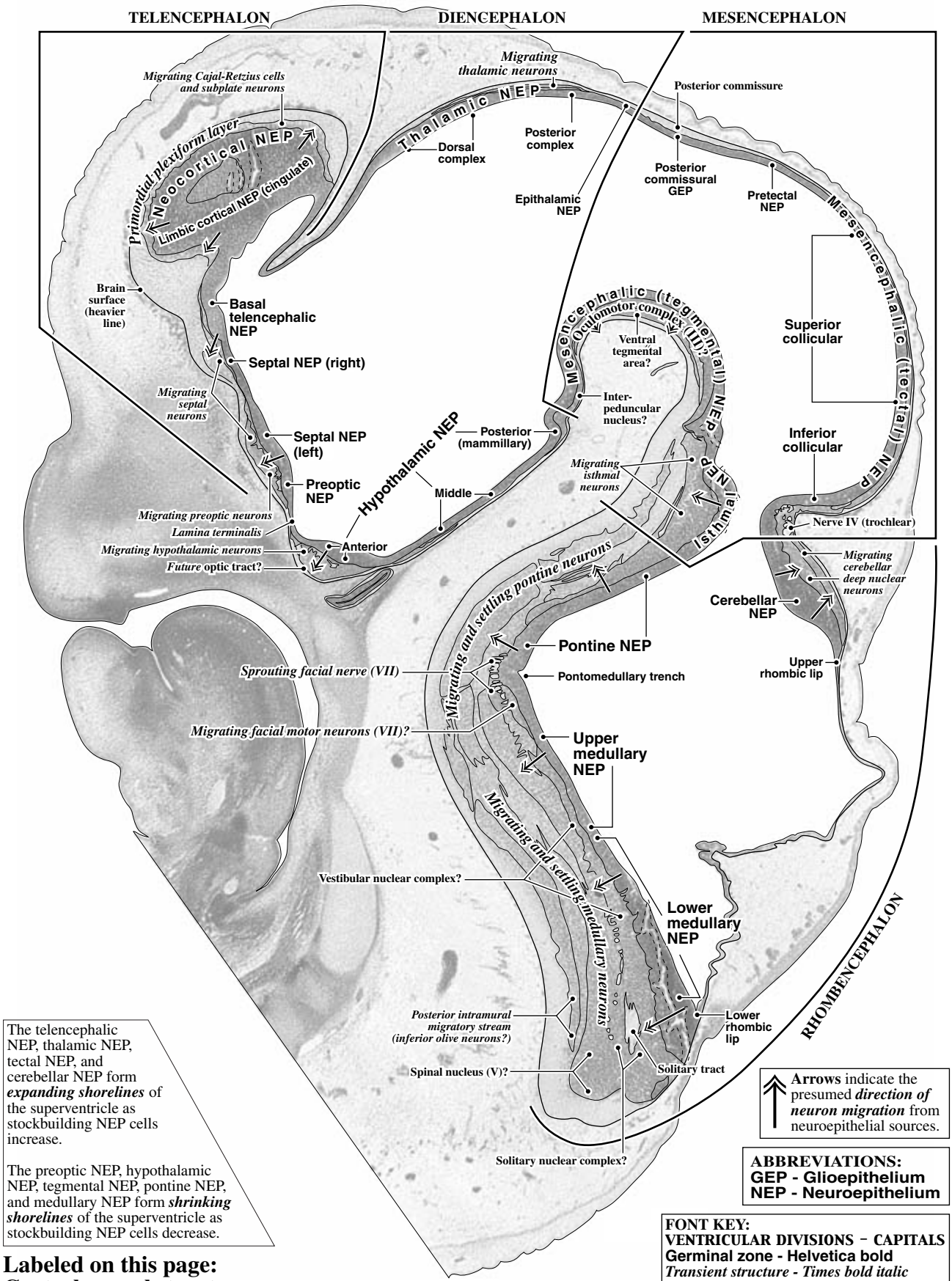
PLATE 23A

GW7 Sagittal, CR 18 mm, C1390
Level 3: Slide 11, Section 5



Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 23B



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Labeled on this page:
Central neural structures

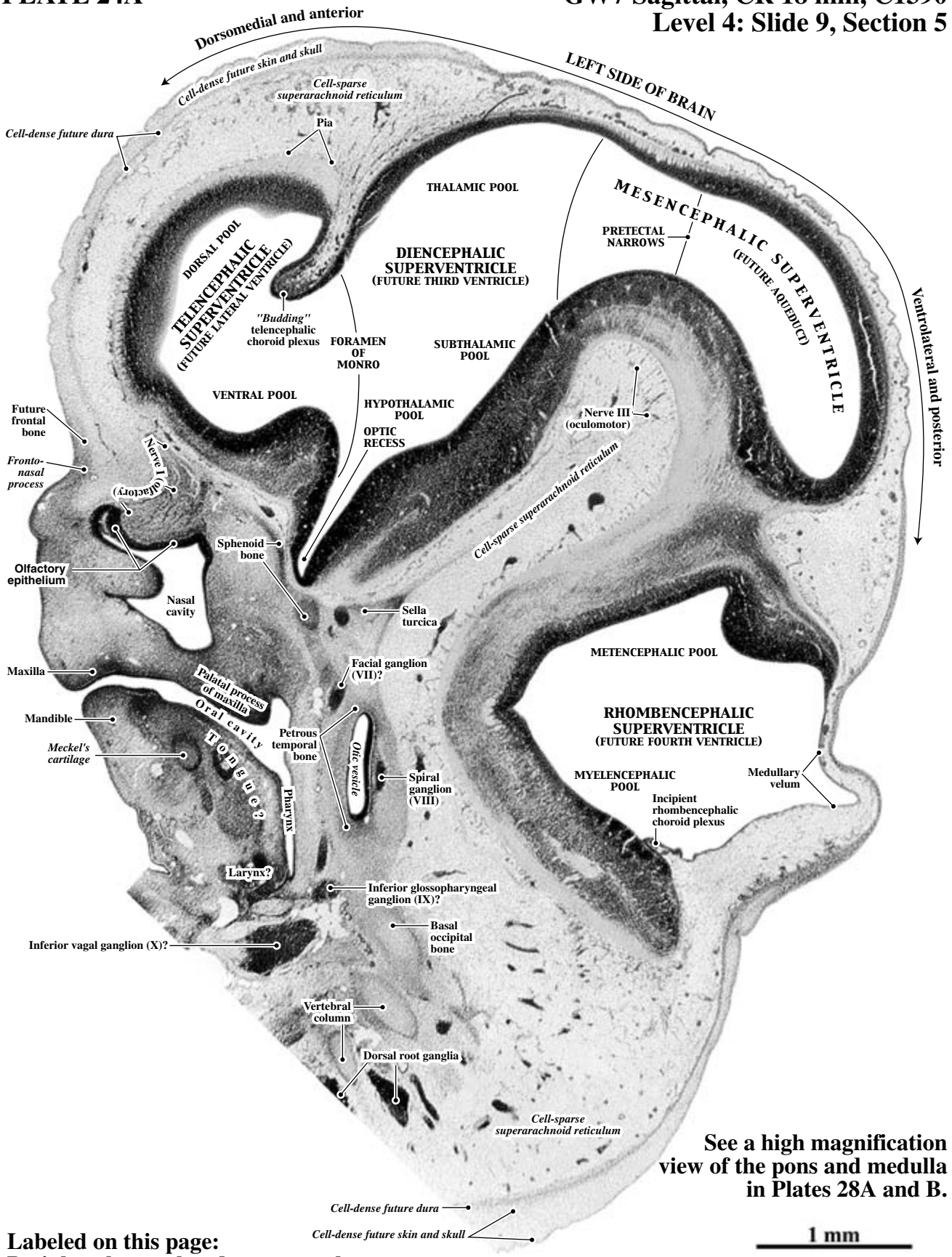
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 24A

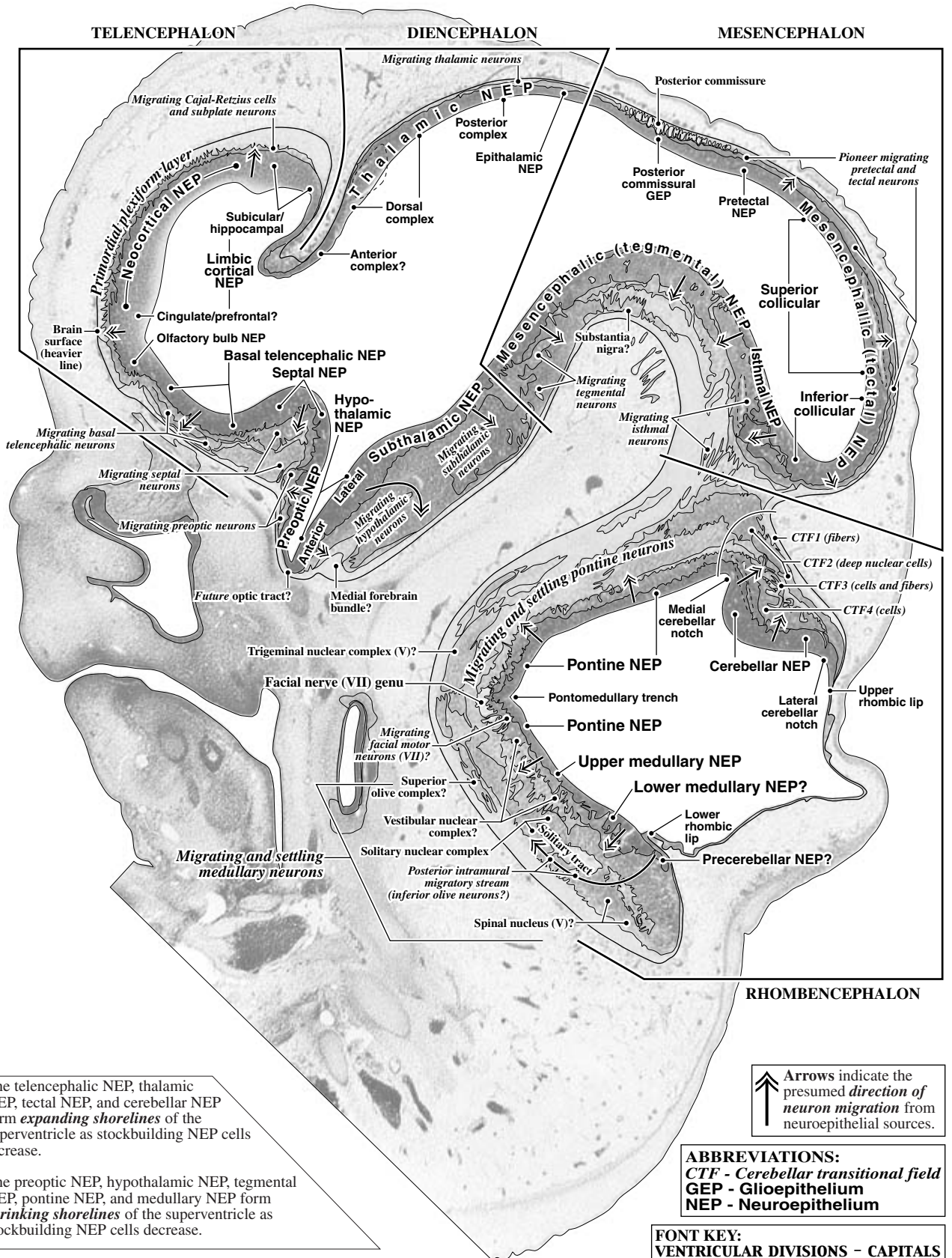
GW7 Sagittal, CR 18 mm, C1390
Level 4: Slide 9, Section 5



See a high magnification view of the pons and medulla in Plates 28A and B.

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 24B



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

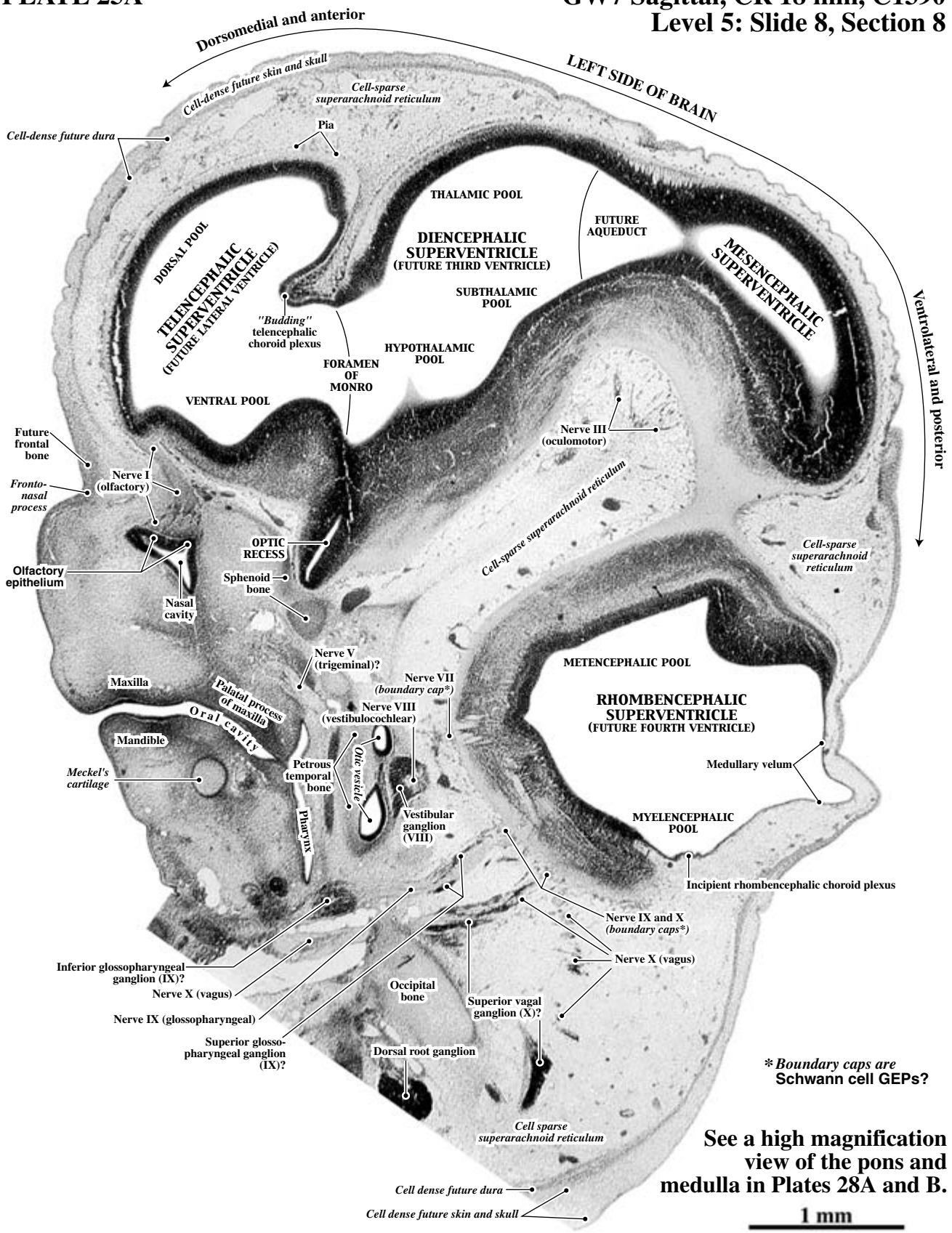
ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Labeled on this page:
Central neural structures

PLATE 25A

GW7 Sagittal, CR 18 mm, C1390
Level 5: Slide 8, Section 8

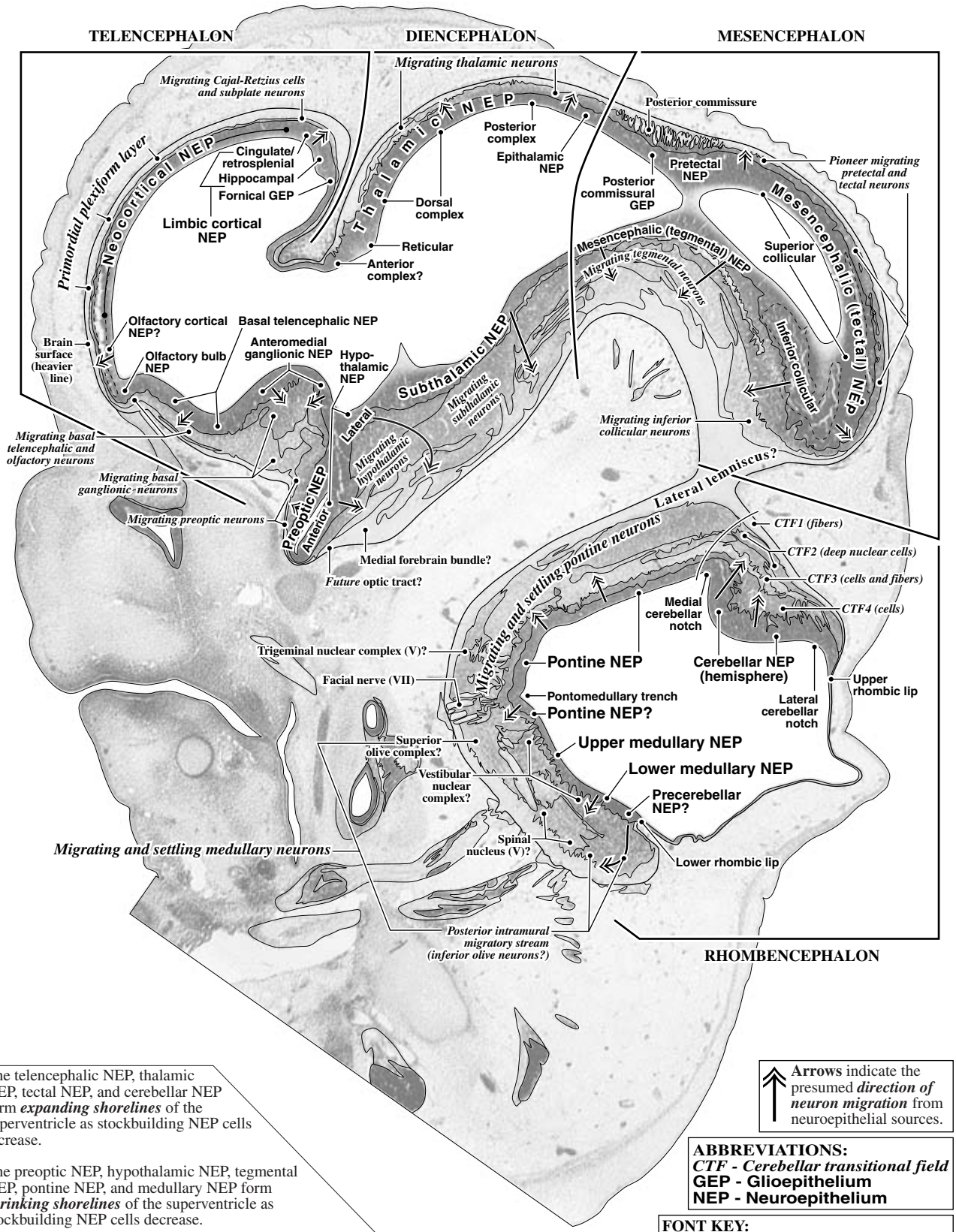


* *Boundary caps are* **Schwann cell GEPs?**

See a high magnification view of the pons and medulla in Plates 28A and B.

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 25B



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

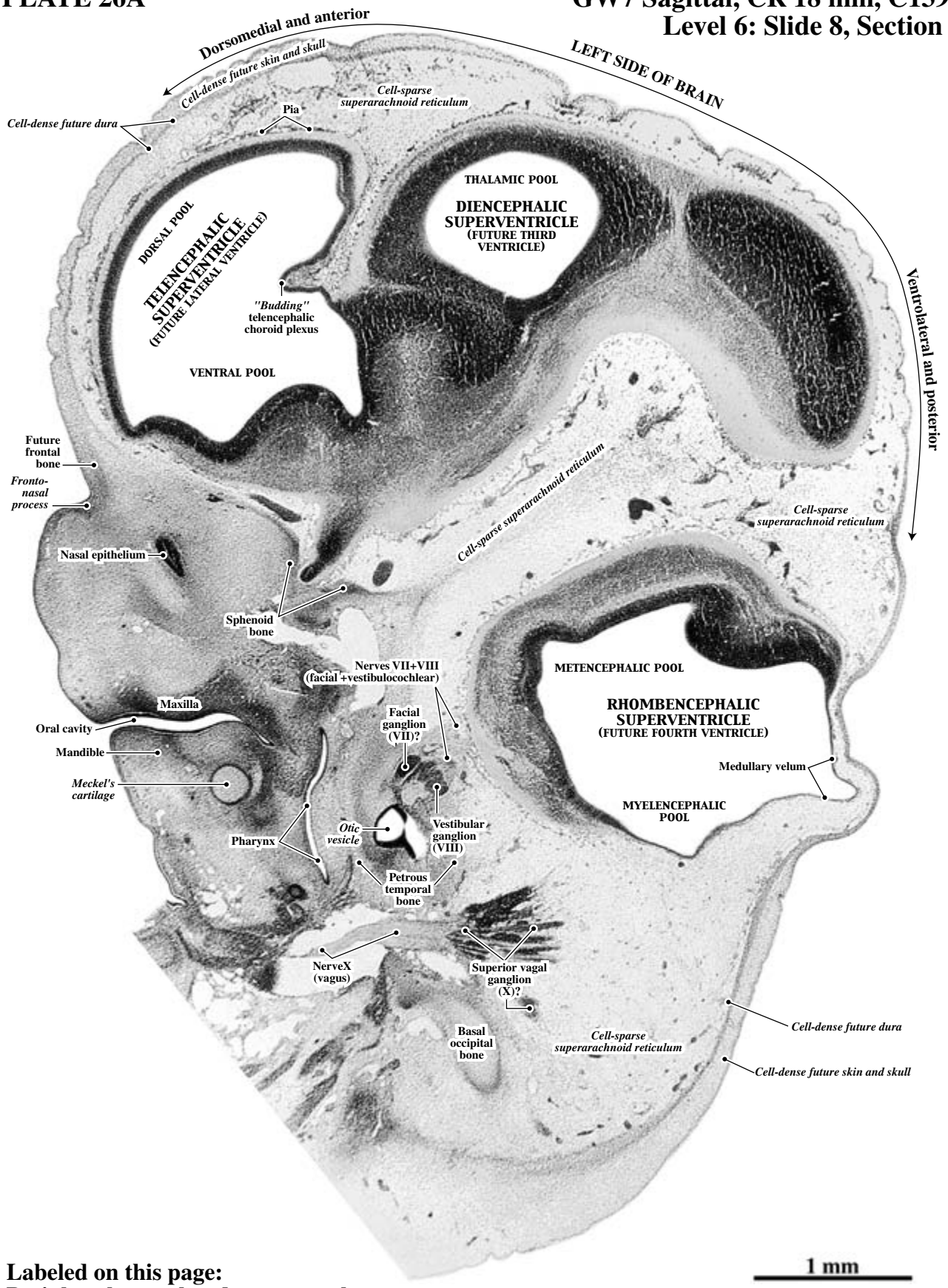
ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Labeled on this page:
Central neural structures

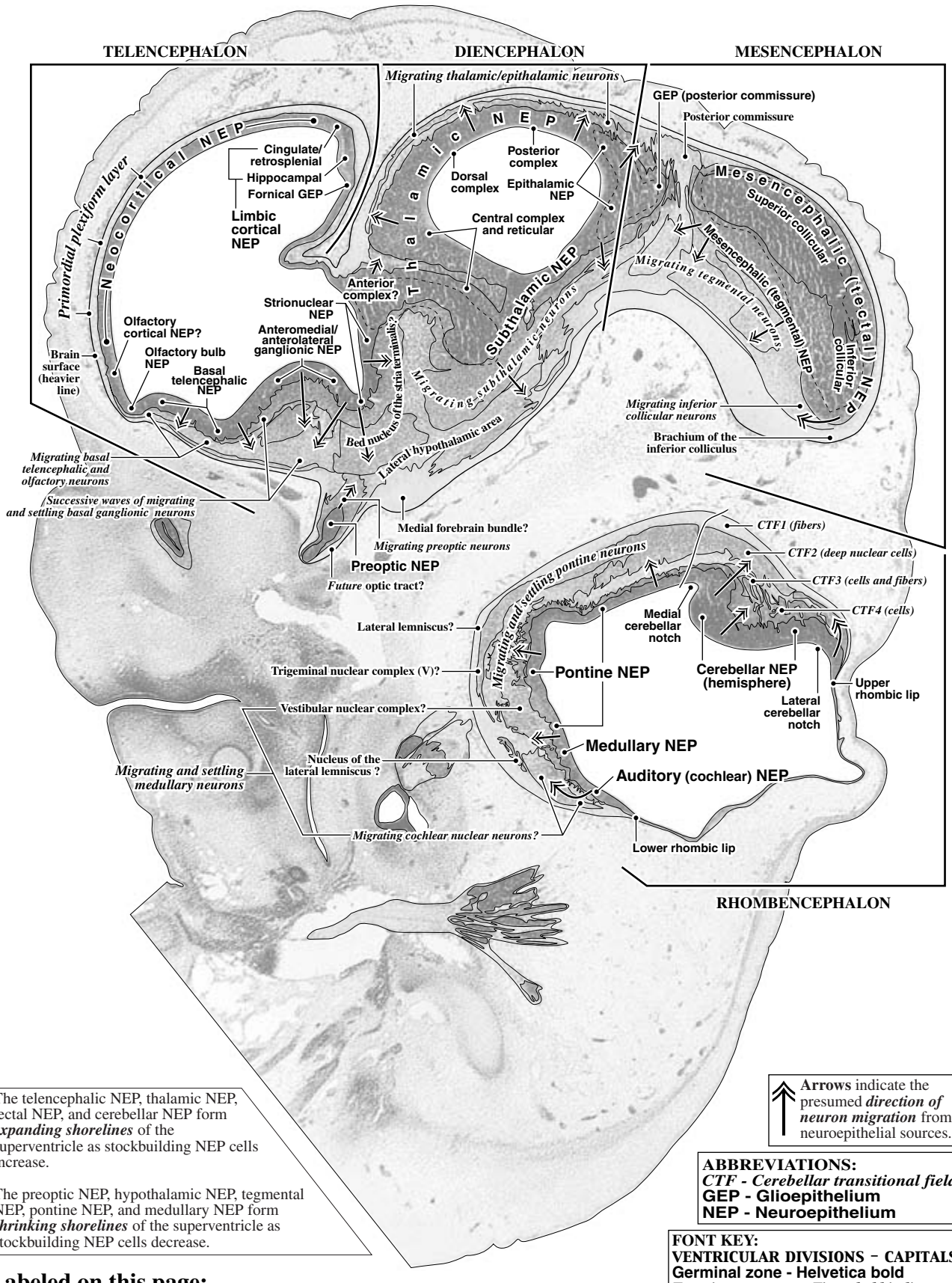
PLATE 26A

GW7 Sagittal, CR 18 mm, C1390
Level 6: Slide 8, Section 2



Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 26B



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

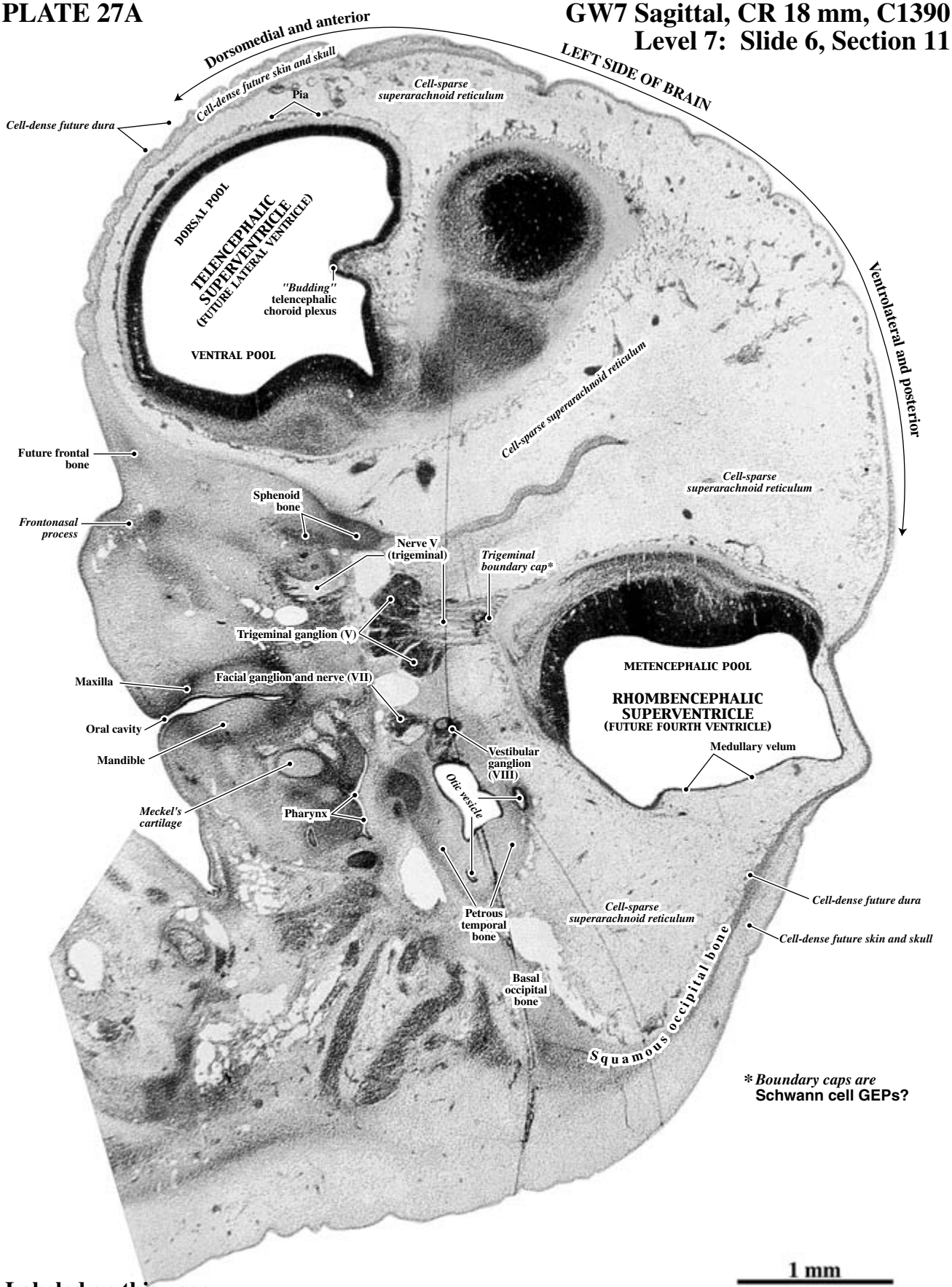
ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Labeled on this page:
Central neural structures

PLATE 27A

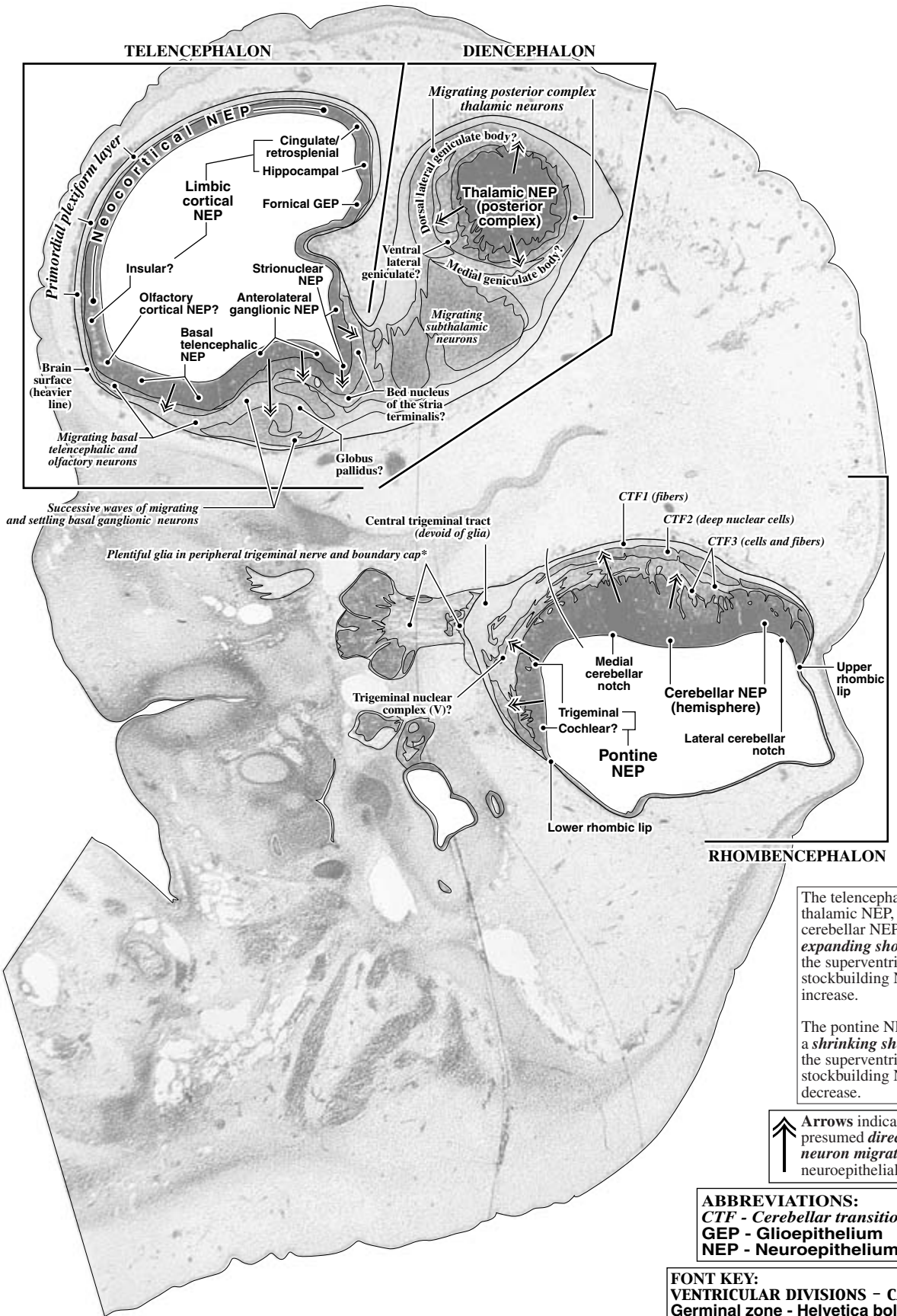
GW7 Sagittal, CR 18 mm, C1390
Level 7: Slide 6, Section 11



* *Boundary caps are* **Schwann cell GEPs?**

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 27B



The telencephalic NEP, thalamic NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The pontine NEP forms a ***shrinking shoreline*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

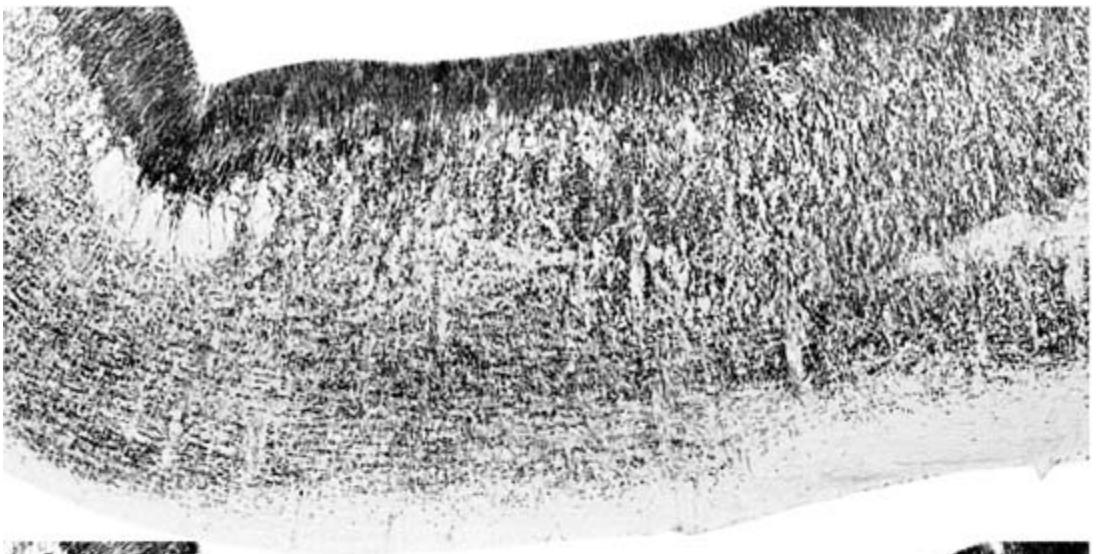
ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Labeled on this page: Central neural structures

PLATE 28A **GW7 Sagittal, CR 18 mm, C1390** **PONS/MEDULLA**

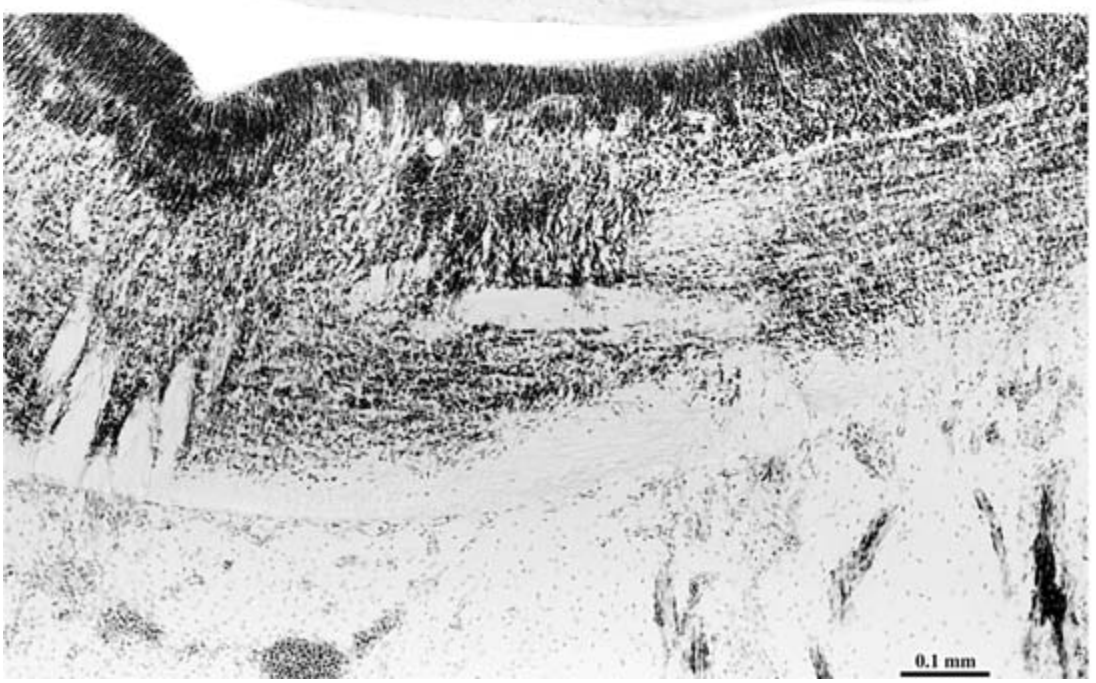
Level 4: Slide 9, Section 5



See Level 4 in Plates 24A and B.

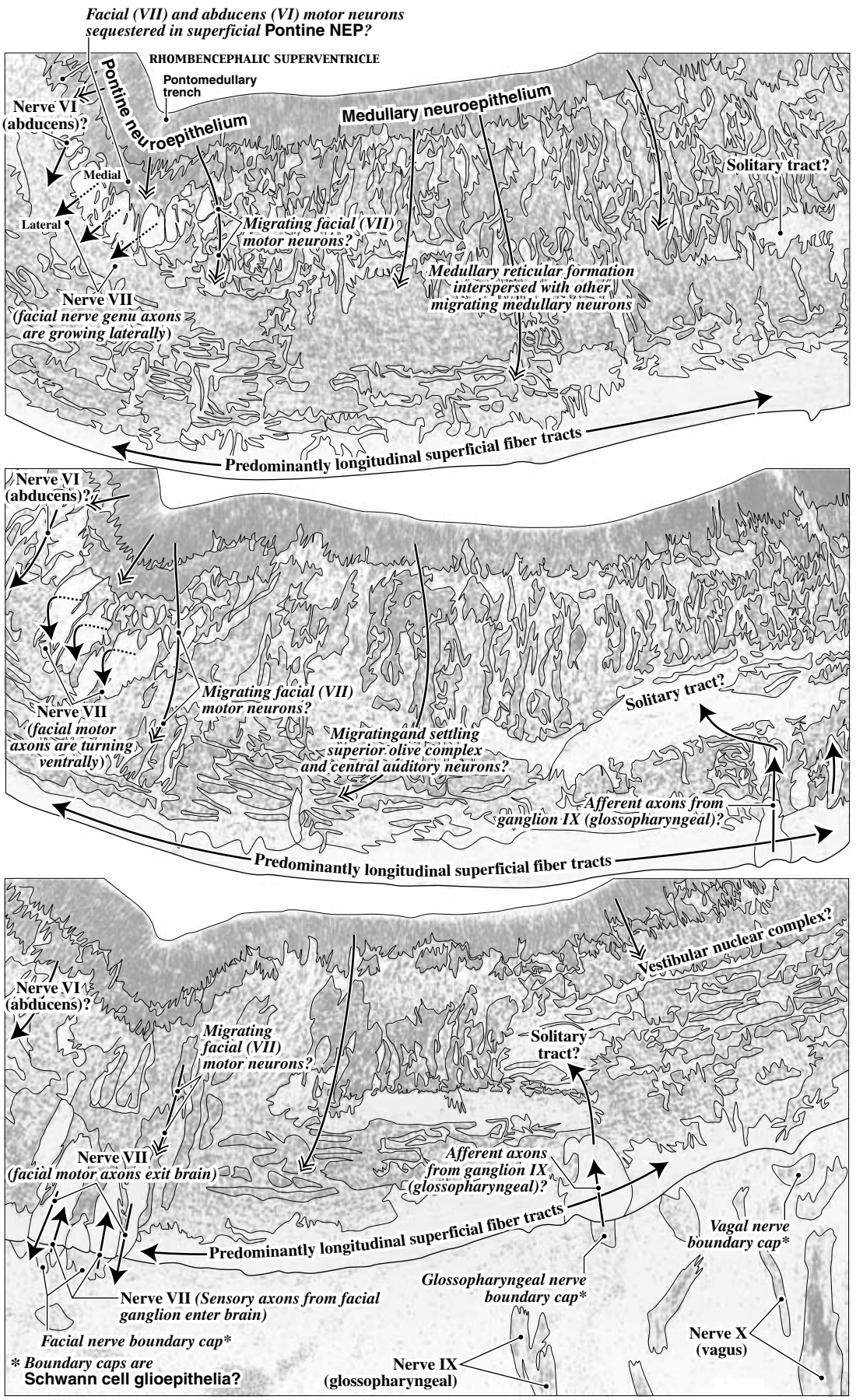
Between Levels 4 and 5: Slide 9, Section 2

Level 5: Slide 8, Section 8



See Level 5 in Plates 25A and B.

PLATE 28B


Facial (VII) and abducens (VI) motor neurons sequestered in superficial Pontine NEP?
RHOMBENCEPHALIC SUPERVENTRICLE
Pontomedullary trench
Pontine neuroepithelium
Medullary neuroepithelium
Nerve VI (abducens)?
Medial
Lateral
Migrating facial (VII) motor neurons?
Solitary tract?
Medullary reticular formation interspersed with other migrating medullary neurons
Nerve VII (facial nerve genu axons are growing laterally)
Predominantly longitudinal superficial fiber tracts
Level 4: Slide 9, Section 5
Nerve VI (abducens)?
Migrating facial (VII) motor neurons?
Solitary tract?
Nerve VII (facial motor axons are turning ventrally)
Migratingand settling superior olive complex and central auditory neurons?
Afferent axons from ganglion IX (glossopharyngeal)?
Predominantly longitudinal superficial fiber tracts
Between Levels 4 and 5: Slide 9, Section 2
Vestibular nuclear complex?
Nerve VI (abducens)?
Migrating facial (VII) motor neurons?
Solitary tract?
Nerve VII (facial motor axons exit brain)
Afferent axons from ganglion IX (glossopharyngeal)?
Predominantly longitudinal superficial fiber tracts
Vagal nerve boundary cap*
Glossopharyngeal nerve boundary cap*
Nerve VII (Sensory axons from facial ganglion enter brain)
Facial nerve boundary cap*
* Boundary caps are Schwann cell glioepithelia?
Nerve IX (glossopharyngeal)
Nerve X (vagus)
Level 5: Slide 8, Section 8
These arrows indicate the direction of neuronal migration.
These arrows indicate the direction of axon growth.

PART IV: GW7 HORIZONTAL

Carnegie Collection specimen #492 (designated here as C492) was obtained in 1911 after a miscarriage. It has a crown-rump length (CR) of 16.8 mm and is estimated to be at gestational week (GW) 7. C492 was preserved in Zenker's fixative, embedded in paraffin, and was cut in 40-µm sections that were stained with aluminum cochineal. The dorsal diencephalon and mesencephalic tectum are cut in the horizontal section plane. The plane shifts to predominantly coronal in the anterior telencephalon, ventral diencephalon, pons, and medulla. In general, C492's sections are cut perpendicular to M2155's sections (Specimen 1, **Part II**). We photographed 101 sections at low magnification from the uppermost tip of the pretectum through the spinal cord. Seventeen of these sections are illustrated in **Plates 29AB to 45AB**. All photographs containing the brain were used to produce computer-aided 3-D reconstructions of the external features of C492's brain (**Figure 3**), and to show each illustrated section *in situ* (*insets,* **Plates 29A to 45A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures.

A "stockbuilding" telencephalic neuroepithelium surrounds the enlarging telencephalic superventricle. As in other GW7 specimens, few migrating neurons are adjacent to the cortical neuroepithelium while there are many adjacent to the basal ganglionic and basal telencephalic neuroepithelia. The plane of C492's sections are ideal to show two features of the telencephalic/diencephalic junction that are not seen as clearly in the other GW7 specimens. First, the telencephalic and diencephalic superventricles are continuous at the very wide foramen of Monro. Second, the posterior basal ganglionic neuroepithelium forms a continuum with the ventral diencephalic neuroepithelium, making it difficult to distinguish telencephalic from diencephalic structures.

The "stockbuilding" thalamic neuroepithelium surrounds an expanding thalamic pool in the superventricle, while "shrinking" subthalamic and hypothalamic neuroepithelia surround subthalamic and hypothalamic pools. Many migrating and settling young neurons are in the parenchyma of the future subthalamus and hypothalamus. There are few neurons outside the thalamic neuroepithelium, except in ventral areas where pioneer reticular nuclear neurons are migrating.

The roof (tectum and pretectum) of the mesencephalon contains a stockbuilding neuroepithelium adjacent to a very thin layer of pioneer migrating neurons. The bundles of fibers in the posterior commissure are very distinct in the uppermost sections of the pretectum. The tegmental and isthmal neuroepithelia are thinning as their neuronal progeny migrate out, but that thinning is less obvious in C492 compared to other GW7 specimens. Similar to the other GW7 specimens, there is a very thick subpial fiber band; no doubt, these are fibers from sources outside the mesencephalon and isthmus.

As in other GW7 specimens, the pons and medulla have neuroepithelia that are shrinking as stem cells unload their neuronal and glial progeny into an expanding parenchyma. For the most part, nuclear subdivisions are indistinct. The superior olivary complex, facial motor nucleus, inferior olivary complex, and solitary nucleus can be tentatively identified. The subpial fiber band is thick and prominent.

The "stockbuilding" cerebellar neuroepithelium sharply juts into the lateral part of the rhombencephalic superventricle at the cerebellar notches. The bands of cells and fibers in the cerebellar transitional fields are similar to other GW7 specimens. These bands are prominent in the future hemisphere and are indistinct in the future vermis.

C492 Computer-aided 3-D Brain Reconstructions

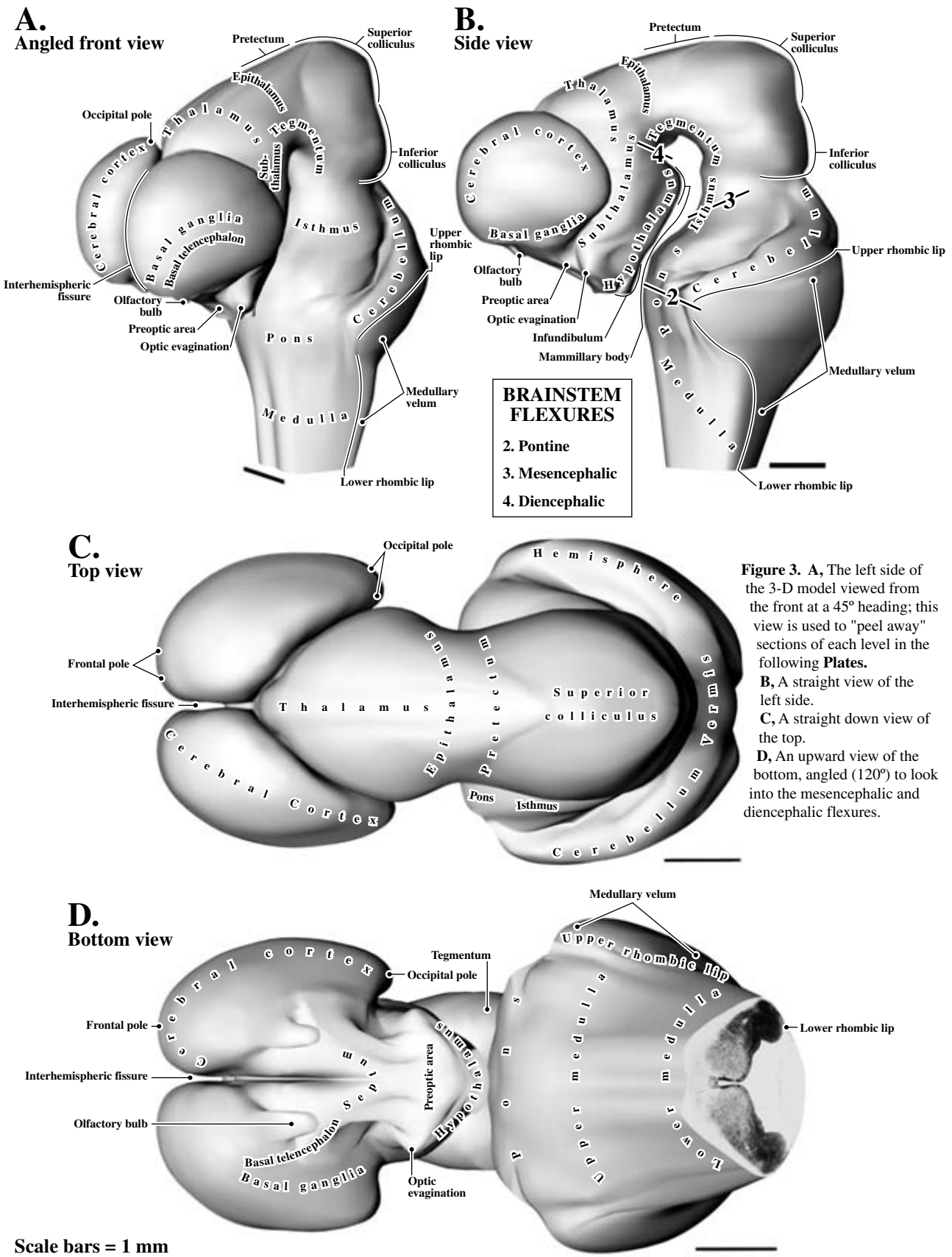


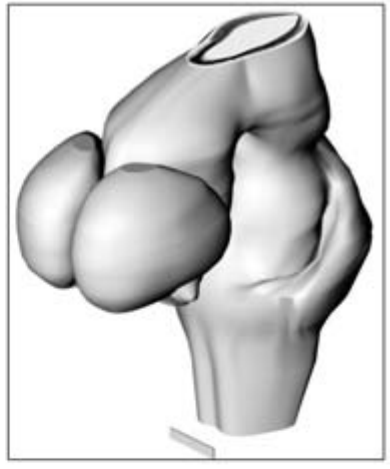
Figure 3. **A,** The left side of the 3-D model viewed from the front at a 45° heading; this view is used to "peel away" sections of each level in the following **Plates.**
B, A straight view of the left side.
C, A straight down view of the top.
D, An upward view of the bottom, angled (120°) to look into the mesencephalic and diencephalic flexures.

Scale bars = 1 mm

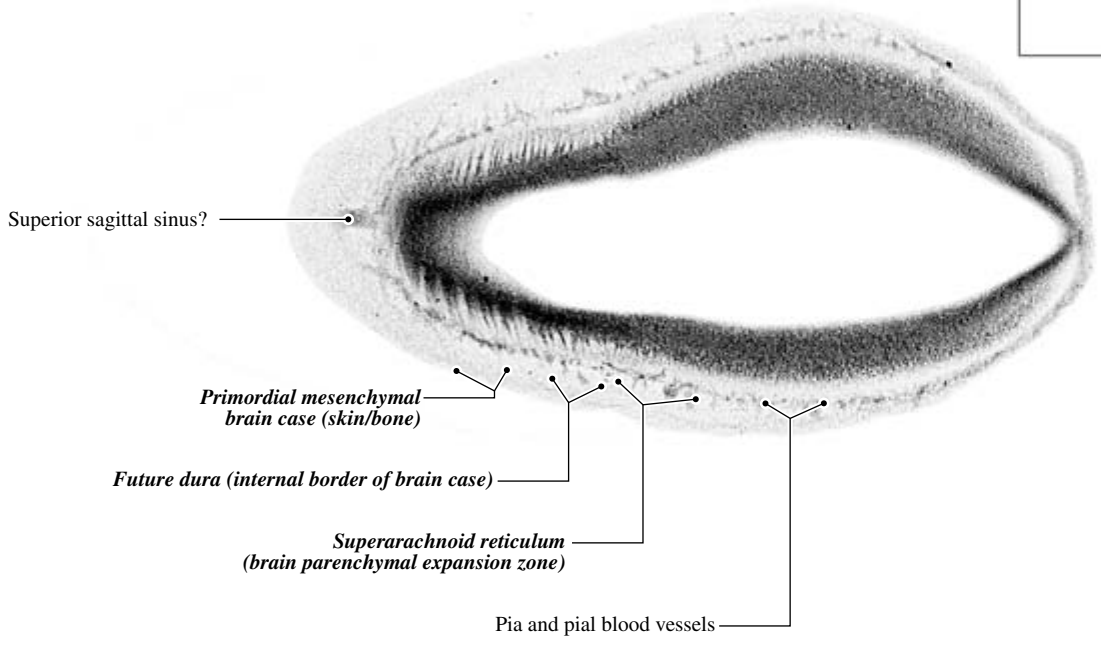
PLATE 29A

GW7 Horizontal
CR 16.8 mm
C492
Level 1: Section 9

Level 1: Computer-aided 3-D Brain Reconstruction



Non-neural structures labeled



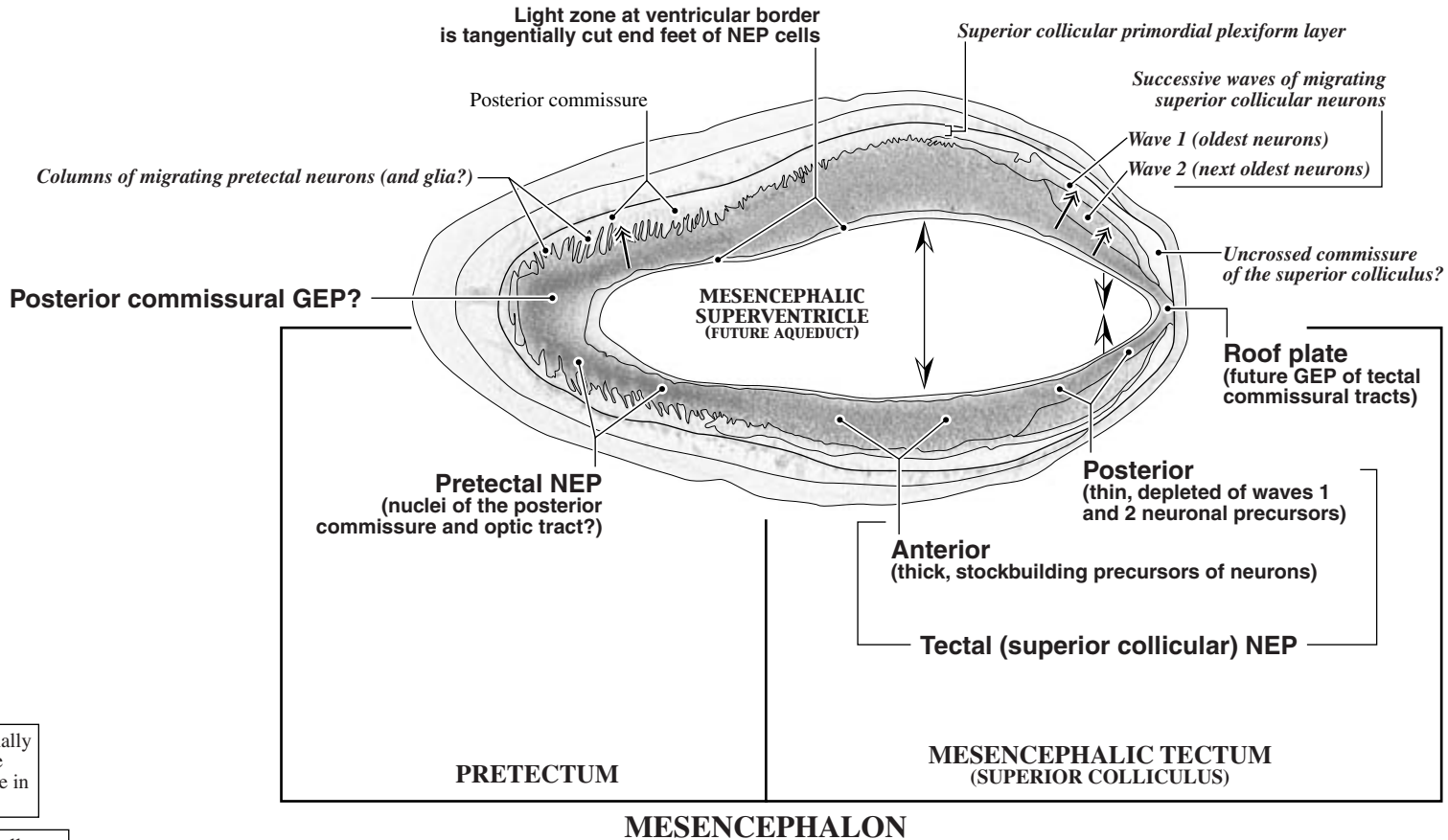
1 mm

PLATE 29B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

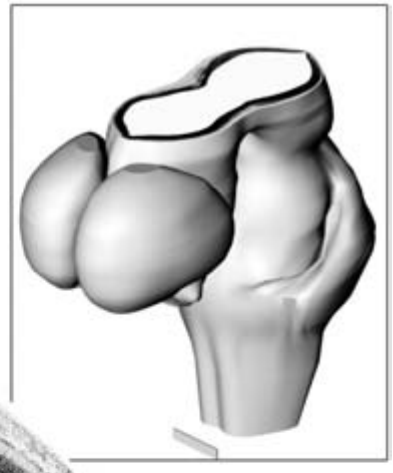
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

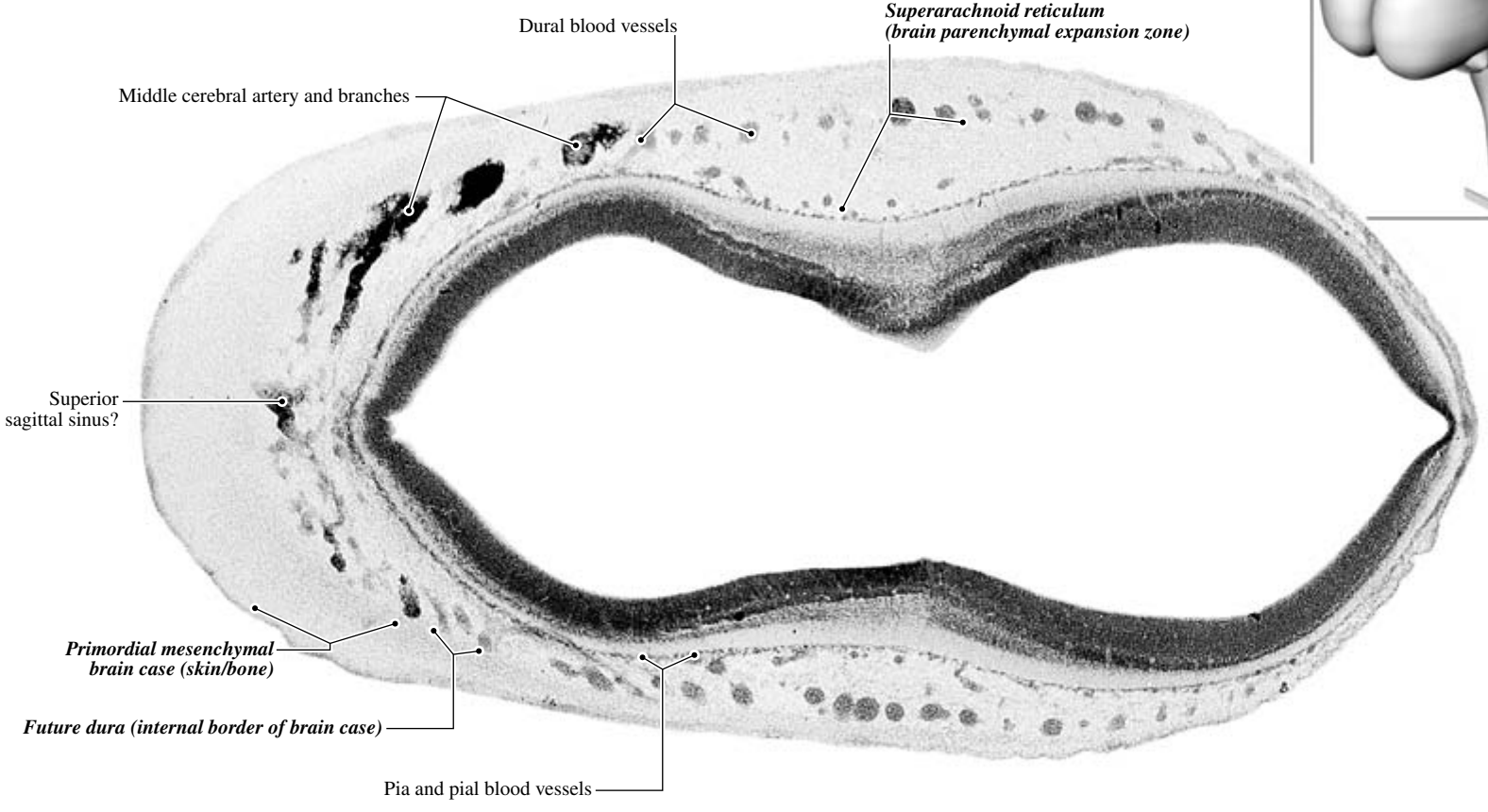
PLATE 30A

GW7 Horizontal
CR 16.8 mm
C492
Level 2: Section 29

Level 2: Computer-aided 3-D Brain Reconstruction



Non-neural structures labeled



1 mm

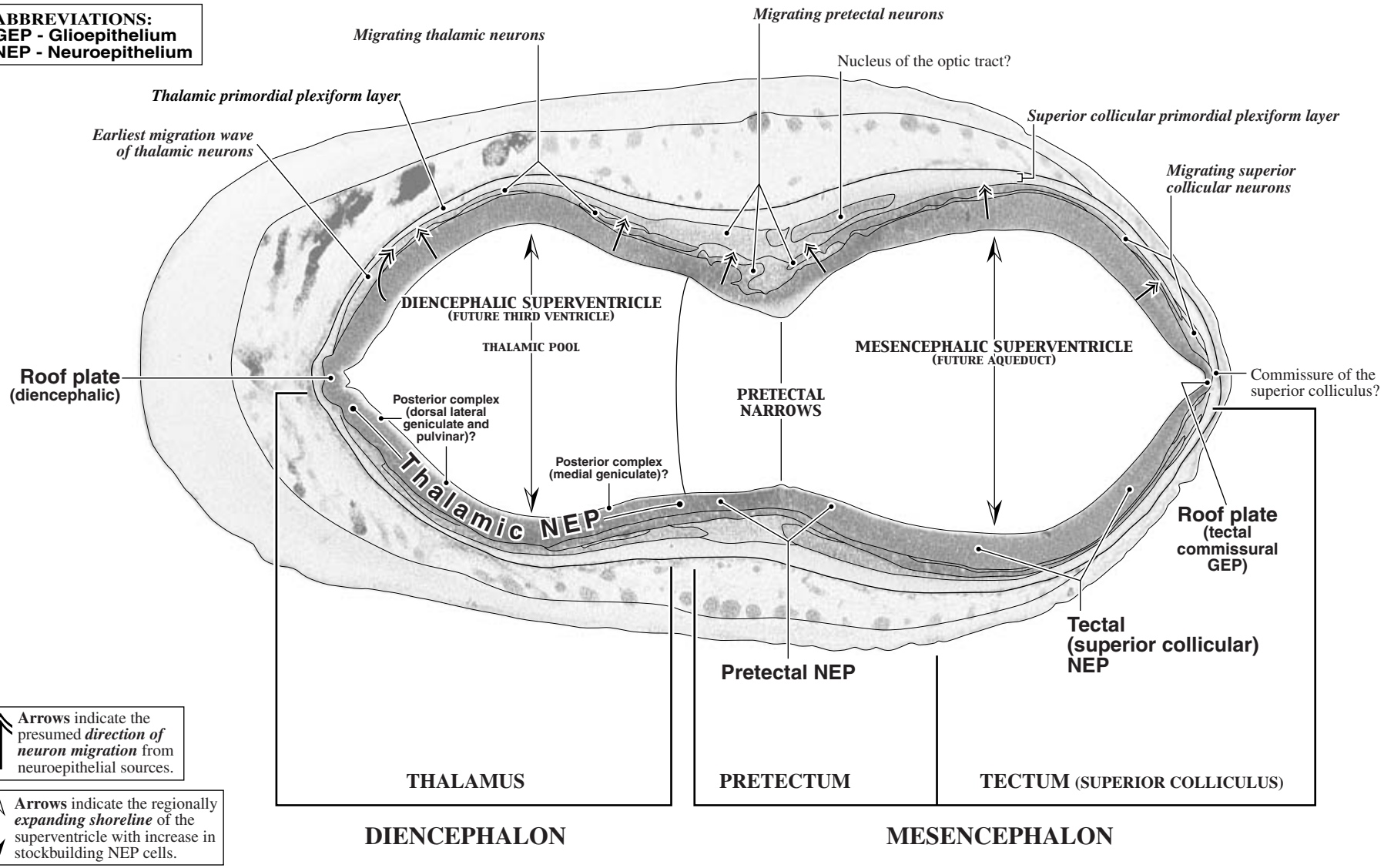
Dark stain in some blood vessels is injected ink.

PLATE 30B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Neural structures labeled



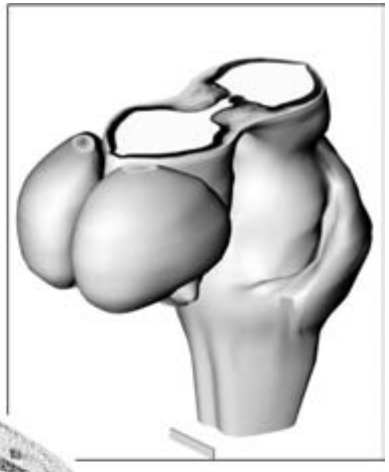
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

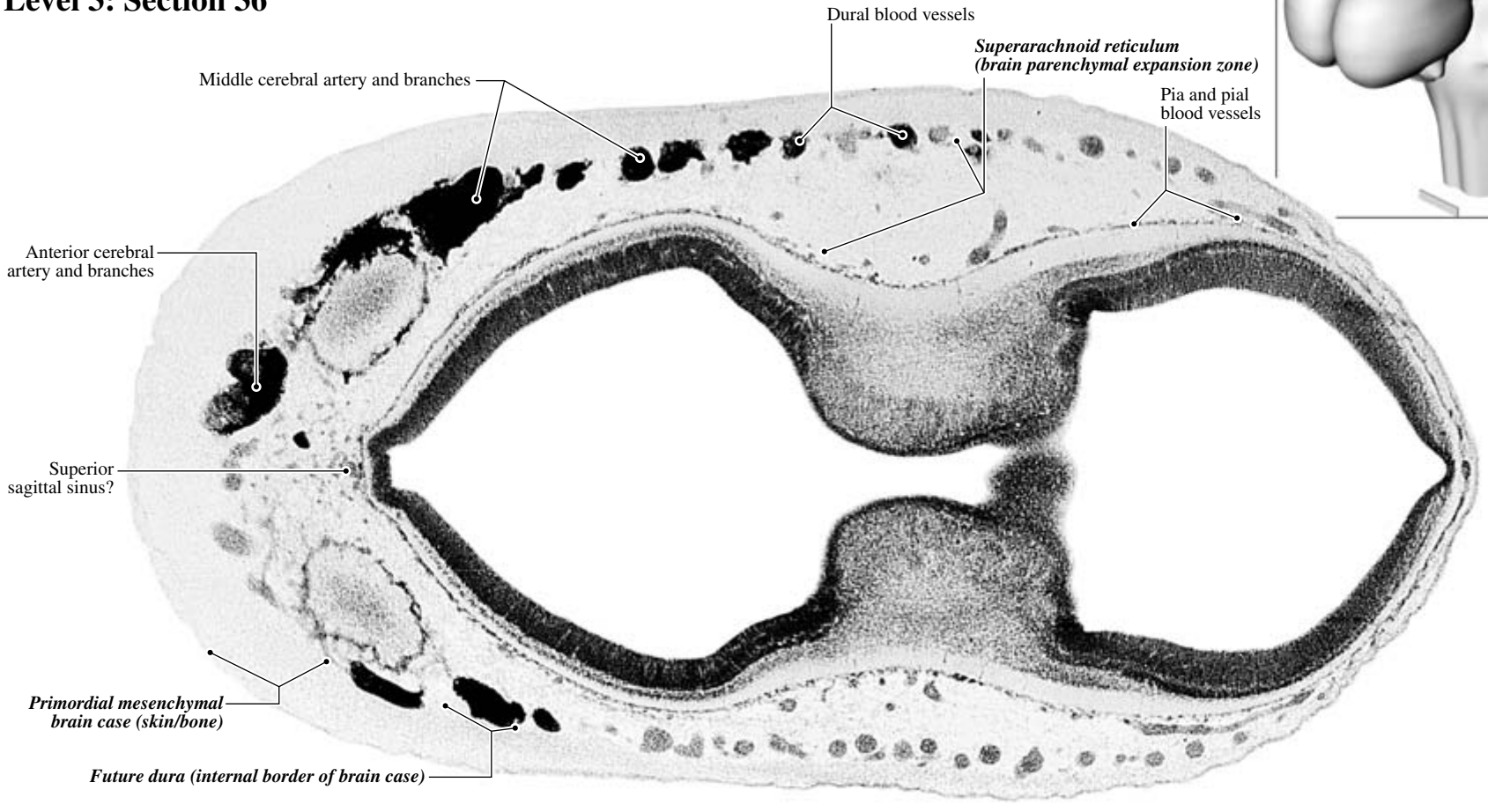
PLATE 31A

GW7 Horizontal
CR 16.8 mm
C492
Level 3: Section 36

Level 3: Computer-aided 3-D Brain Reconstruction



Non-neural structures labeled



1 mm

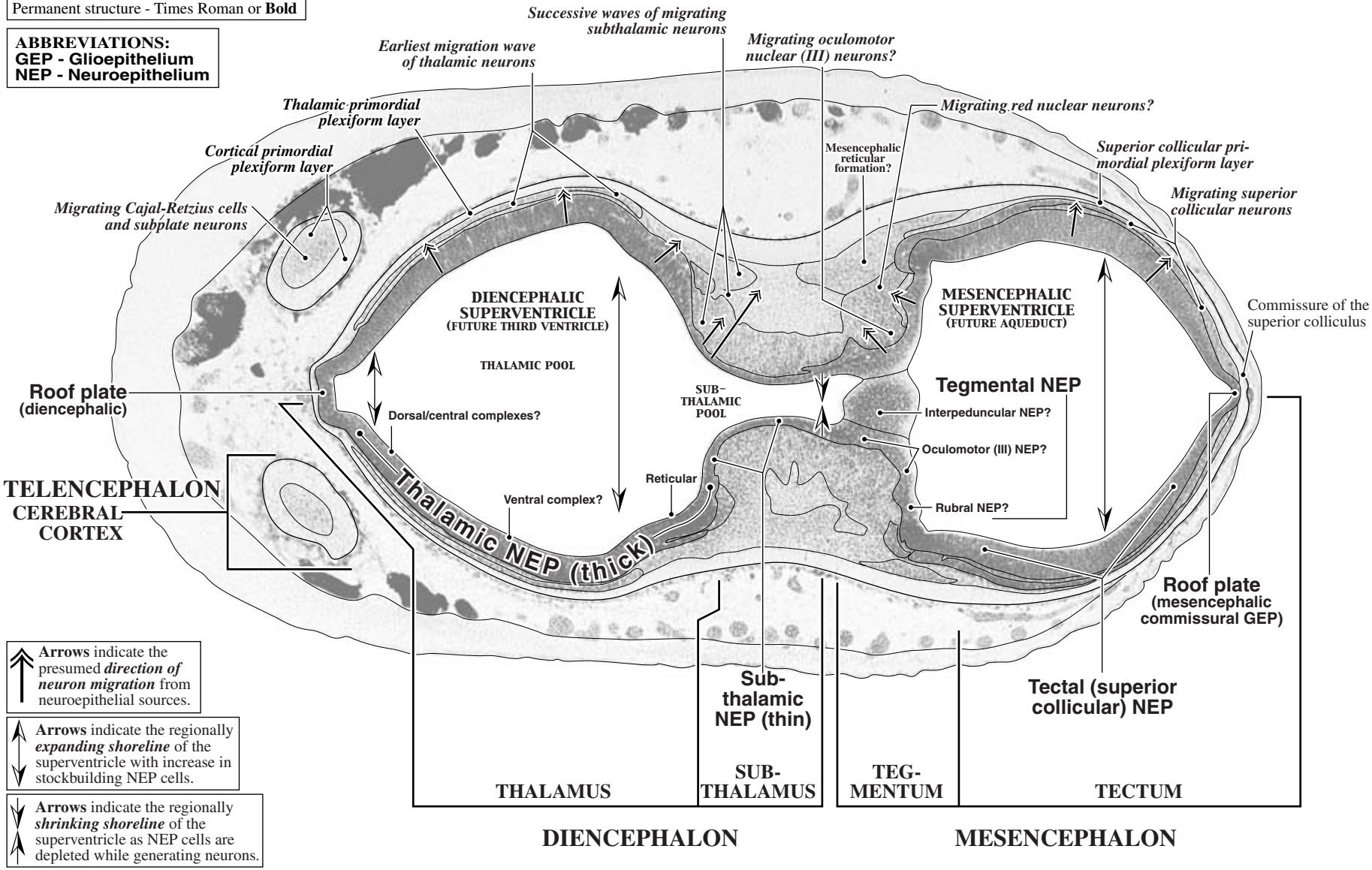
Dark stain in some blood vessels is injected ink.

PLATE 31B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

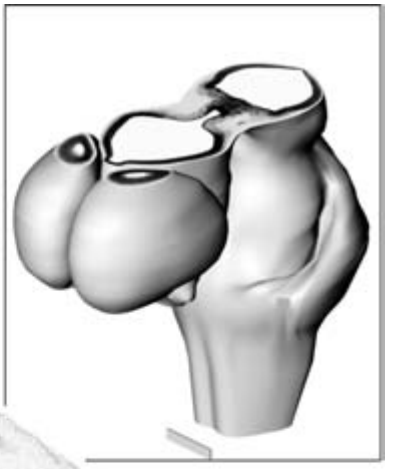
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

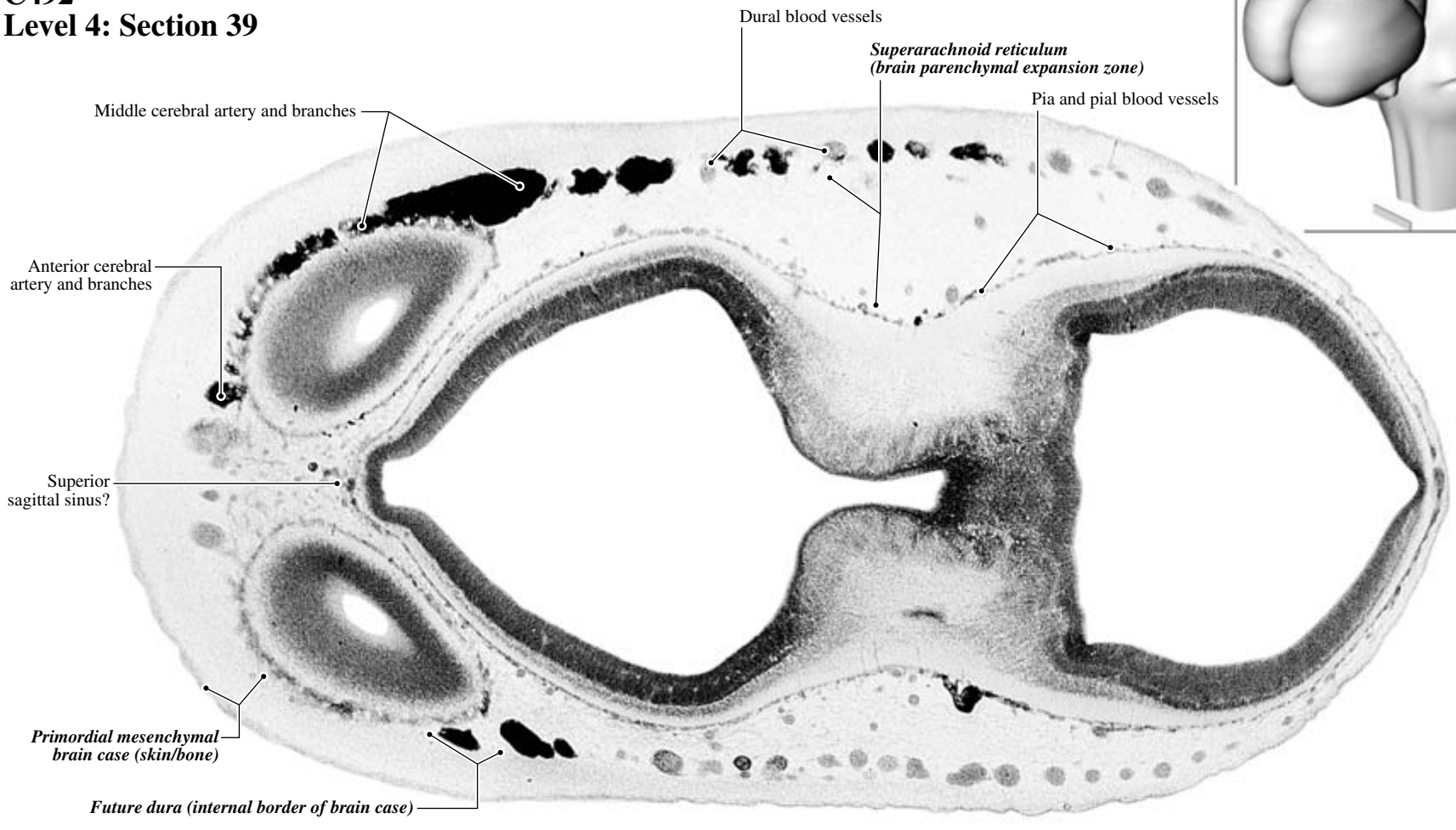
PLATE 32A

GW7 Horizontal
CR 16.8 mm
C492
Level 4: Section 39

Level 4: Computer-aided 3-D Brain Reconstruction



Non-neural structures labeled



Dark stain in some blood vessels is injected ink.

PLATE 32B

Neural structures labeled

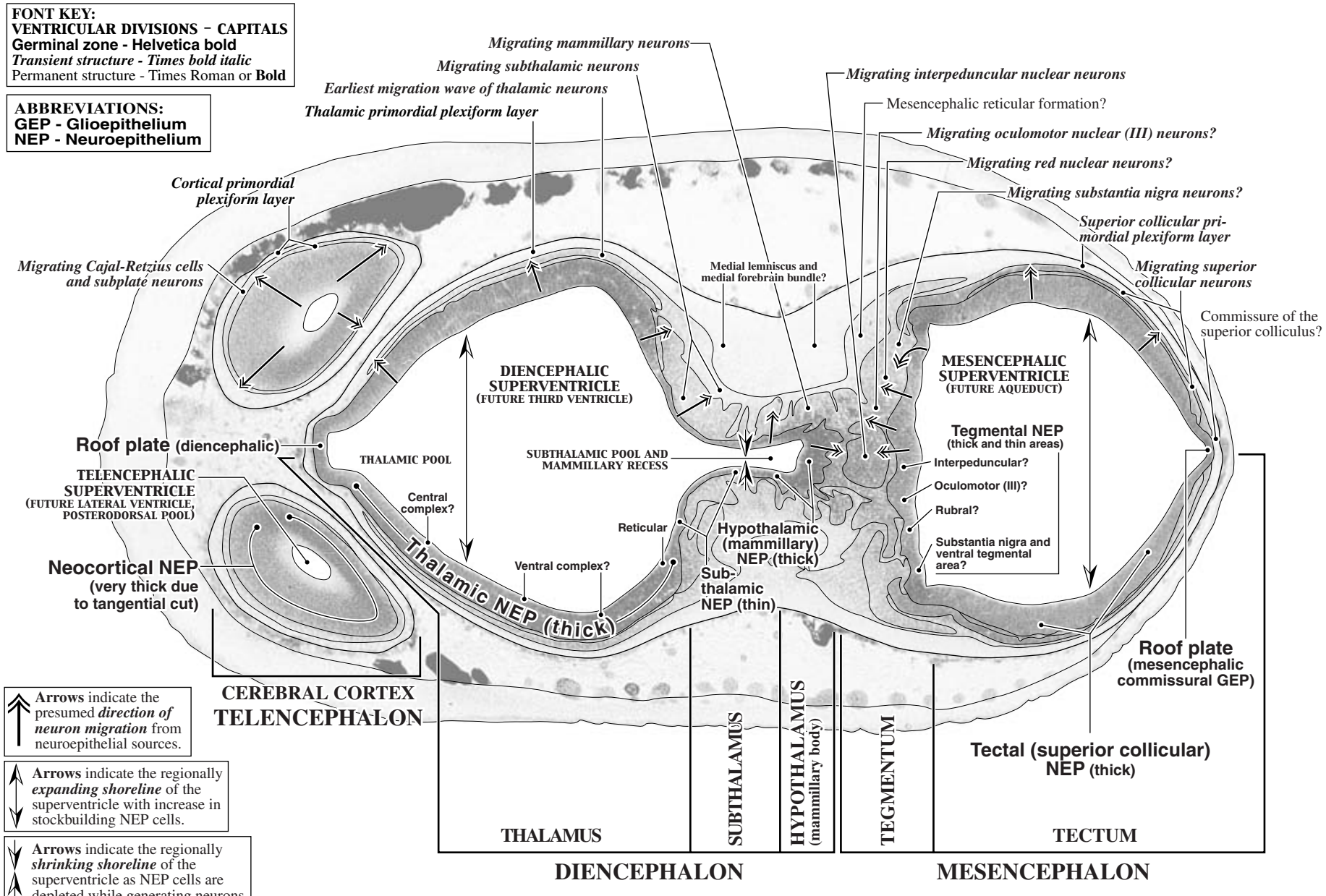
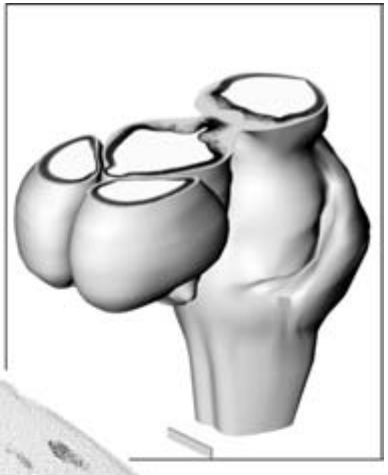


PLATE 33A

GW7 Horizontal
CR 16.8 mm
C492
Level 5: Section 45

Level 5: Computer-aided 3-D Brain Reconstruction



Non-neural structures labeled

Dark stain in some blood vessels is injected ink.

PLATE 33B

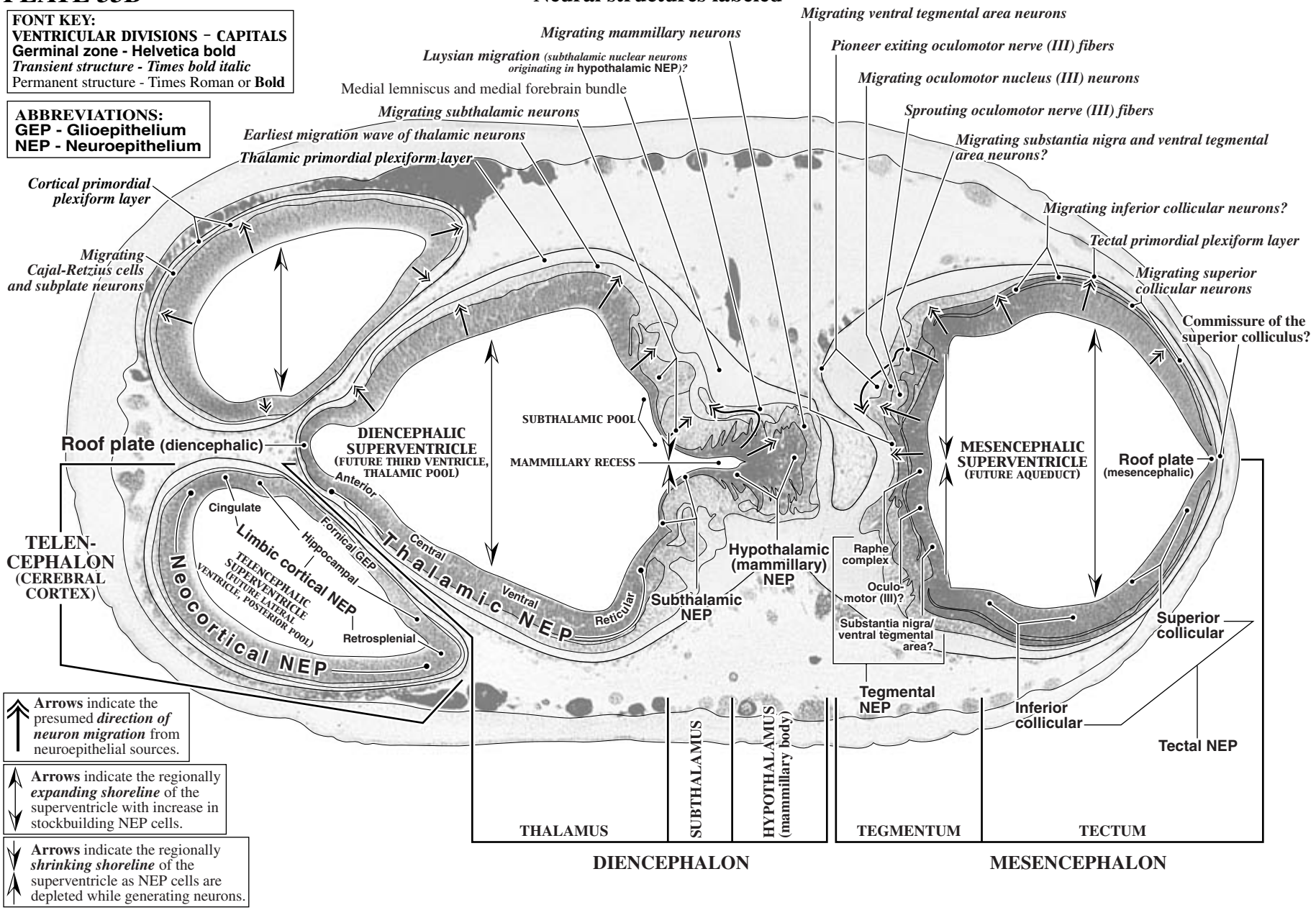

Neural structures labeled
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
Migrating ventral tegmental area neurons
Migrating mammillary neurons
Pioneer exiting oculomotor nerve (III) fibers
Luysian migration (subthalamic nuclear neurons originating in hypothalamic NEP)?
Migrating oculomotor nucleus (III) neurons
Medial lemniscus and medial forebrain bundle
Migrating subthalamic neurons
Sprouting oculomotor nerve (III) fibers
Earliest migration wave of thalamic neurons
Migrating substantia nigra and ventral tegmental area neurons?
Thalamic primordial plexiform layer
Cortical primordial plexiform layer
Migrating inferior collicular neurons?
Tectal primordial plexiform layer
Migrating Cajal-Retzius cells and subplate neurons
Migrating superior collicular neurons
Commissure of the superior colliculus?
SUBTHALAMIC POOL
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE, THALAMIC POOL)
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Roof plate (diencephalic)
MAMMILLARY RECESS
Roof plate (mesencephalic)
Anterior
Cingulate
Limbic cortical NEP
Fornical GEP
Hippocampal
Central
Thalamic NEP
Ventral
Reticular
Retrosplenial
Neocortical NEP
TELENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL VENTRICLE, POSTERIOR POOL)
TELEN-CEPHALON (CEREBRAL CORTEX)
Hypothalamic (mammillary) NEP
Subthalamic NEP
Raphe complex
Oculo-motor (III)?
Substantia nigra/ ventral tegmental area?
Tegmental NEP
Superior collicular
Inferior collicular
Tectal NEP
THALAMUS
SUBTHALAMUS
HYPOTHALAMUS (mammillary body)
TEGMENTUM
TECTUM
DIENCEPHALON
MESENCEPHALON
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.
Arrows indicate the regionally shrinking shoreline of the superventricle as NEP cells are depleted while generating neurons.

PLATE 34A

GW7 Horizontal
CR 16.8 mm
C492
Level 6: Section 50

Level 6: Computer-aided 3-D Brain Reconstruction

Non-neural structures labeled

Dark stain in some blood vessels is injected ink.

PLATE 34B

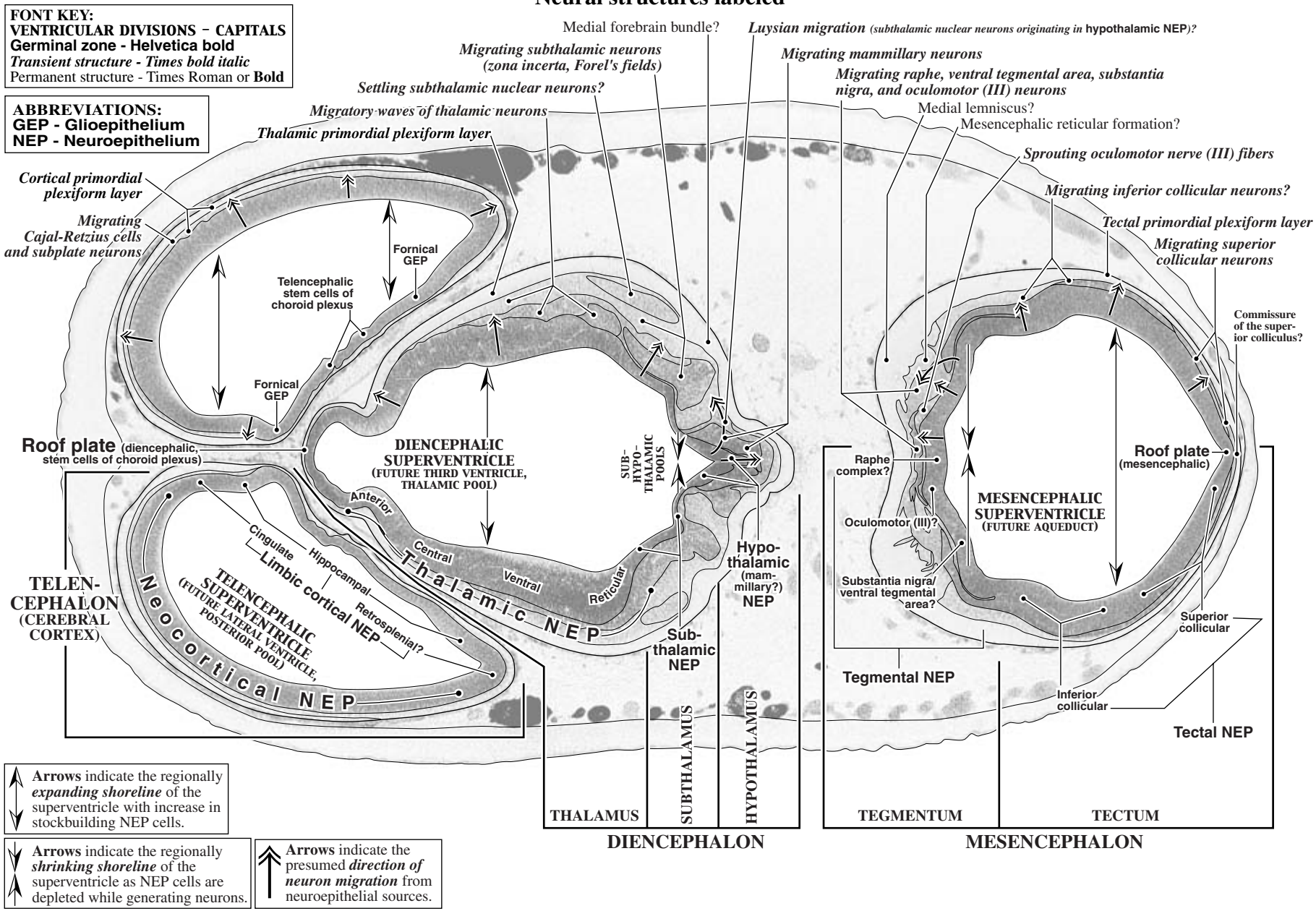
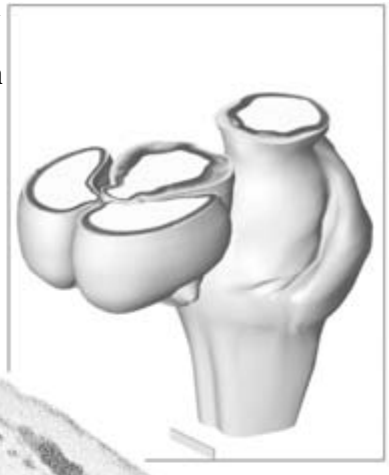

Neural structures labeled
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
Medial forebrain bundle?
Luysian migration (subthalamic nuclear neurons originating in hypothalamic NEP)?
Migrating subthalamic neurons (zona incerta, Forel's fields)
Migrating mammillary neurons
Migrating raphe, ventral tegmental area, substantia nigra, and oculomotor (III) neurons
Settling subthalamic nuclear neurons?
Migratory waves of thalamic neurons
Medial lemniscus?
Mesencephalic reticular formation?
Thalamic primordial plexiform layer
Sprouting oculomotor nerve (III) fibers
Cortical primordial plexiform layer
Migrating inferior collicular neurons?
Tectal primordial plexiform layer
Migrating Cajal-Retzius cells and subplate neurons
Migrating superior collicular neurons
Fornical GEP
Telencephalic stem cells of choroid plexus
Commissure of the superior colliculus?
Fornical GEP
Roof plate (diencephalic, stem cells of choroid plexus)
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE, THALAMIC POOL)
SUB-HYPO-THALAMIC POOLS
Raphe complex?
Roof plate (mesencephalic)
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Anterior
Oculomotor (III)?
Cingulate
Hippocampal
Central
Ventral
Reticular
Thalamic NEP
Hypothalamic (mammillary?) NEP
TELENCEPHALON (CEREBRAL CORTEX)
TELENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL VENTRICLE, POSTERIOR POOL)
Limbic cortical NEP
Retrosplenial?
Neocortical NEP
Subthalamic NEP
Substantia nigra/ ventral tegmental area?
Superior collicular
Tegmental NEP
Inferior collicular
Tectal NEP
THALAMUS
SUBTHALAMUS
HYPOTHALAMUS
TEGMENTUM
TECTUM
DIENCEPHALON
MESENCEPHALON
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.
Arrows indicate the regionally shrinking shoreline of the superventricle as NEP cells are depleted while generating neurons.
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.

PLATE 35A

GW7 Horizontal
CR 16.8 mm
C492
Level 7: Section 55

Level 7: Computer-aided 3-D Brain Reconstruction



Non-neural and peripheral neural structures labeled

Dural blood vessels

Middle cerebral artery and branches

Pia and pial blood vessels

Pia and pial blood vessels

Anterior cerebral artery and branches

Superior sagittal sinus?

Superarachnoid reticulum (brain parenchymal expansion zone)

Primordial mesenchymal brain case (skin/bone)

Future dura (internal border of brain case)

Circle of Willis arteries?

Nerve III (oculomotor)

1 mm

Dark stain in some blood vessels is injected ink.

PLATE 35B

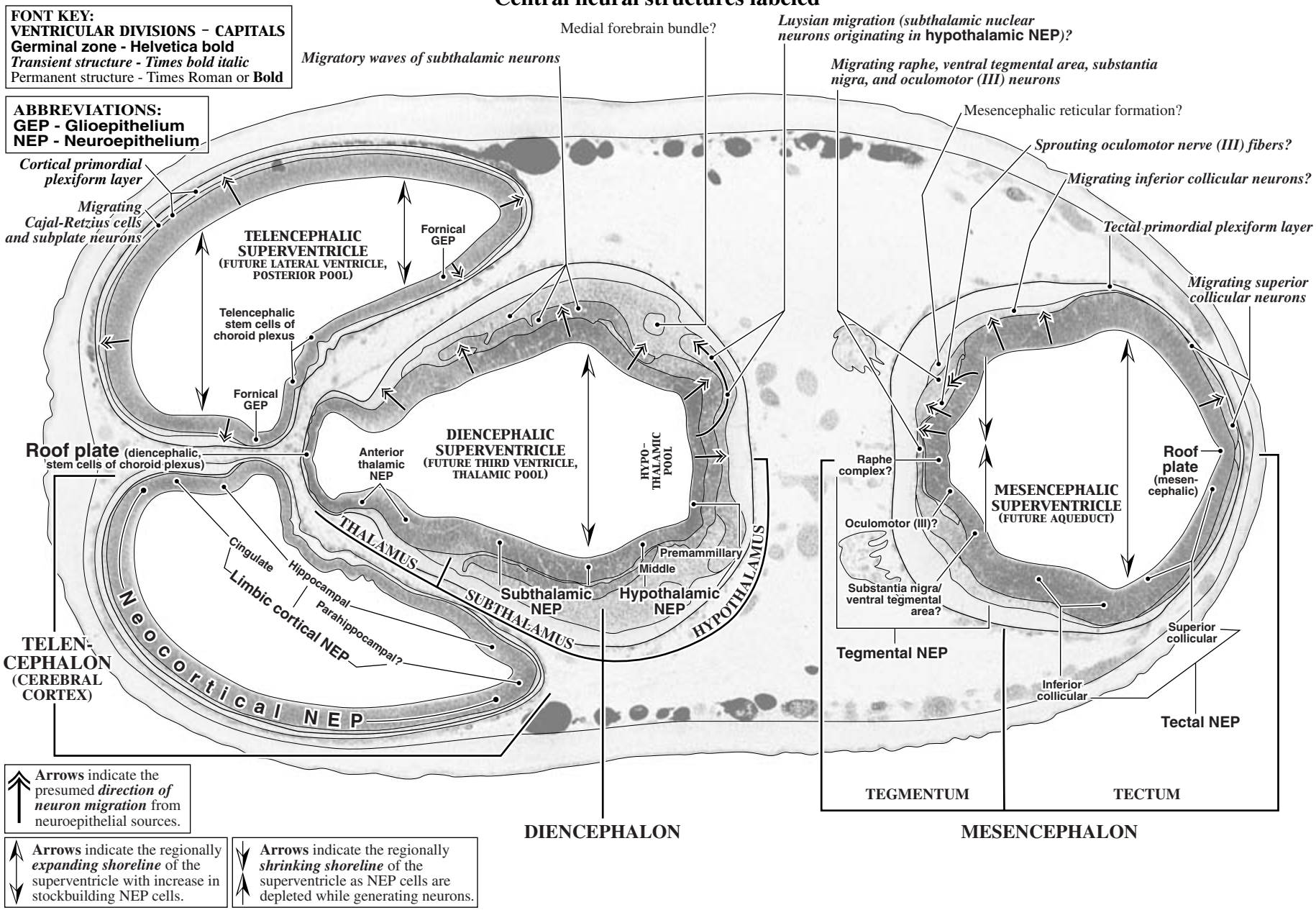

Central neural structures labeled
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
Medial forebrain bundle?
Luysian migration (subthalamic nuclear neurons originating in hypothalamic NEP)?
Migratory waves of subthalamic neurons
Migrating raphe, ventral tegmental area, substantia nigra, and oculomotor (III) neurons
Mesencephalic reticular formation?
Sprouting oculomotor nerve (III) fibers?
Migrating inferior collicular neurons?
Tectal primordial plexiform layer
Migrating superior collicular neurons
Cortical primordial plexiform layer
Migrating Cajal-Retzius cells and subplate neurons
TELENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL VENTRICLE, POSTERIOR POOL)
Fornical GEP
Telencephalic stem cells of choroid plexus
Fornical GEP
Roof plate (diencephalic, stem cells of choroid plexus)
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE, THALAMIC POOL)
Anterior thalamic NEP
HYPO-THALAMIC POOL
THALAMUS
SUBTHALAMUS
HYPOTHALAMUS
Cingulate
Hippocampal
Parahippocampal?
Limbic cortical NEP
Neocortical NEP
Subthalamic NEP
Premammillary
Middle
Hypothalamic NEP
TELEN-CEPHALON (CEREBRAL CORTEX)
Raphe complex?
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Roof plate (mesen-cephalic)
Oculomotor (III)?
Substantia nigra/ ventral tegmental area?
Tegmental NEP
Superior collicular
Inferior collicular
Tectal NEP
TEGMENTUM
TECTUM
DIENCEPHALON
MESENCEPHALON
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.
Arrows indicate the regionally shrinking shoreline of the superventricle as NEP cells are depleted while generating neurons.

PLATE 36A

GW7 Horizontal
CR 16.8 mm
C492, Level 8: Section 65

Level 8: Computer-aided 3-D Brain Reconstruction

Non-neural and peripheral neural structures labeled

Middle cerebral artery
Dural blood vessels
Pia and pial blood vessels
Posterior cerebral artery
Branches of anterior cerebral artery
Superior sagittal sinus?
Superarachnoid reticulum (brain parenchymal expansion zone)
Vascular bed of choroid plexus
Cerebellar artery?
Primordial mesenchymal brain case (skin/bone)
Nerve III (oculomotor)
Circle of Willis arteries?
Future dura (internal border of brain case)
1 mm

Dark stain in some blood vessels is injected ink.

PLATE 36B

Central neural structures labeled

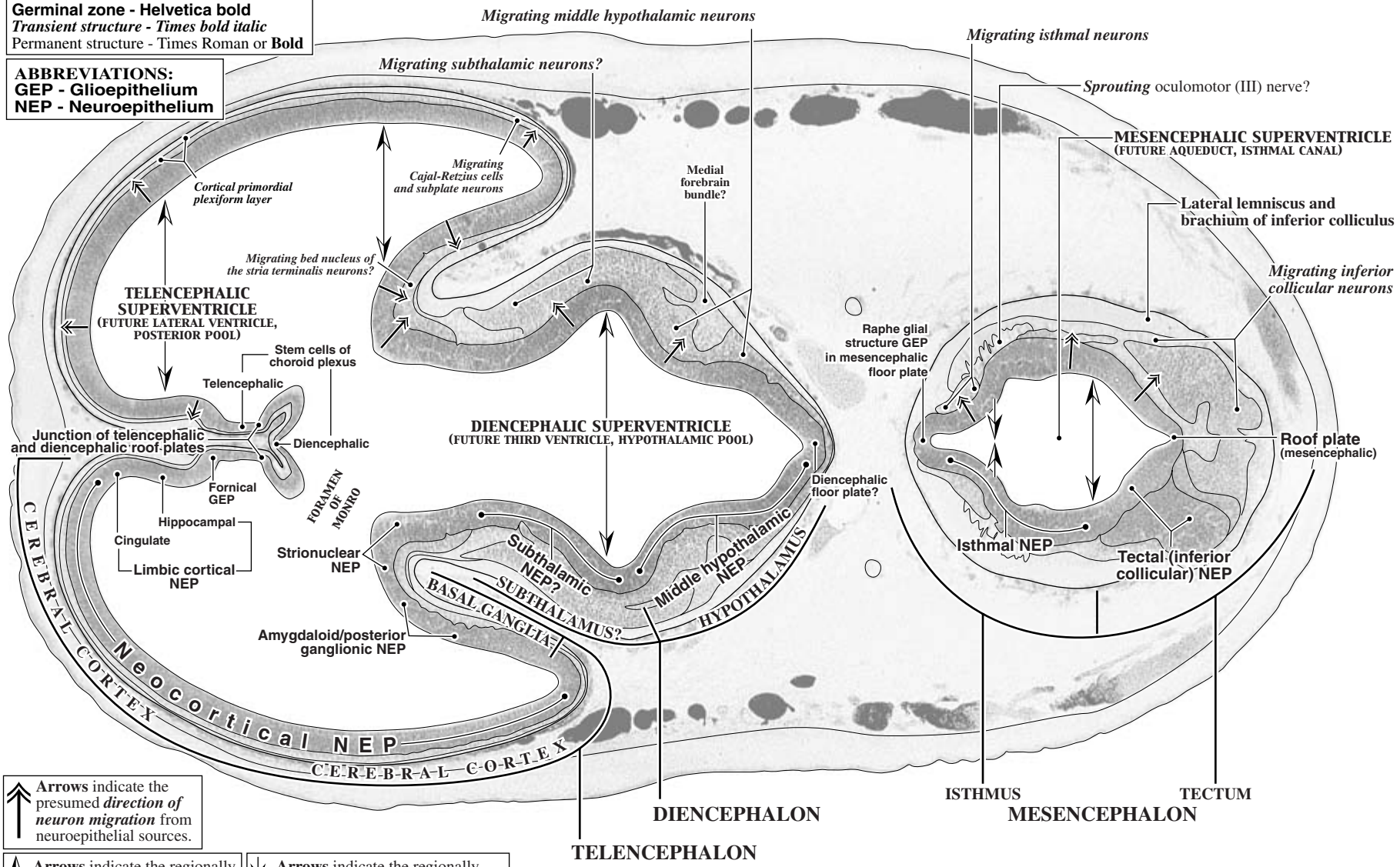
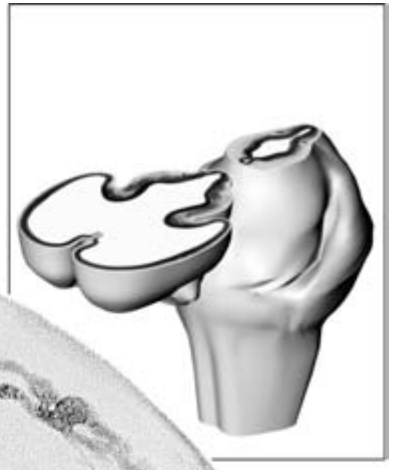


PLATE 37A

GW7 Horizontal
CR 16.8 mm
C492, Level 9: Section 71

Level 9: Computer-aided 3-D Brain Reconstruction



Non-neural and peripheral neural structures labeled

Pia and pial blood vessels
Middle cerebral artery
Dural blood vessels
Superior sagittal sinus?
Superarachnoid reticulum (brain parenchymal expansion zone)
Cerebellar artery?
Vascular bed of choroid plexus
Basilar artery?
1 mm
Primordial mesenchymal brain case (skin/bone)
Nerve III (oculomotor)
Circle of Willis arteries?
Future dura (internal border of brain case)

Dark stain in some blood vessels is injected ink.

PLATE 37B

Central neural structures labeled

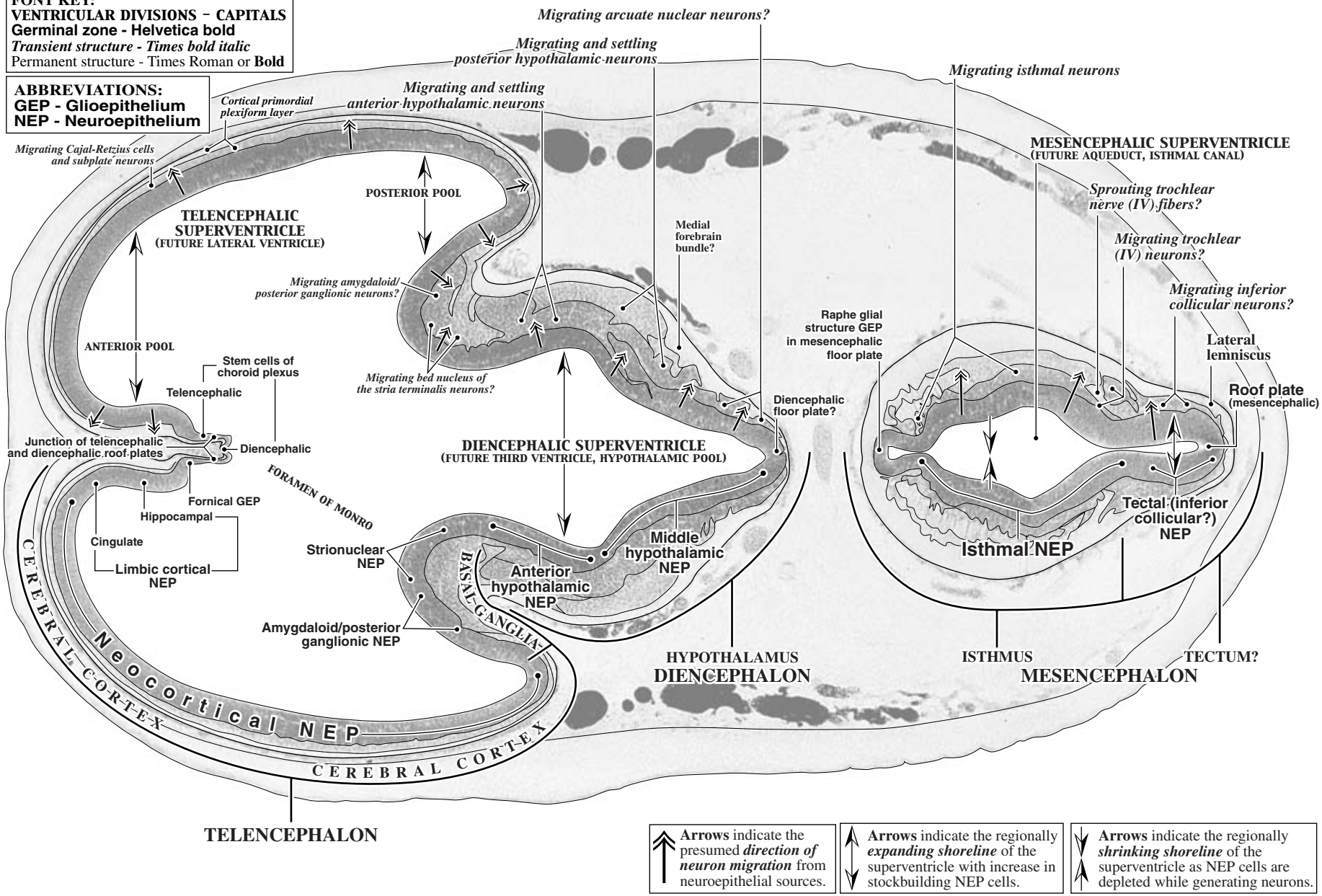
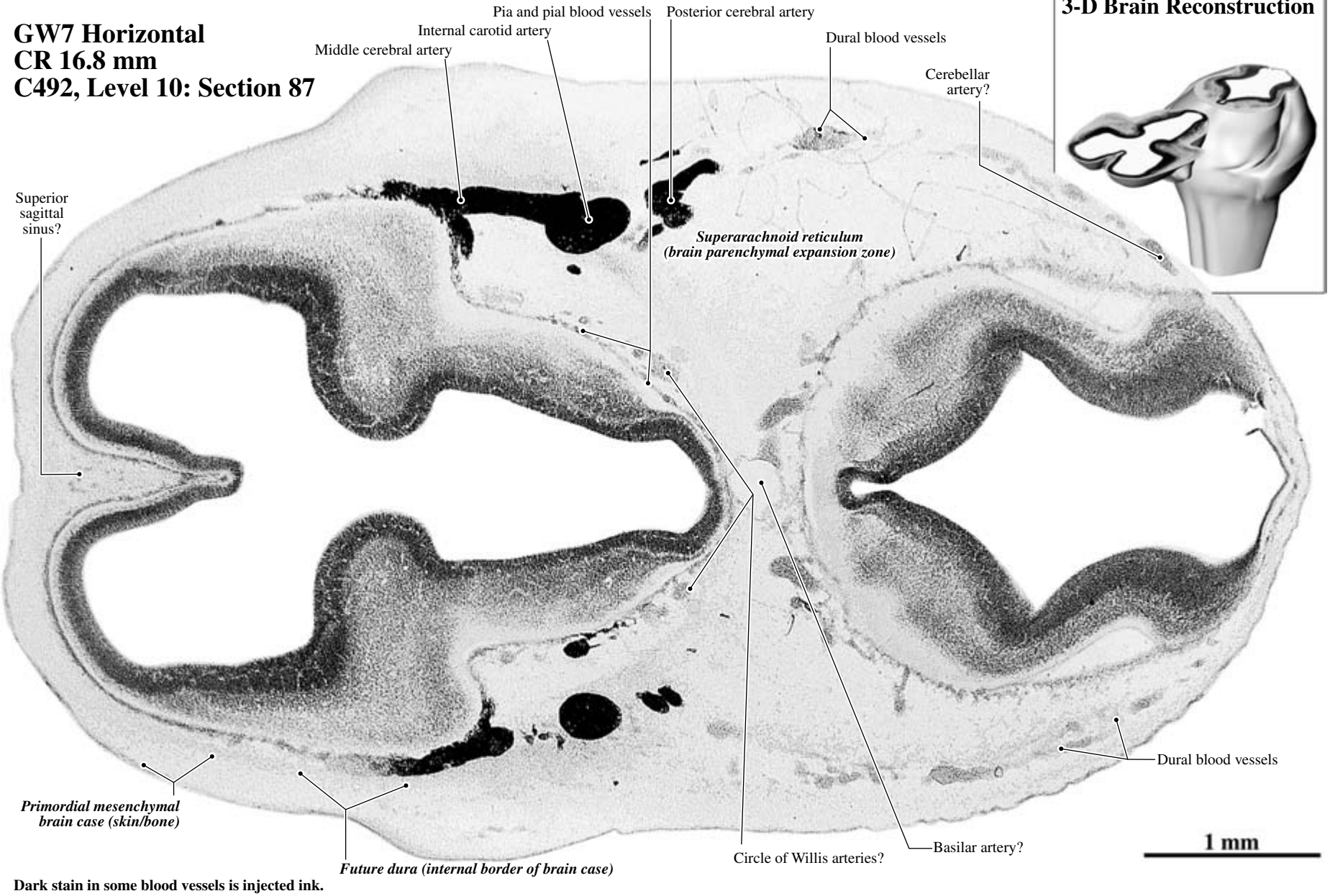


PLATE 38A

GW7 Horizontal
CR 16.8 mm
C492, Level 10: Section 87

Non-neural structures labeled



Level 10: Computer-aided 3-D Brain Reconstruction

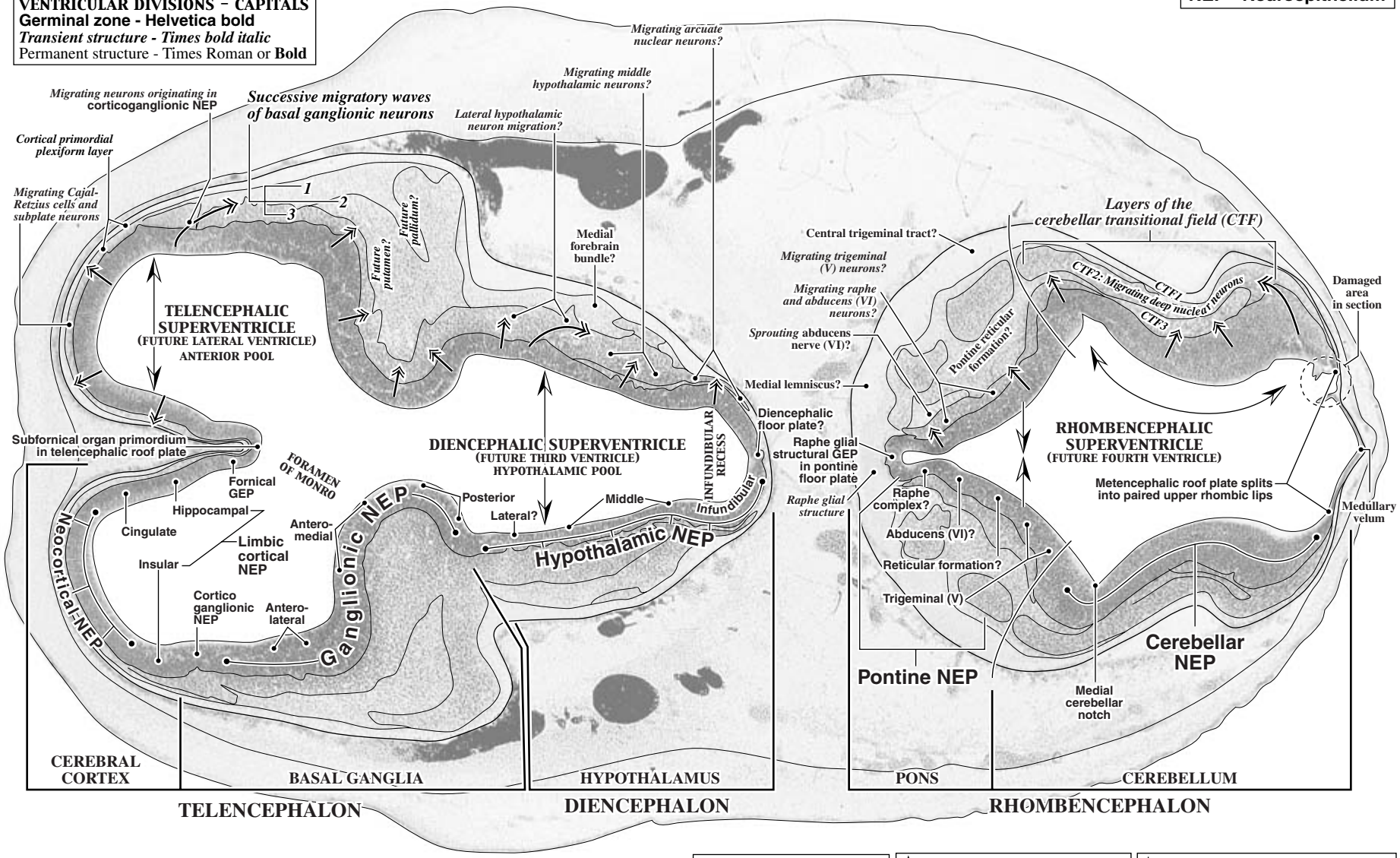
Dark stain in some blood vessels is injected ink.

PLATE 38B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Neural structures labeled

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

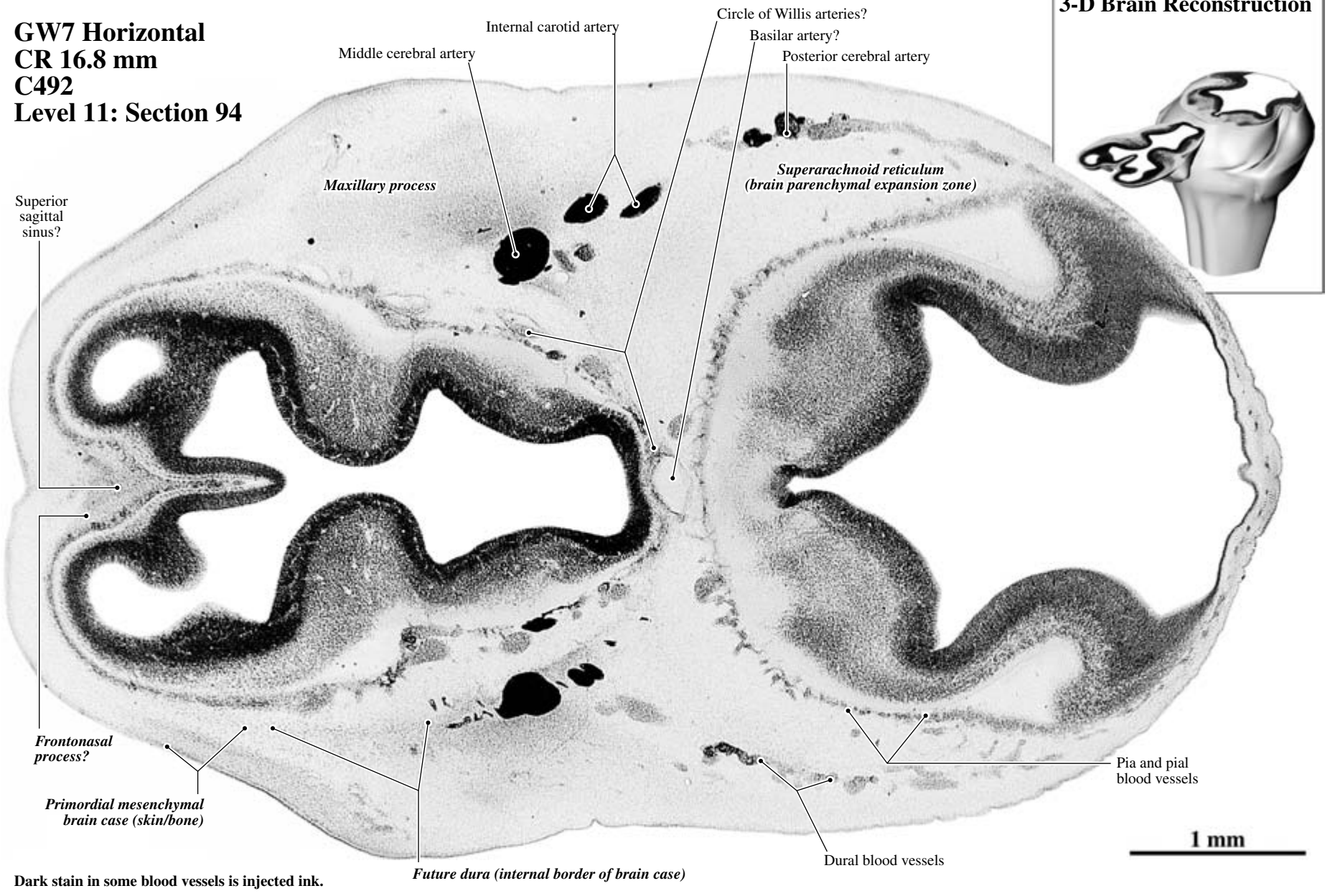
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 39A

GW7 Horizontal
CR 16.8 mm
C492
Level 11: Section 94

Non-neural structures labeled



Level 11: Computer-aided 3-D Brain Reconstruction

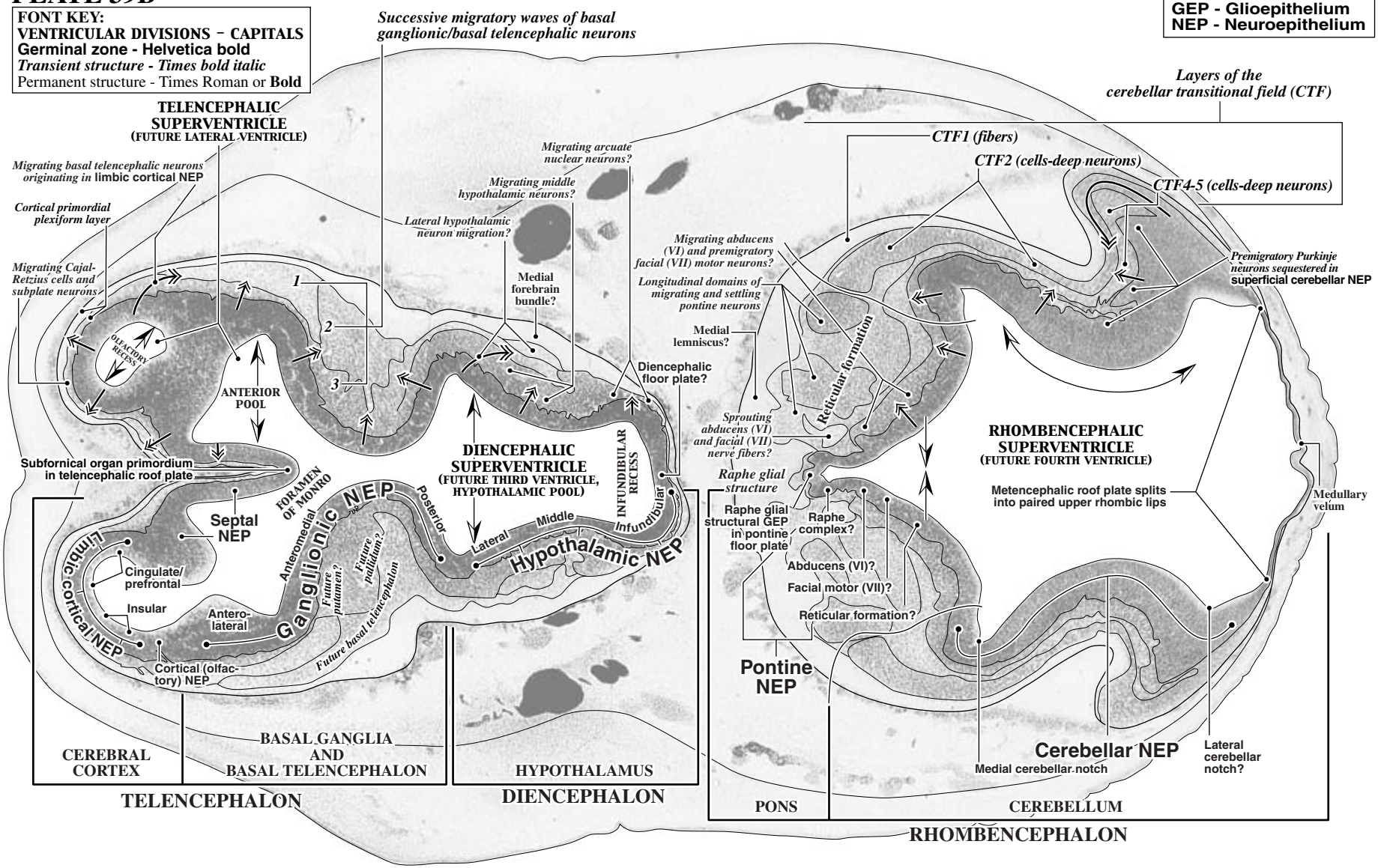
Dark stain in some blood vessels is injected ink.

PLATE 39B

Neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

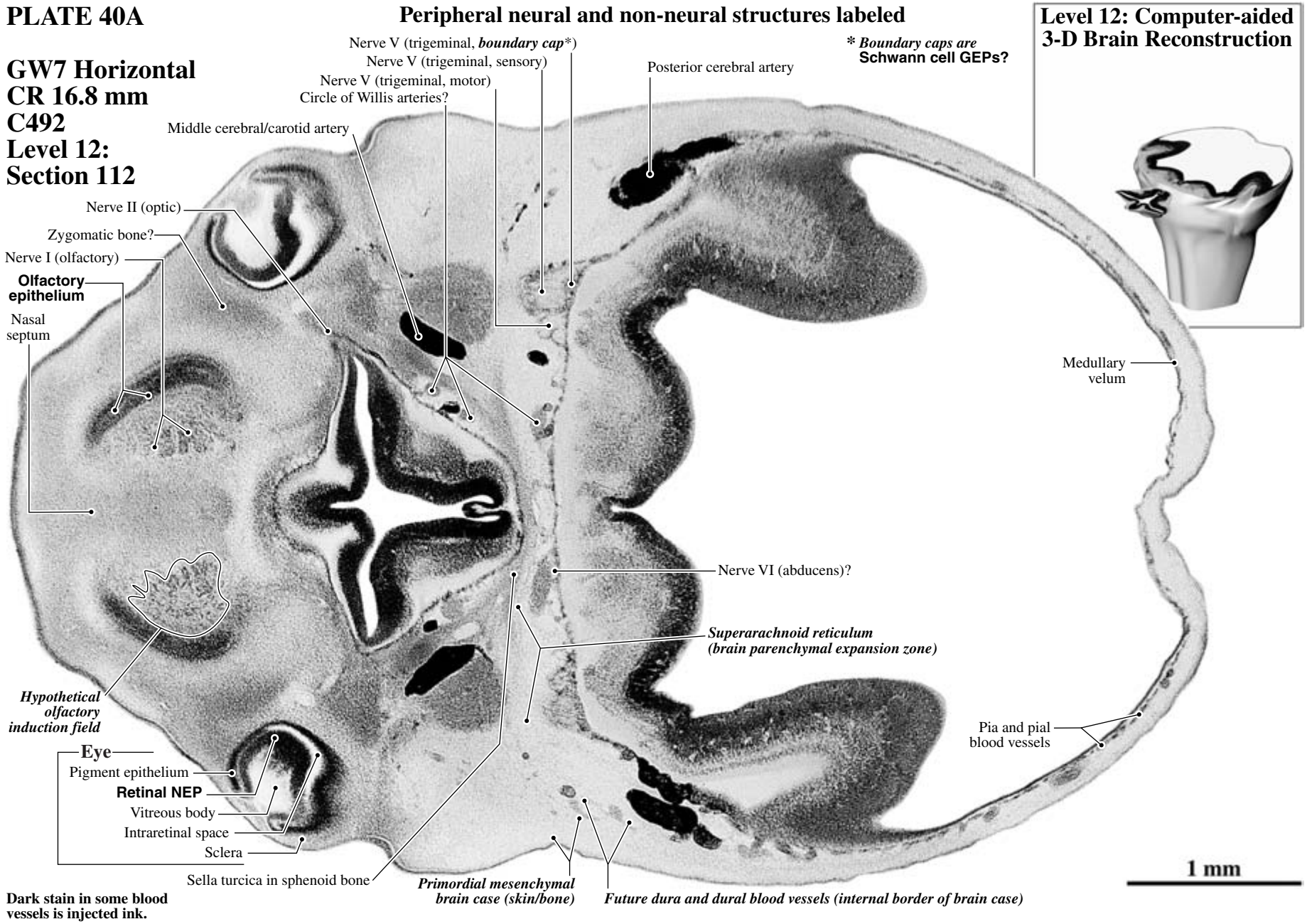
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 40A

GW7 Horizontal
CR 16.8 mm
C492
Level 12:
Section 112

Peripheral neural and non-neural structures labeled



* *Boundary caps are* **Schwann cell GEPs?**

Level 12: Computer-aided 3-D Brain Reconstruction

Dark stain in some blood vessels is injected ink.

PLATE 40B

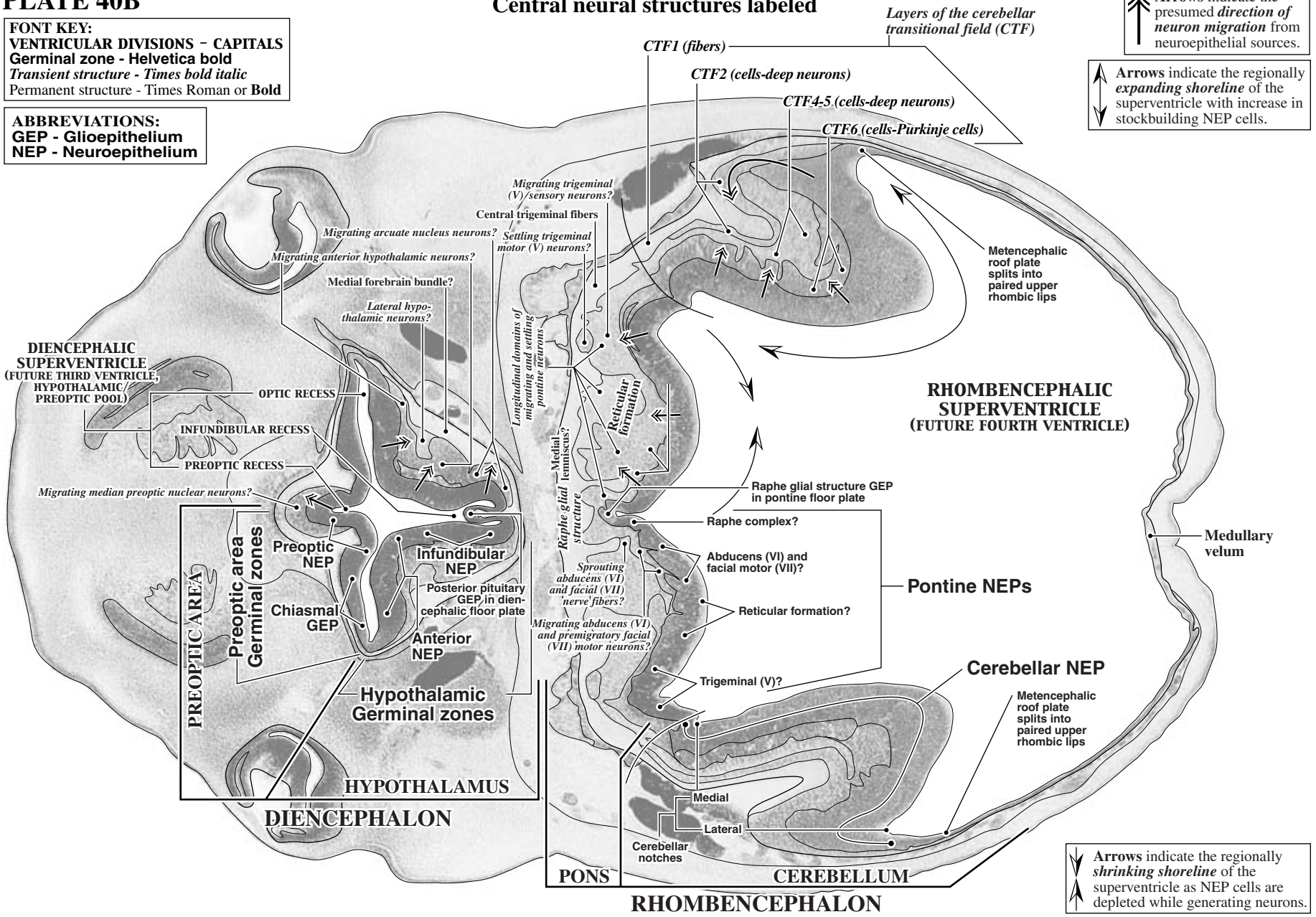
Central neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

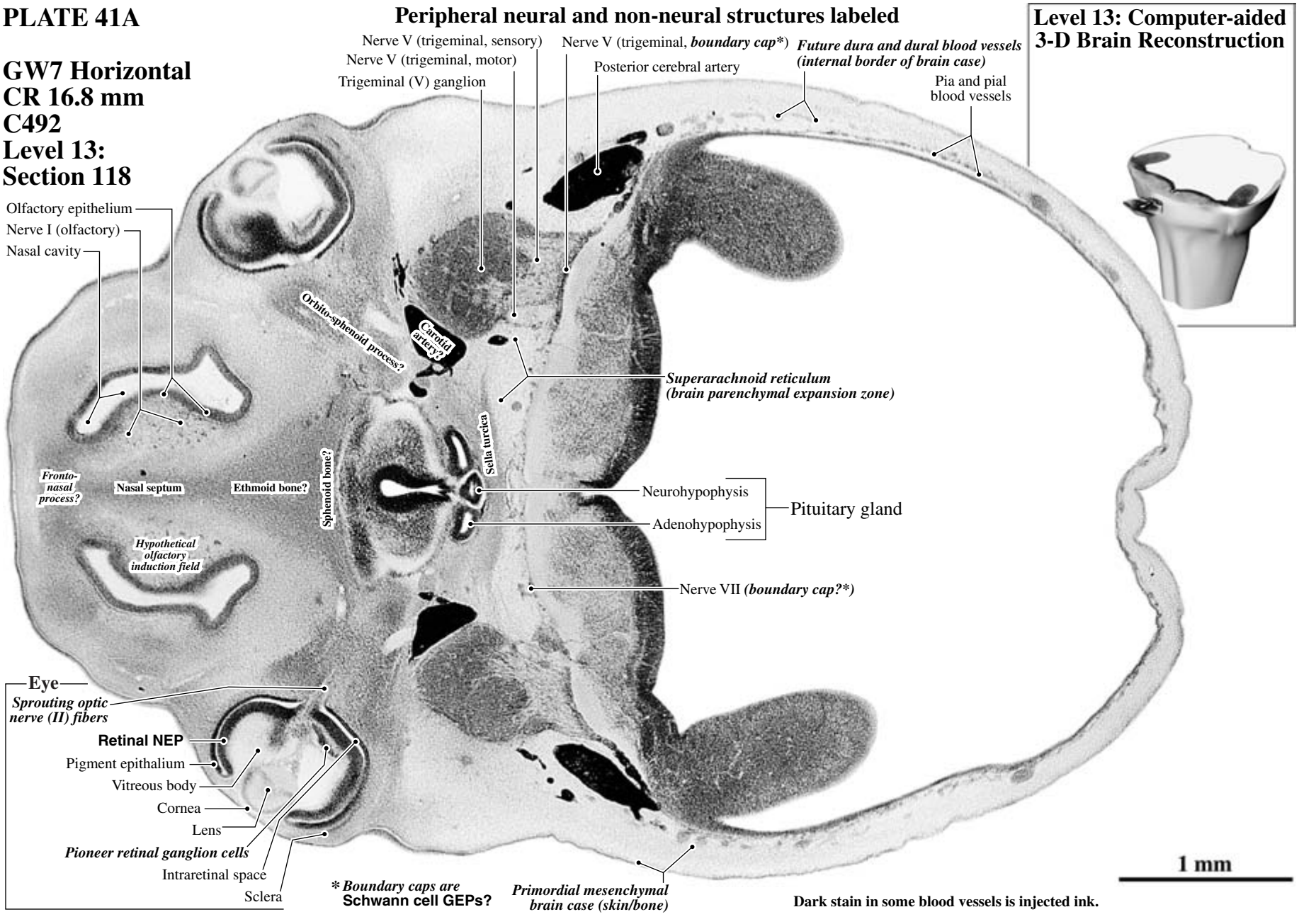


Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 41A

GW7 Horizontal
CR 16.8 mm
C492
Level 13:
Section 118

Peripheral neural and non-neural structures labeled



Level 13: Computer-aided 3-D Brain Reconstruction

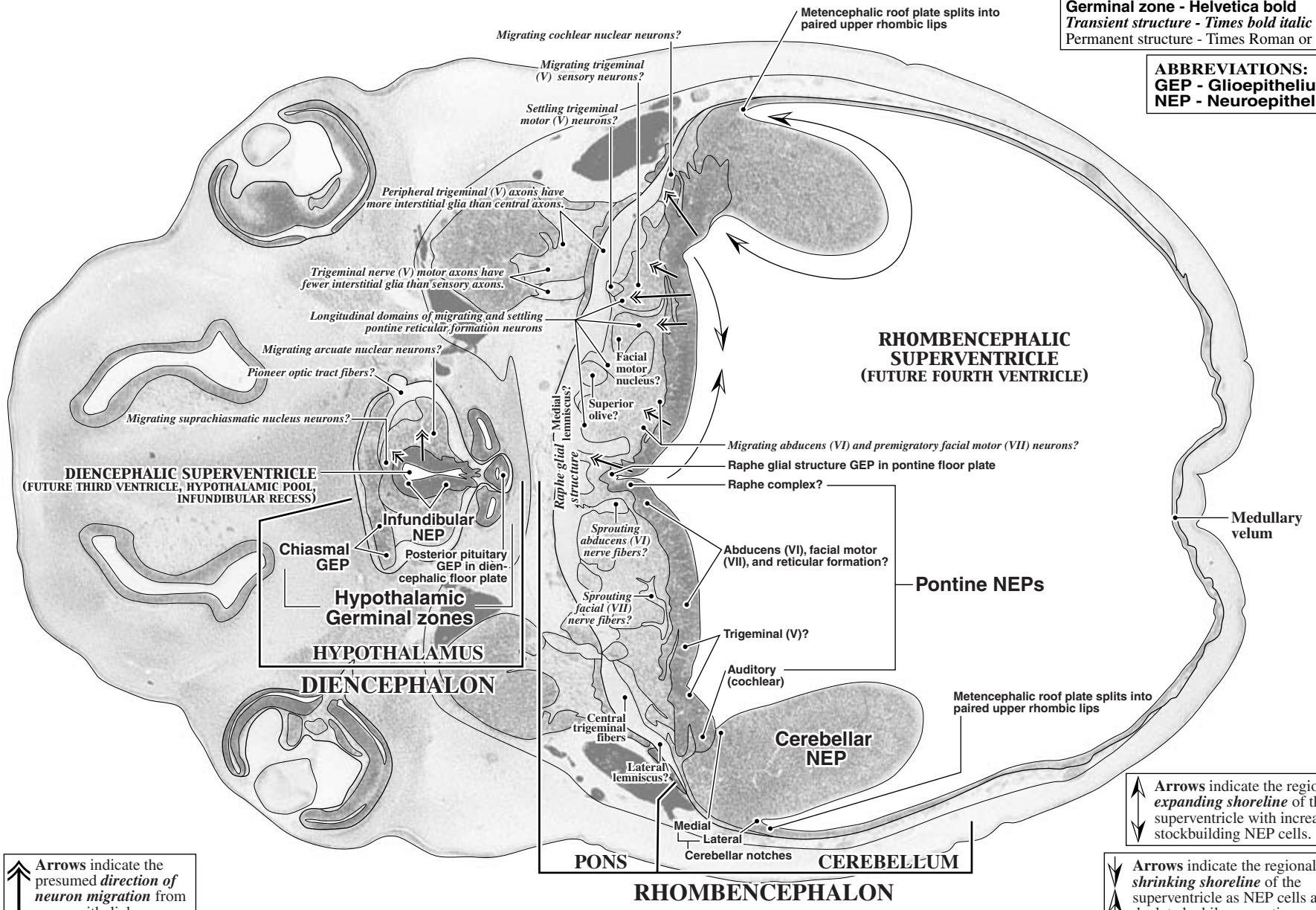
Dark stain in some blood vessels is injected ink.

PLATE 41B

Central neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

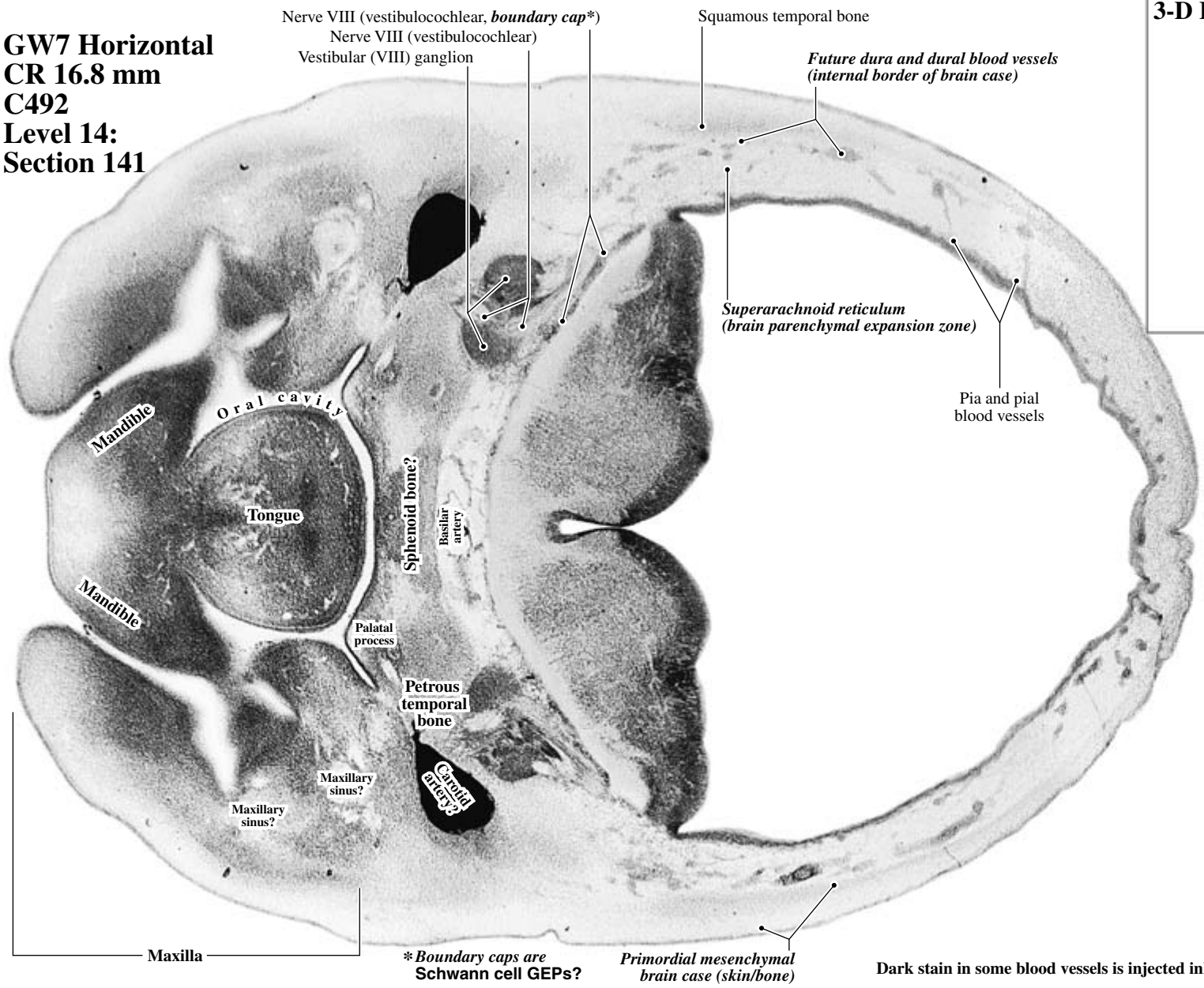
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 42A

GW7 Horizontal
CR 16.8 mm
C492
Level 14:
Section 141

Peripheral neural and non-neural structures labeled



Level 14: Computer-aided 3-D Brain Reconstruction

1 mm

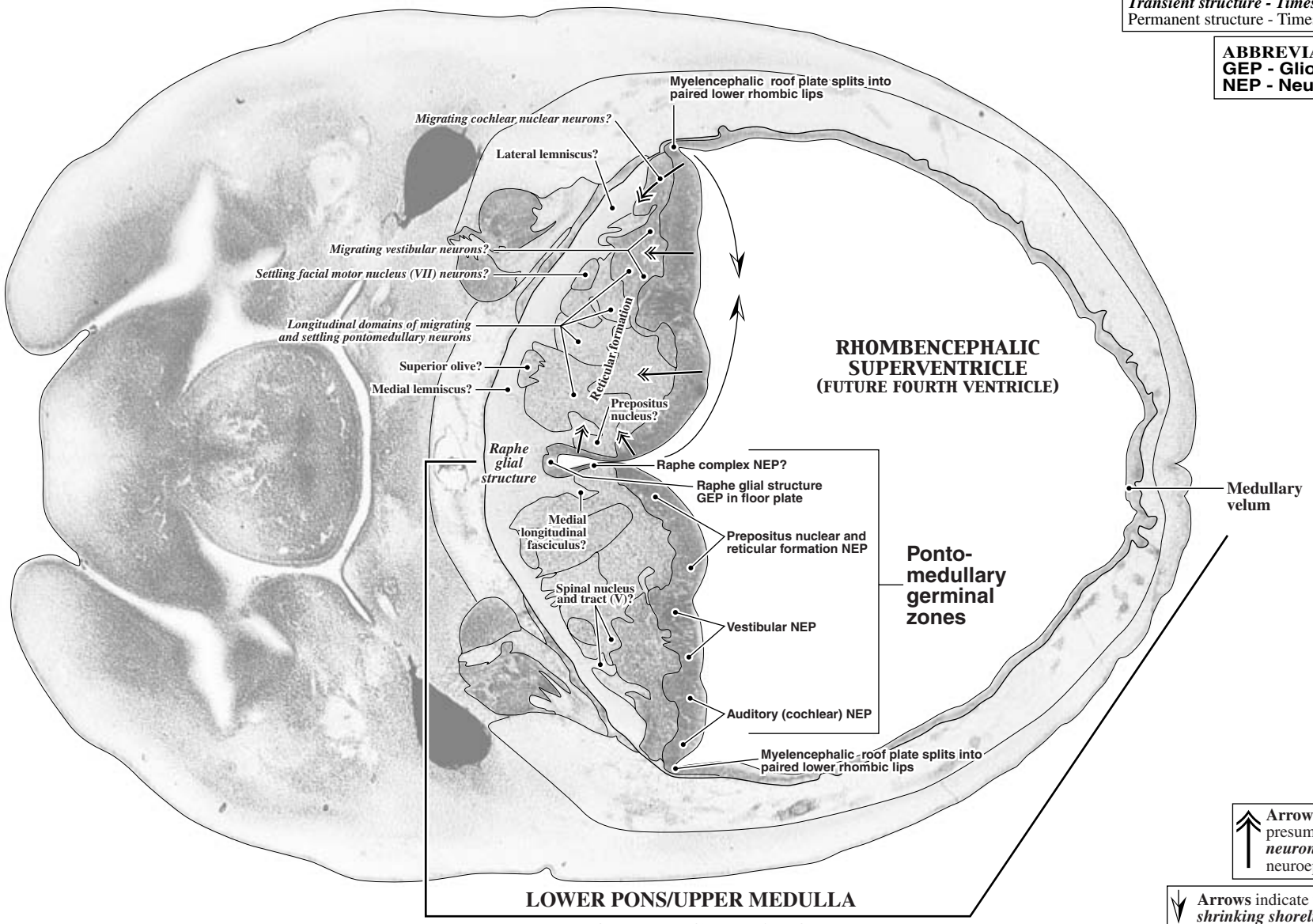
Dark stain in some blood vessels is injected ink.

PLATE 42B

Central neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



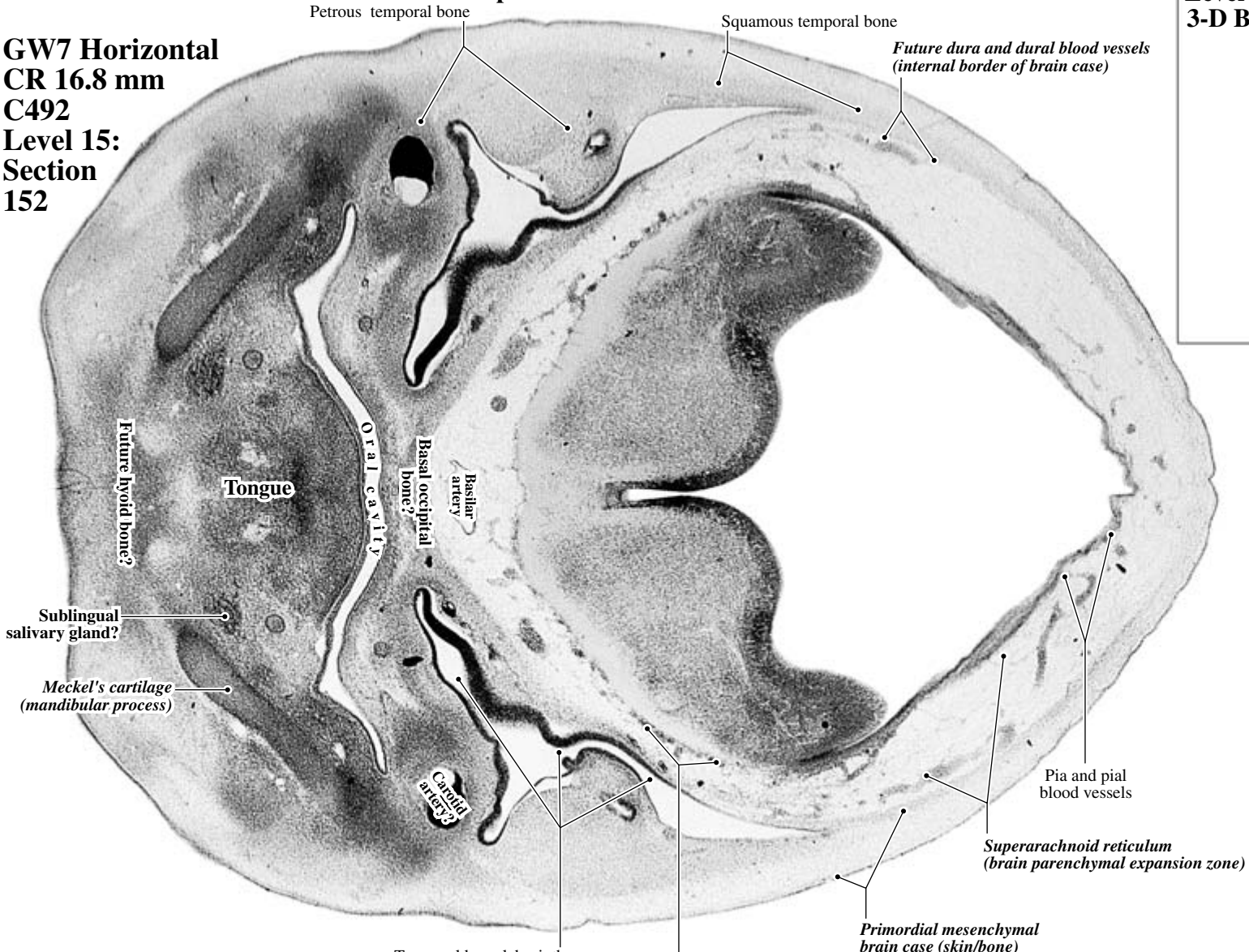
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 43A

GW7 Horizontal
CR 16.8 mm
C492
Level 15:
Section
152

Peripheral neural and non-neural structures labeled



Level 15: Computer-aided 3-D Brain Reconstruction

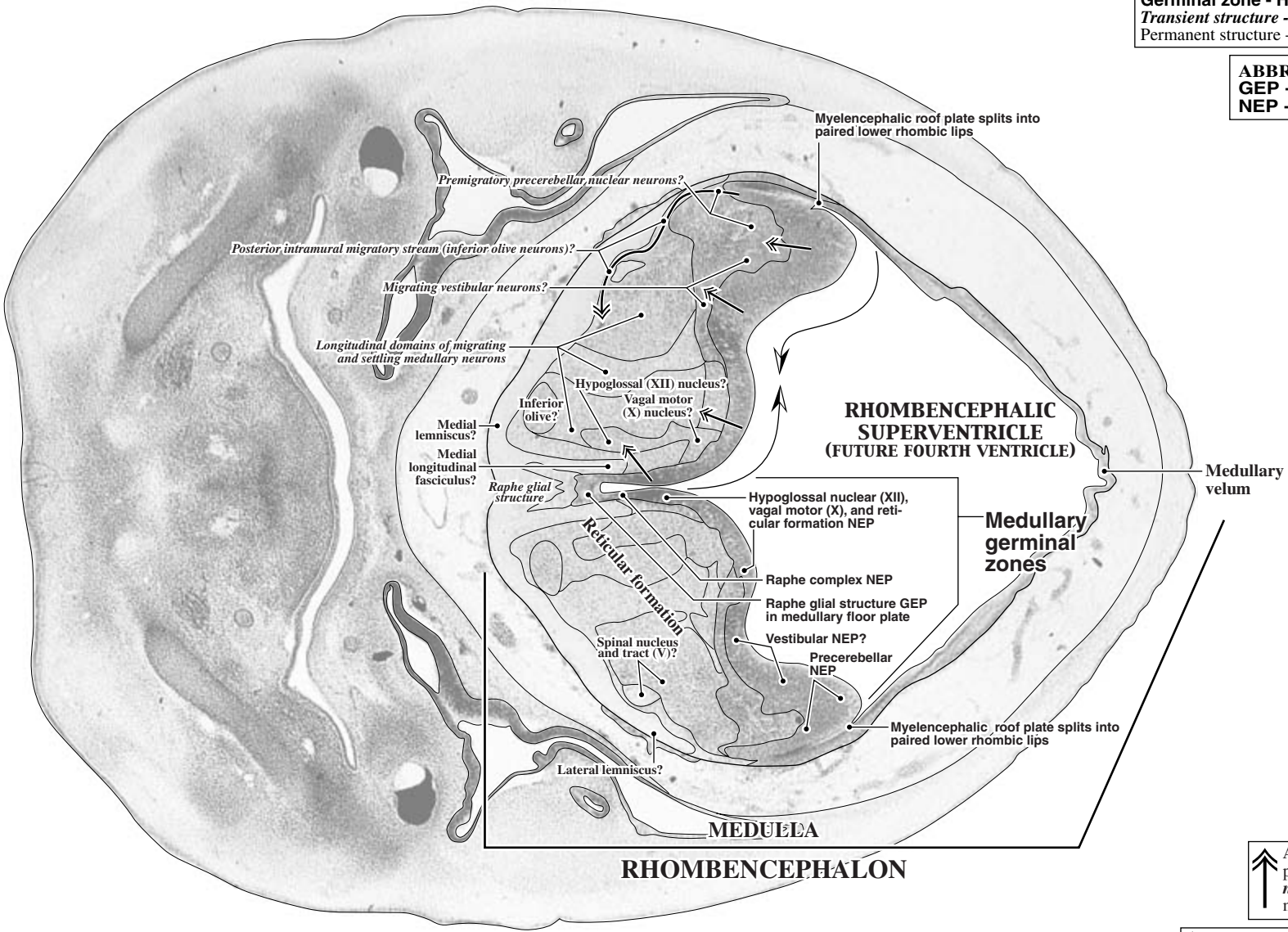
Dark stain in some blood vessels is injected ink.

PLATE 43B

Central neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

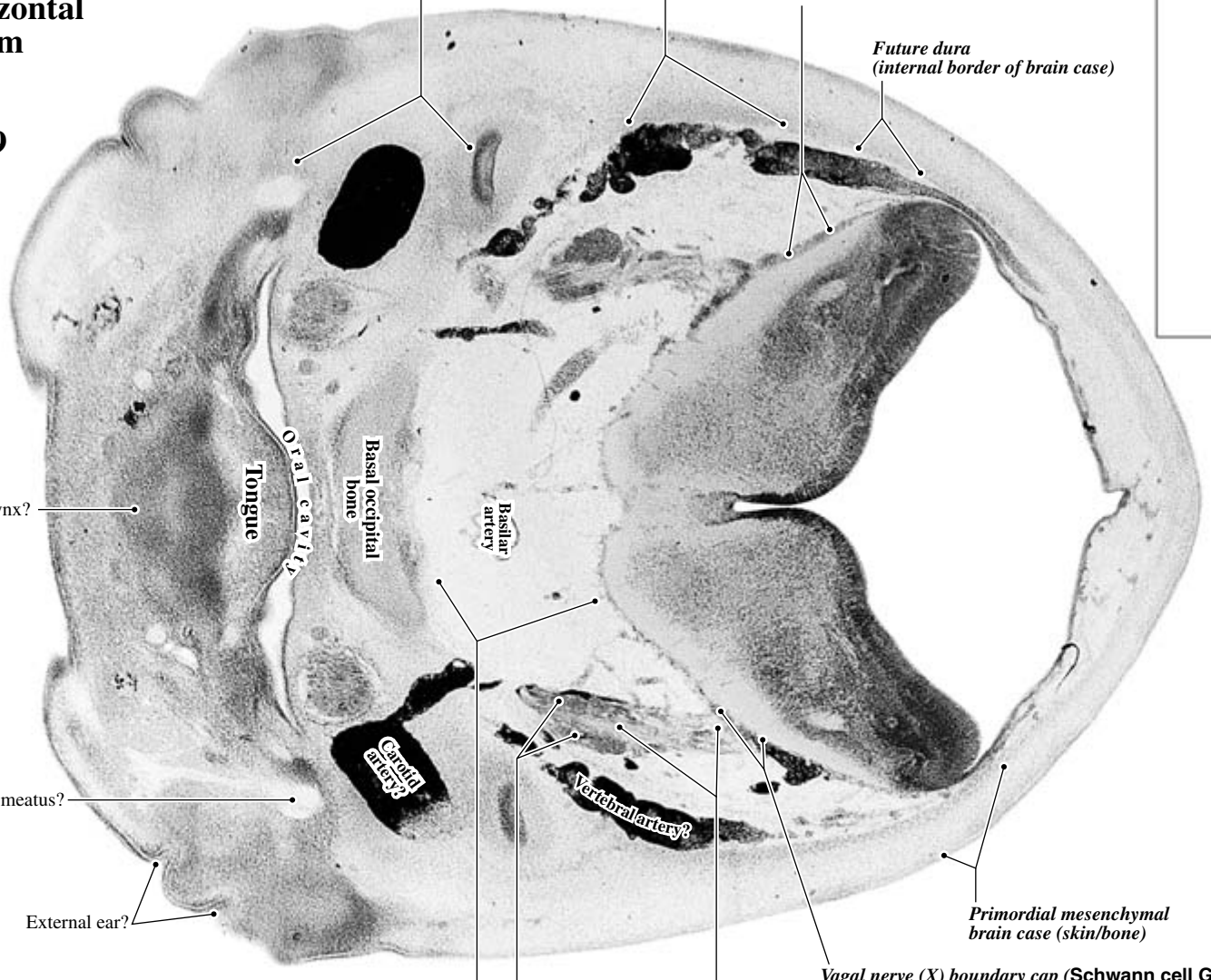
Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 44A

GW7 Horizontal
CR 16.8 mm
C492
Level 16:
Section 169

Peripheral neural and non-neural structures labeled

Level 16: Computer-aided 3-D Brain Reconstruction



1 mm

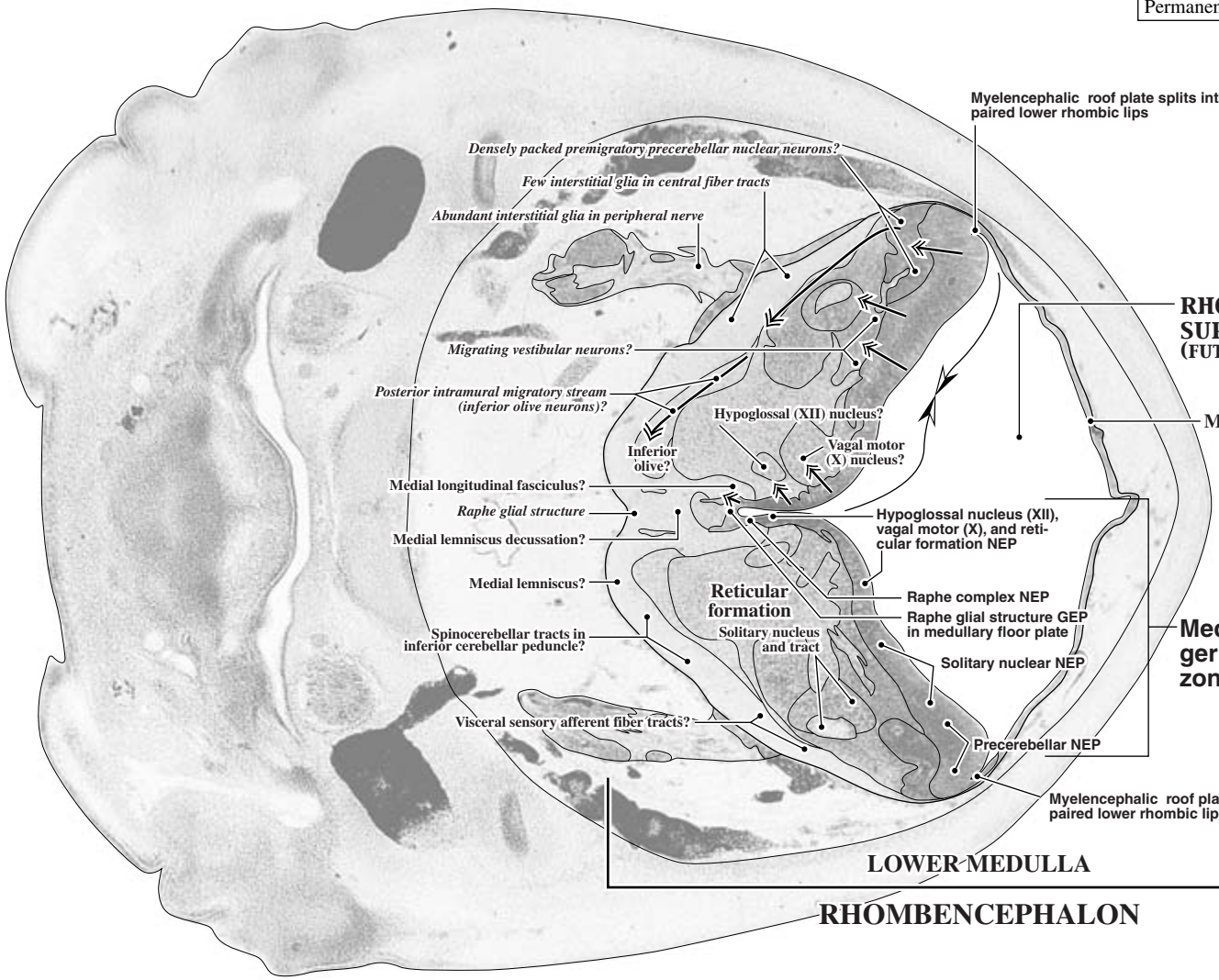
Dark stain in some blood vessels is injected ink.

PLATE 44B

Central neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



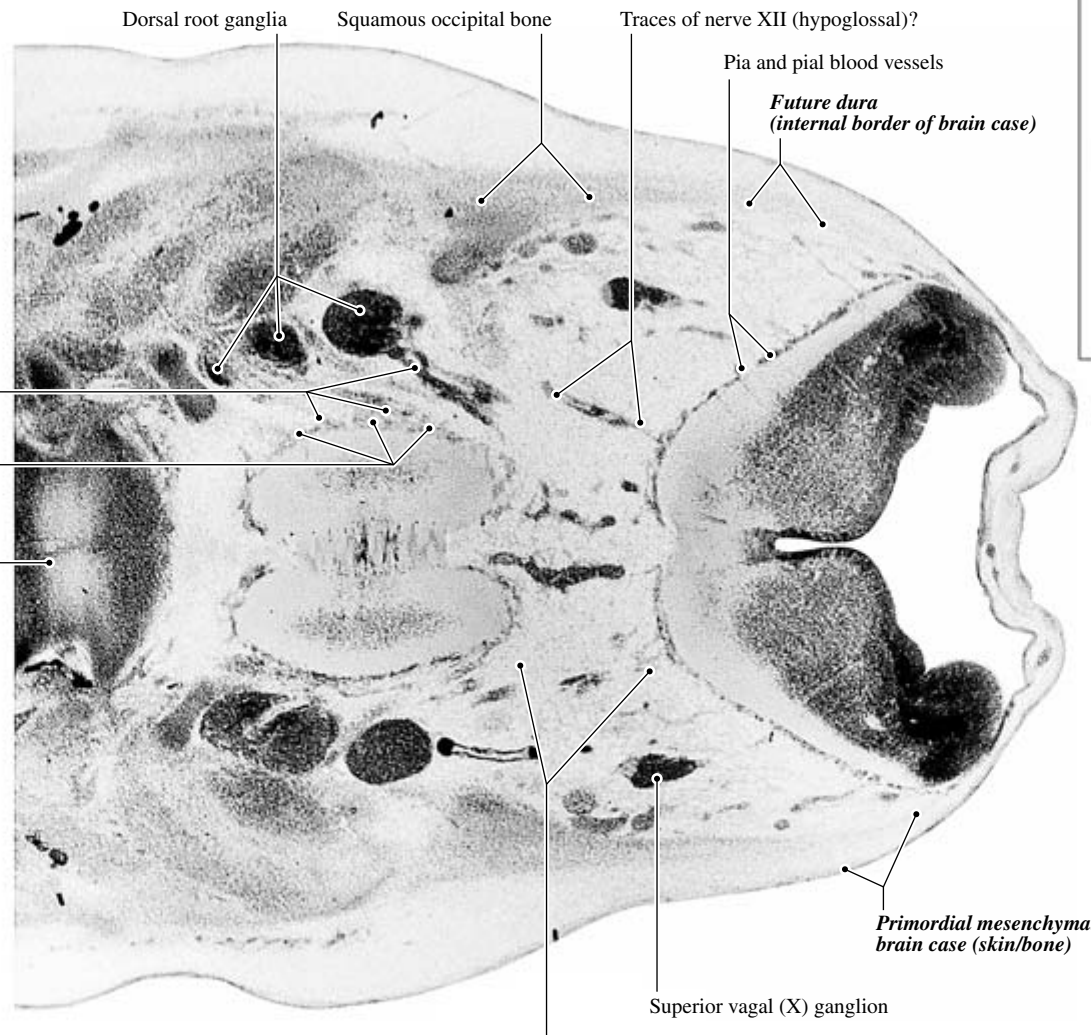
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 45A

GW7 Horizontal
CR 16.8 mm
C492
Level 17: Section 205

Peripheral neural and non-neural structures labeled



Level 17: Computer-aided 3-D Brain Reconstruction

1 mm

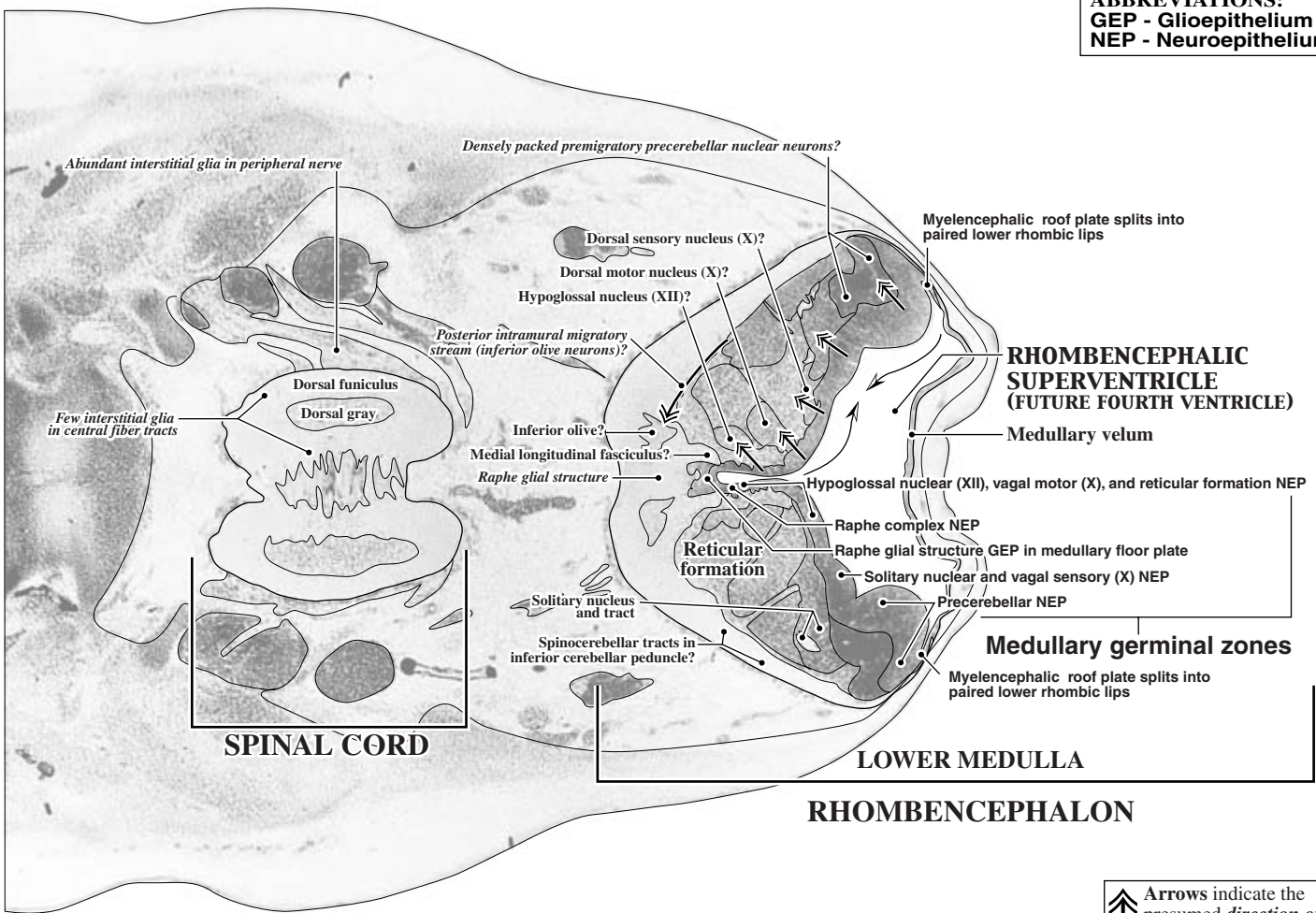
Dark stain in some blood vessels is injected ink.

PLATE 45B

Central neural structures labeled

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PART V: GW6.5 CORONAL

This specimen is embryo #2051 in the Minot Collection, designated here as M2051. The crown-rump length (CR) is 15 mm estimated to be at gestational week (GW) 6.5. Most of M2051's brain sections are cut (10 μm) in the coronal plane, but the plane shifts to predominantly horizontal in the posterior medulla. We photographed 87 sections at low magnification from the frontal prominence to the posterior tips of the mesencephalon and medulla. Seventeen of these sections are illustrated in **Plates 46AB to 62AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of M2051's brain (**Figure 4**), and to show each illustrated section *in situ* (*insets,* **Plates 46A to 62A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 63AB** show a high-magnification view of the neocortical neuroepithelium.

All parts of the telencephalic neuroepithelium are rapidly increasing their pool of neuronal and glial stem cells as they expand the shorelines of the enlarging telencephalic superventricle. Only very few pioneer Cajal-Retzius neurons have migrated into the cell-sparse primordial plexiform layer adjacent to the cerebral cortical neuroepithelium. The rest of the cortical neuronal population has yet to be generated. The basal ganglionic and basal telencephalic neuroepithelia, although increasing their stock of stem cells, do have adjacent migrating neurons. There are many fewer neurons in these areas than in the GW7 specimens (**Parts II, III,** and **IV**). As in the GW7 specimens, these neurons appear to migrate together in early (outermost and less dense) to late (innermost and most dense) waves.

The diencephalic neuroepithelium surrounds a narrowing superventricle. It is thinnest in the hypothalamic and subthalamic areas, where it is surrounded by densely-packed waves of migrating neurons. It is postulated that these areas of the superventricle have shrinking shorelines as the neuroepithelia "unload" their stock of neuronal precursors. In contrast, the superventricle shoreline is still expanding as the thalamic neuroepithelium continues to add more neuronal precursors than to unload postmitotic neurons. There are only a few neurons migrating outside the thalamic neuroepithelium.

The mesencephalon contains a stockbuilding neuroepithelium in the pretectum and tectum (relatively few adjacent migrating neurons). On the other hand, the tegmental and isthmal neuroepithelia are thinner. Migrating neurons are leaving in large numbers and accumulate in clumps so dense that the superficial border of the neuroepithelium is indistinct. Some cells lie farther out in the tegmental and isthmal parenchyma and are more sparsely scattered adjacent to the subpial fiber band.

Both the pons and medulla have neuroepithelia that are thicker than at GW7, but are nevertheless shrinking as they unloaded their neuronal and glial progeny into an expanding parenchyma. Cells are migrating and settling in longitudinal arrays at the pontine flexure. A few cells are settling in the faintly discernable superior olivary complex and many are settling in the reticular formation throughout the pons and medulla. Some facial motor neurons are migrating from medial to lateral, leaving behind their axons in a small, but definite genu of the facial nerve. Migrating inferior olive neurons are in the posterior intramural migratory stream outside the precerebellar neuroepithelium in the posterior lower rhombic lip, but very few neurons have settled in the inferior olive. Many neurons have settled in the solitary nucleus, surrounding a definite solitary tract.

The cerebellar neuroepithelium is in the stockbuilding phase, mainly adding precursors of Purkinje cells and some late-generated deep nuclear neurons. Many deep nuclear neurons are migrating in the cellular layers of the cerebellar transitional field, but these and the fibrous layers are thinner and less definite than at GW7.

M2051 Computer-aided 3-D Brain Reconstructions

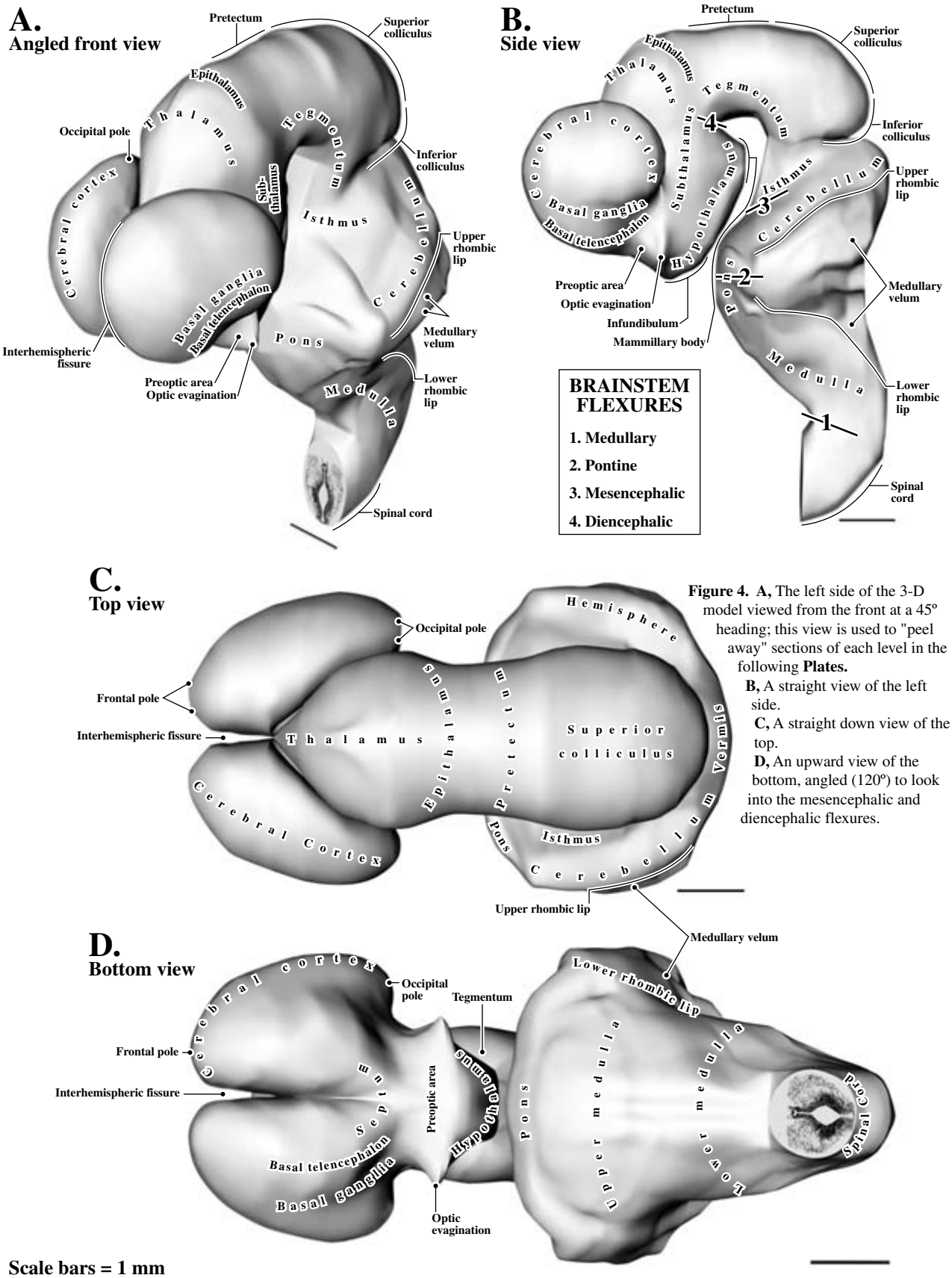


Figure 4. **A,** The left side of the 3-D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.**

B, A straight view of the left side.

C, A straight down view of the top.

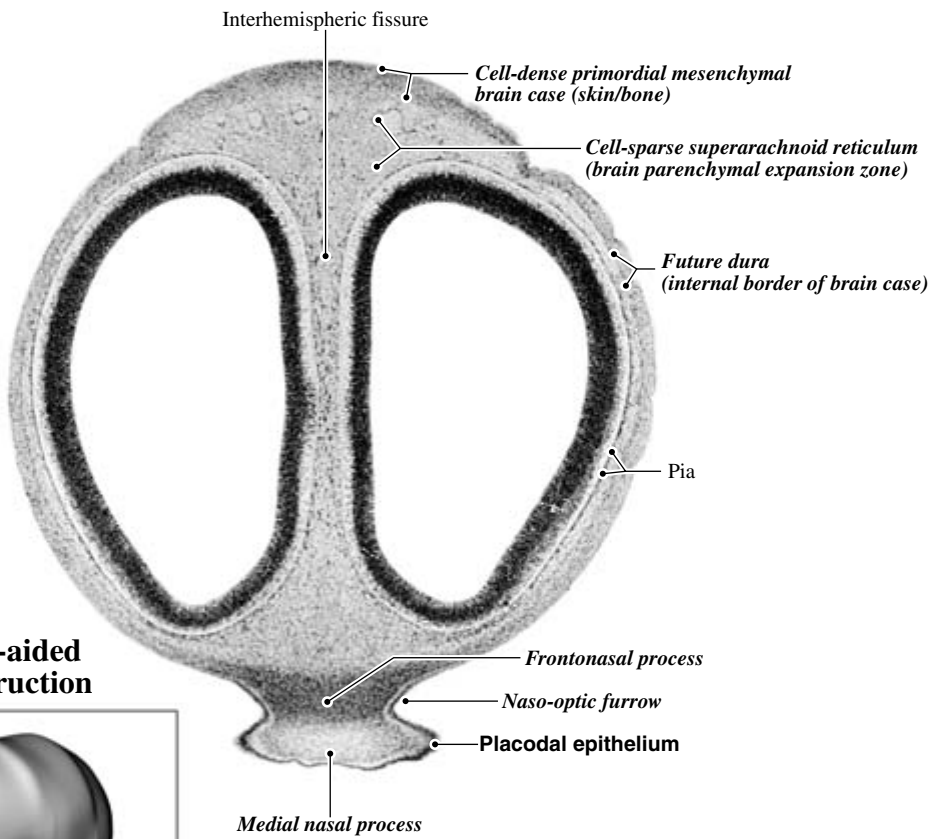
D, An upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures.

Scale bars = 1 mm

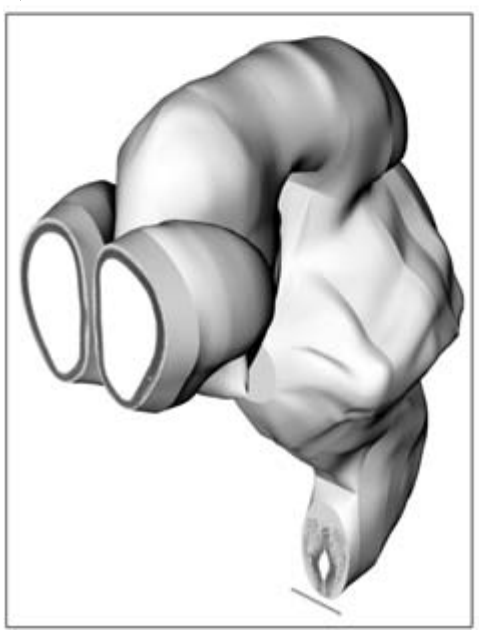
PLATE 46A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 1: Section 66

Non-neural structures labeled



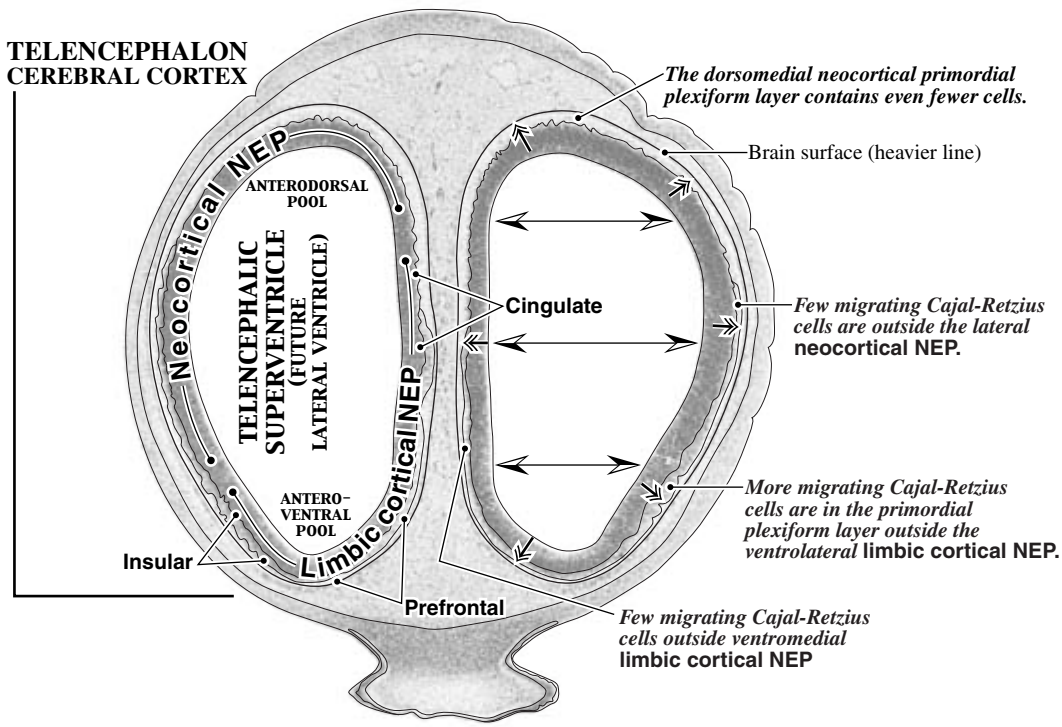
Level 1: Computer-aided 3-D Brain Reconstruction



1 mm

PLATE 46B

Neural structures labeled



The density of migrating cells in the primordial plexiform layer indicates ventrolateral-to-dorsomedial and ventrolateral-to-ventromedial maturation gradients in the cerebral cortex.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - Neuroepithelium

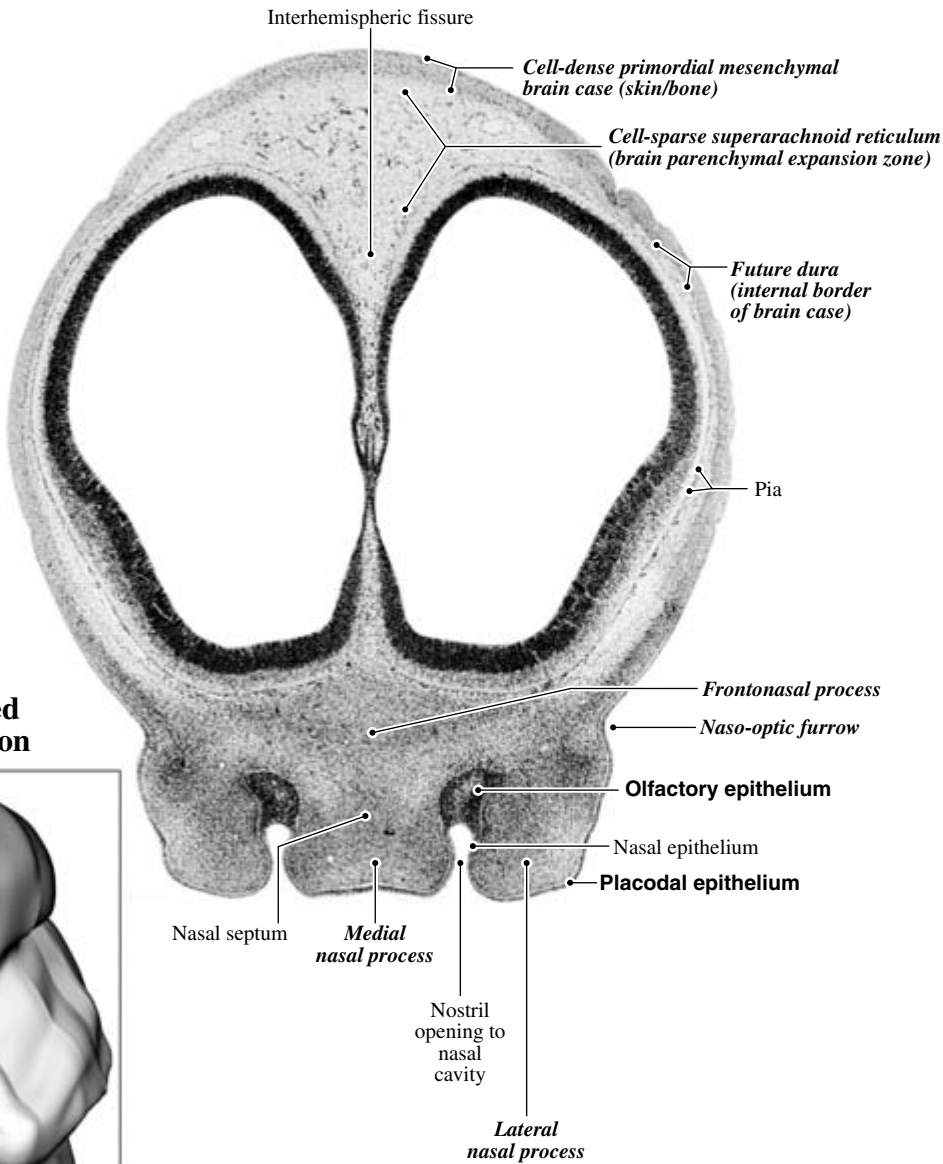
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 47A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 2: Section 107

Non-neural and peripheral neural structures labeled



Level 2: Computer-aided 3-D Brain Reconstruction

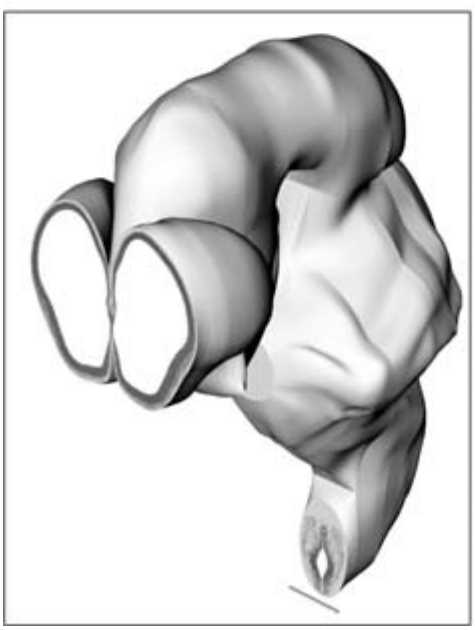
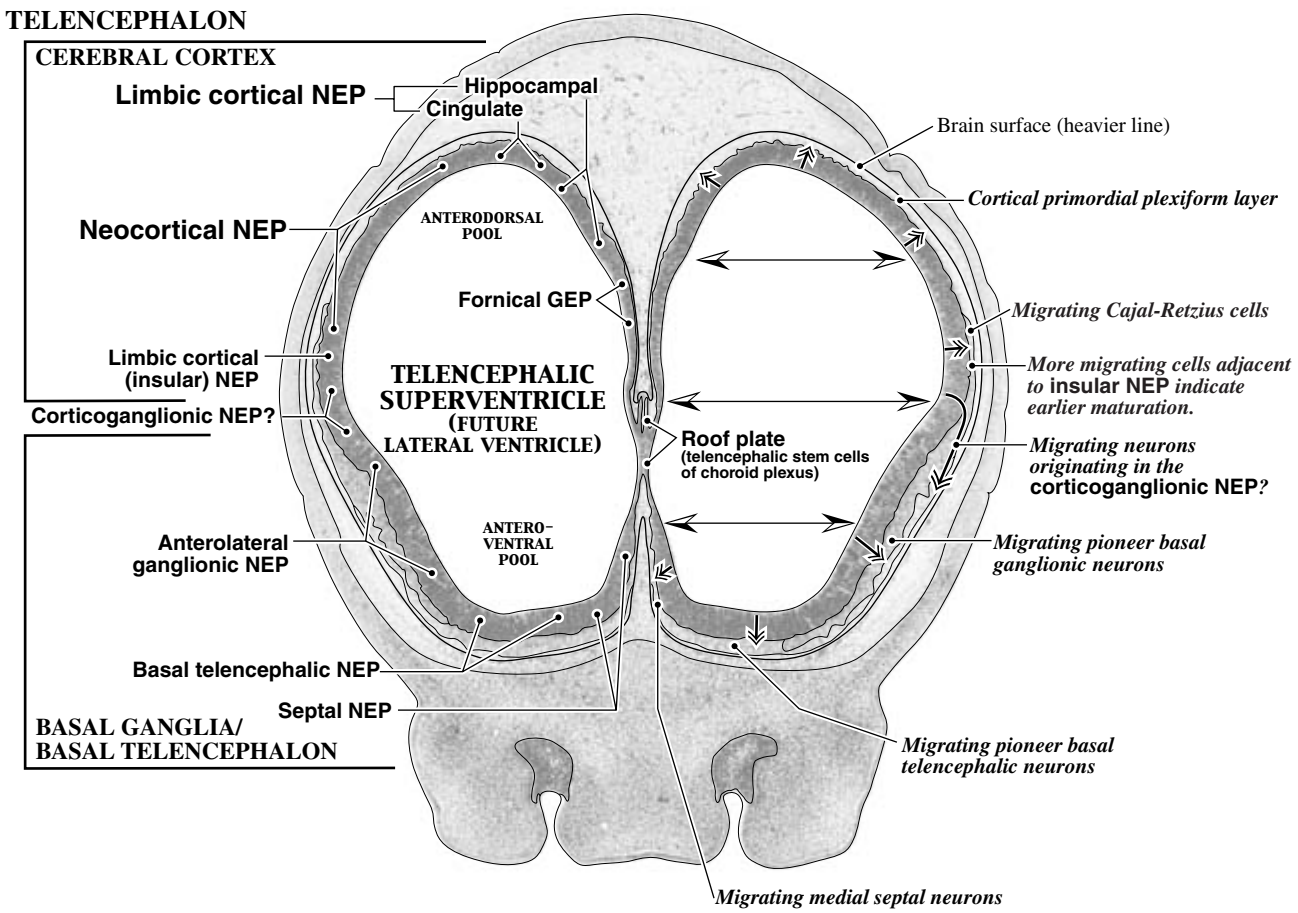


PLATE 47B

Central neural structures labeled



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

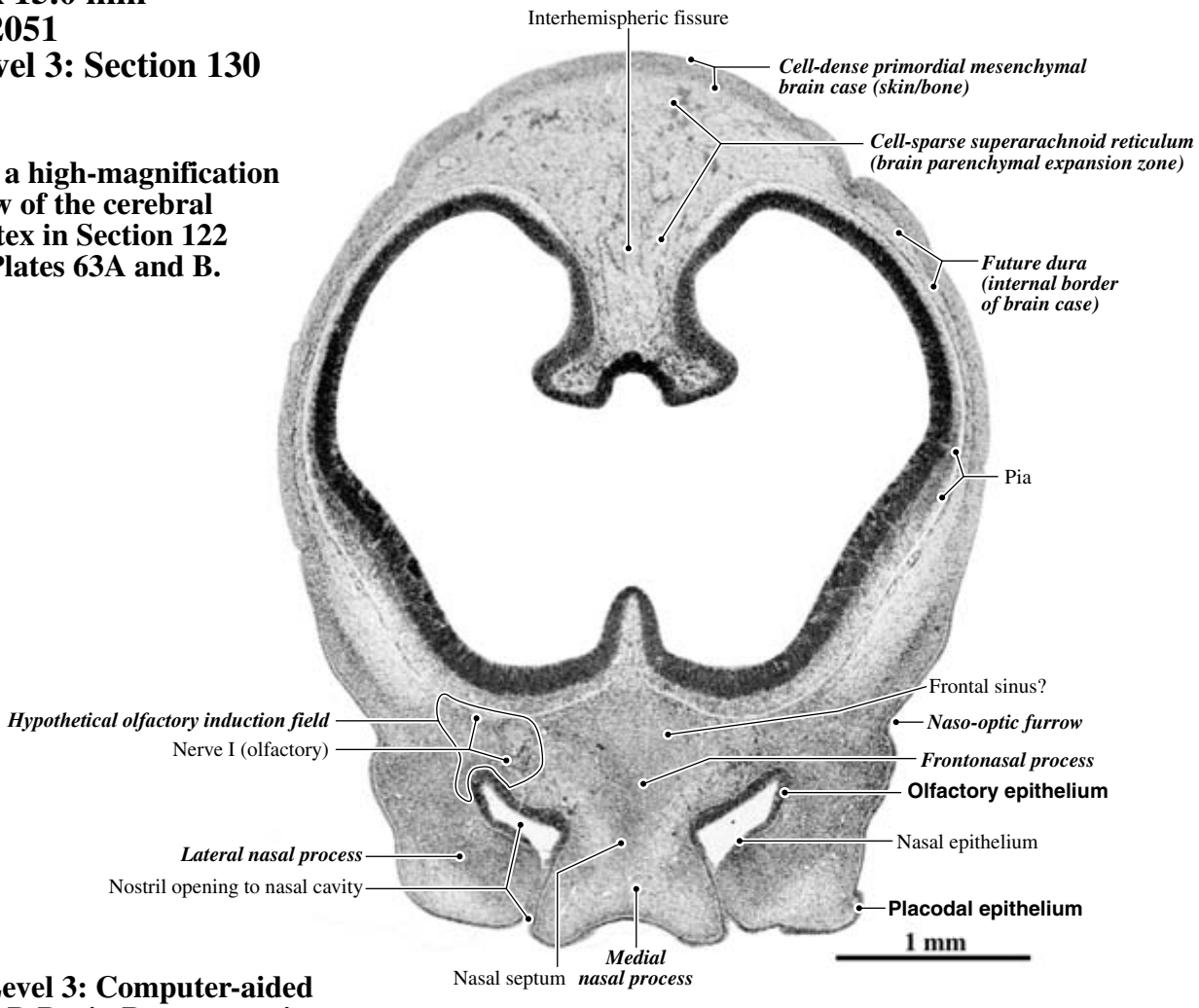
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 48A

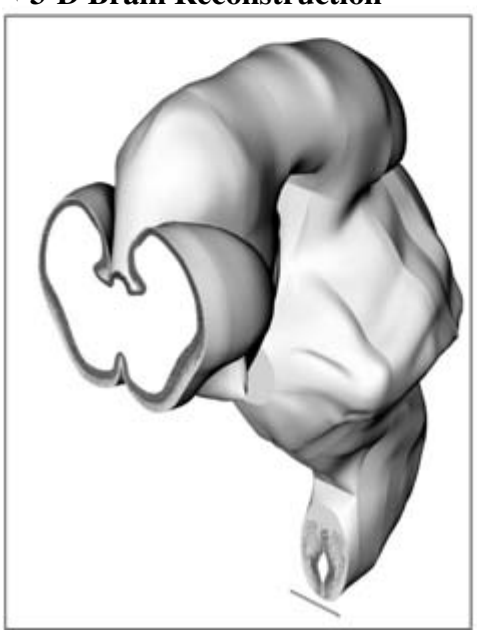
GW6.5 Coronal
CR 15.0 mm
M2051
Level 3: Section 130

See a high-magnification view of the cerebral cortex in Section 122 in Plates 63A and B.

Non-neural and peripheral neural structures labeled



Level 3: Computer-aided 3-D Brain Reconstruction



The GW6 Face and Neck

Figure 247D modified (Patten, 1953, p. 429.)

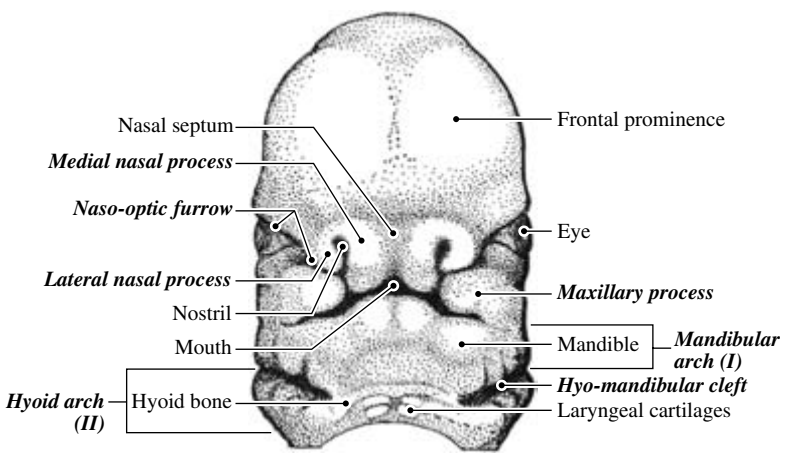
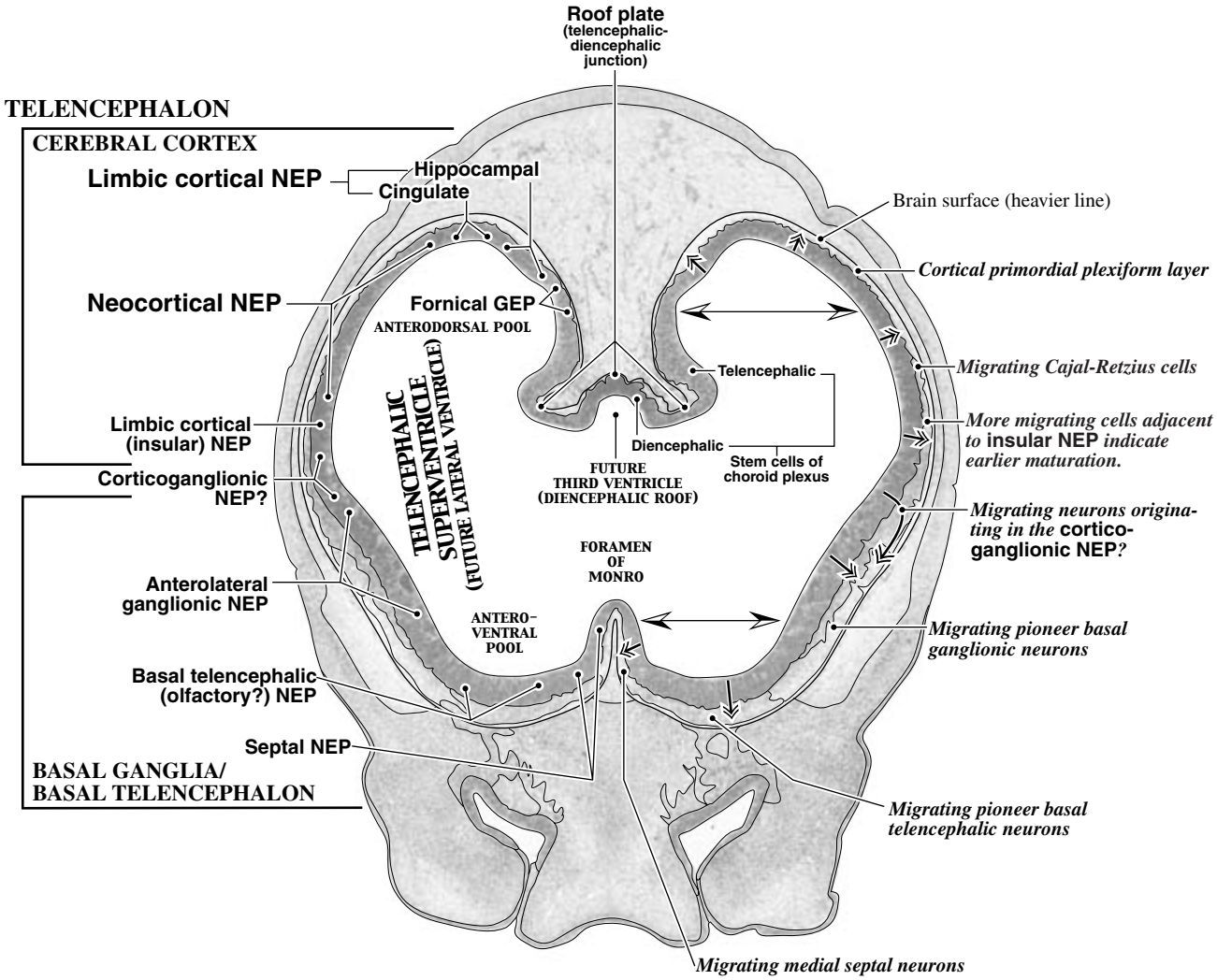


PLATE 48B

Central neural structures labeled



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

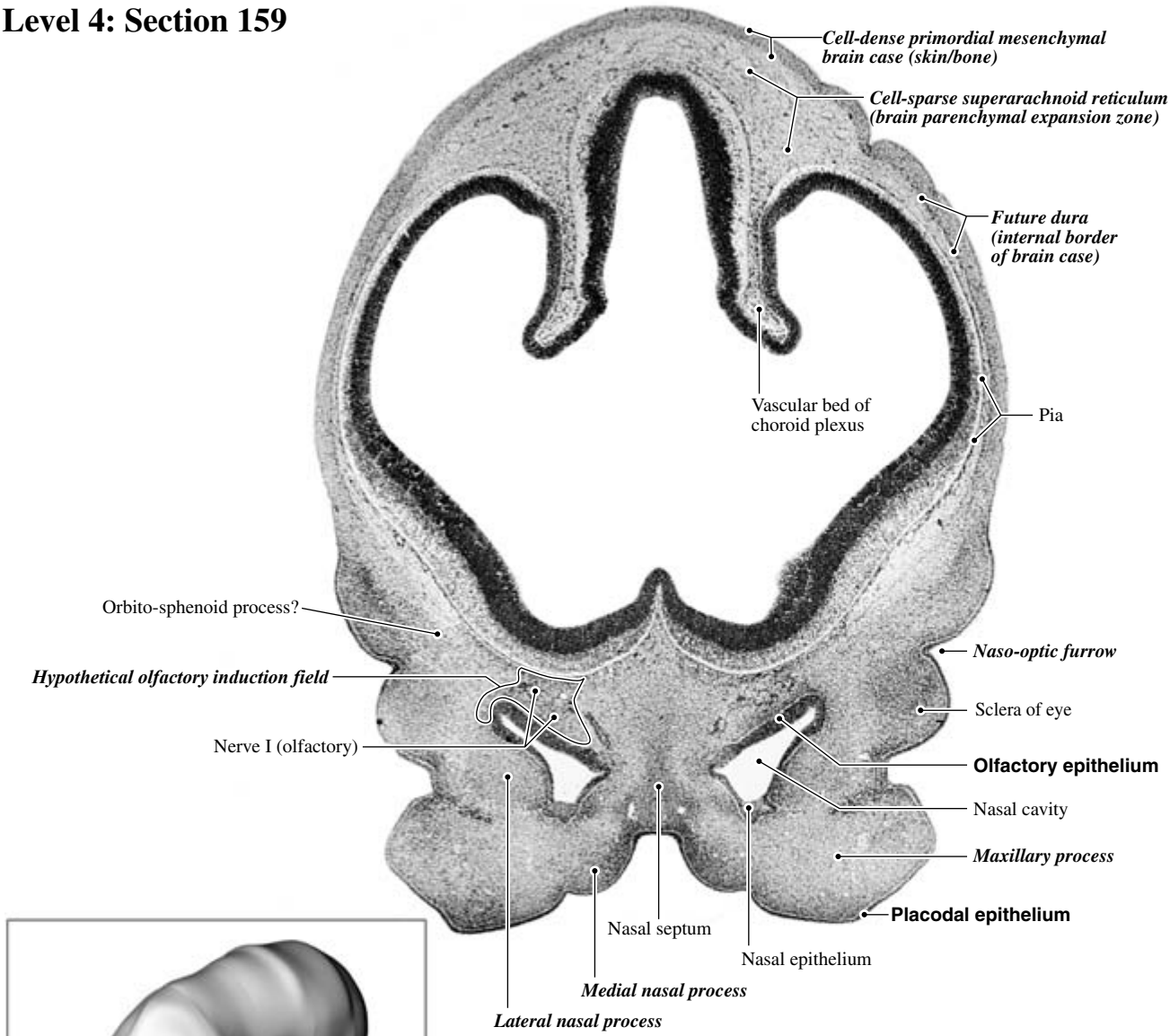
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

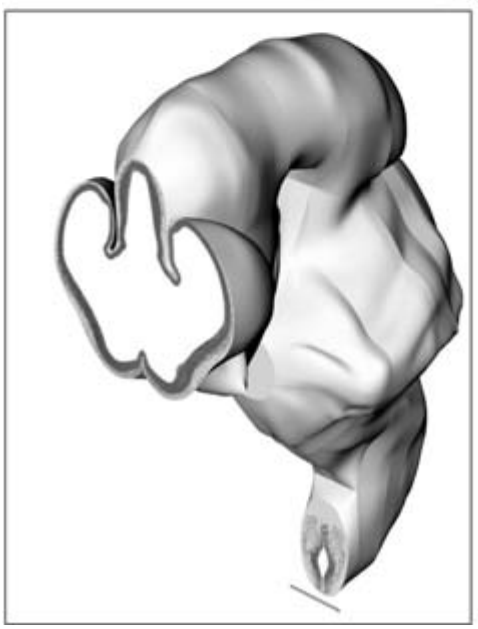
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 49A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 4: Section 159

Non-neural and peripheral neural structures labeled



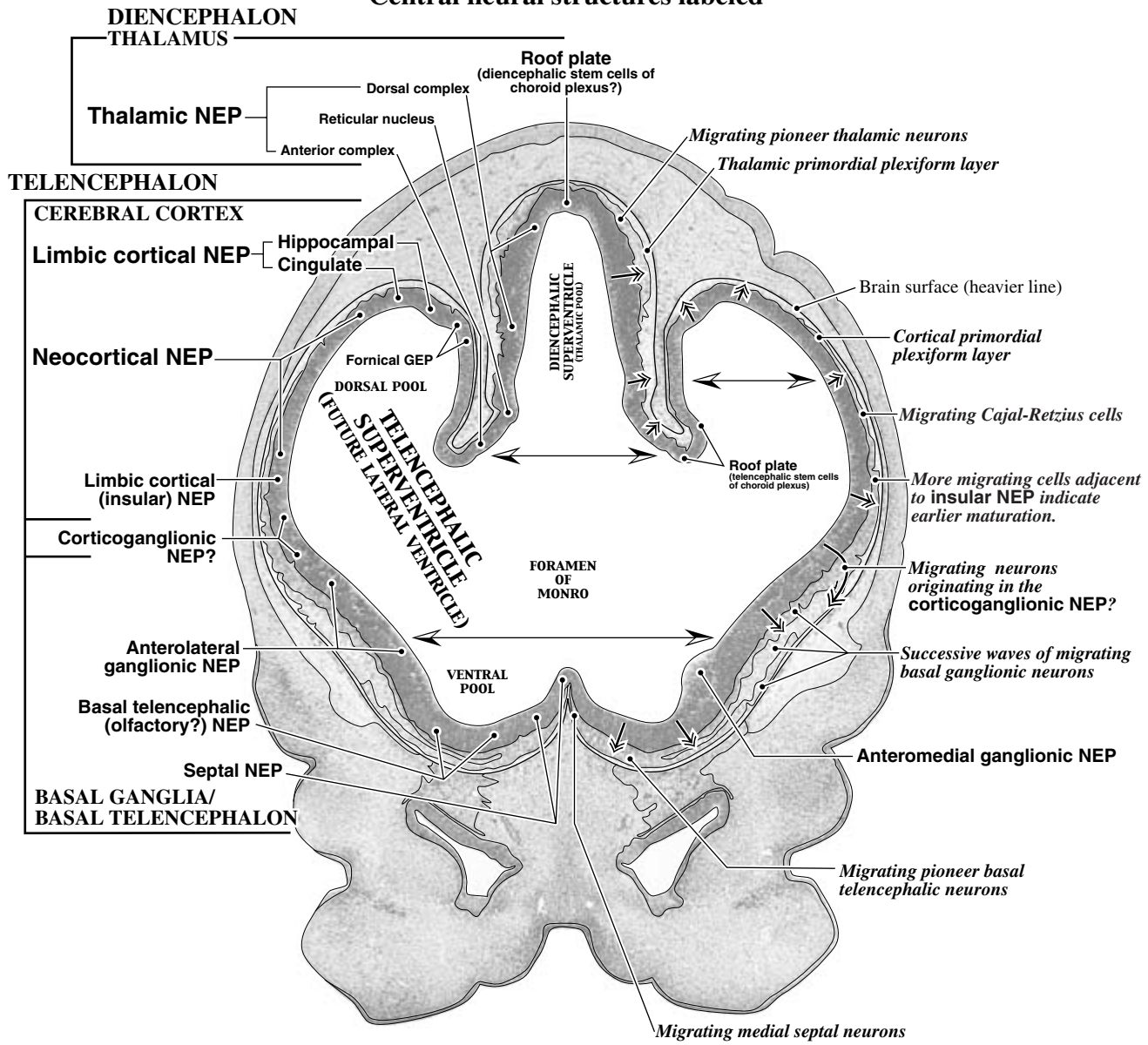


Level 4: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 49B

Central neural structures labeled



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

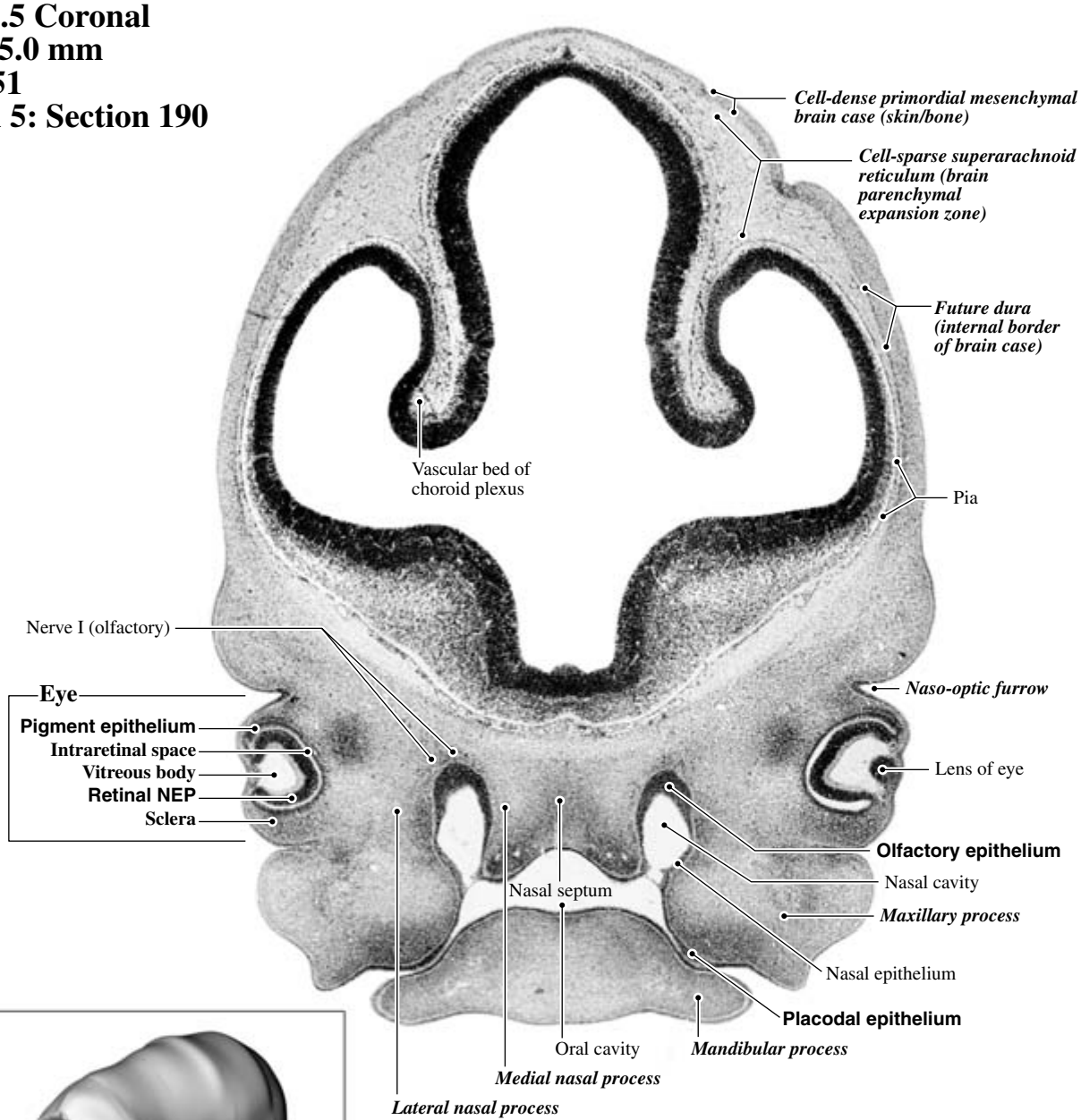
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

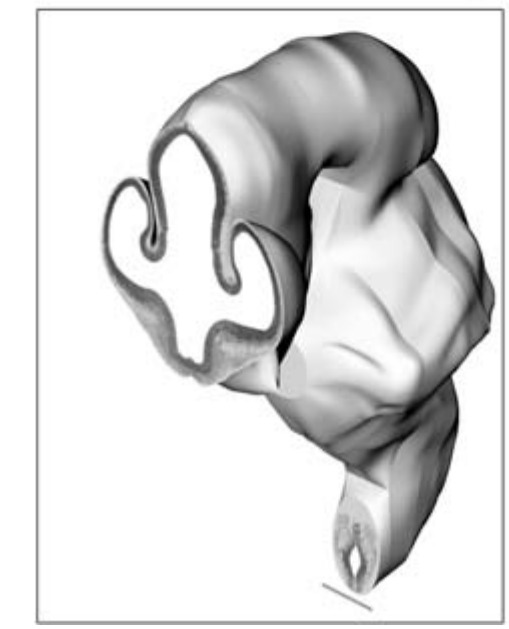
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 50A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 5: Section 190

Non-neural and peripheral neural structures labeled



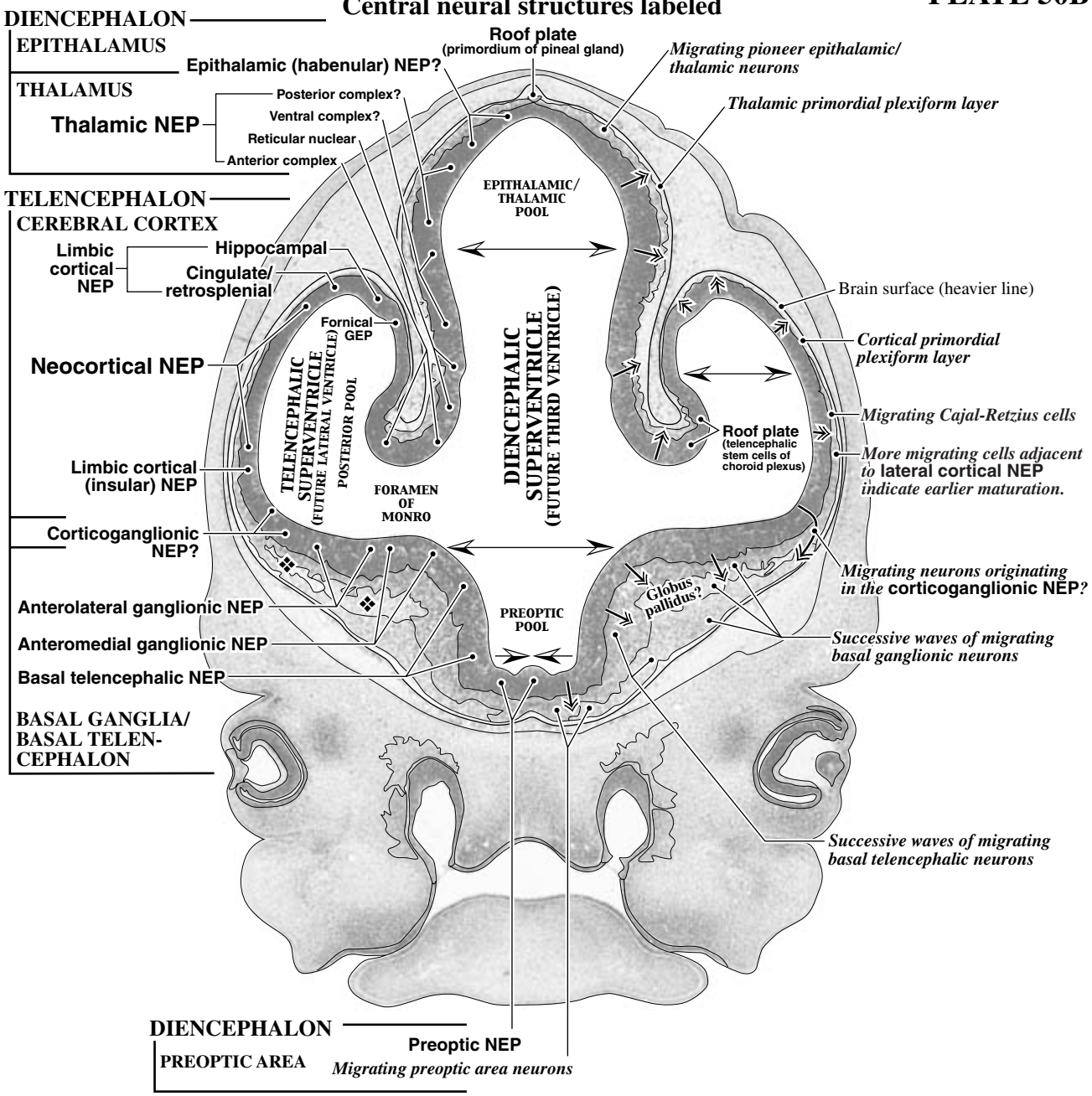


Level 5: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 50B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

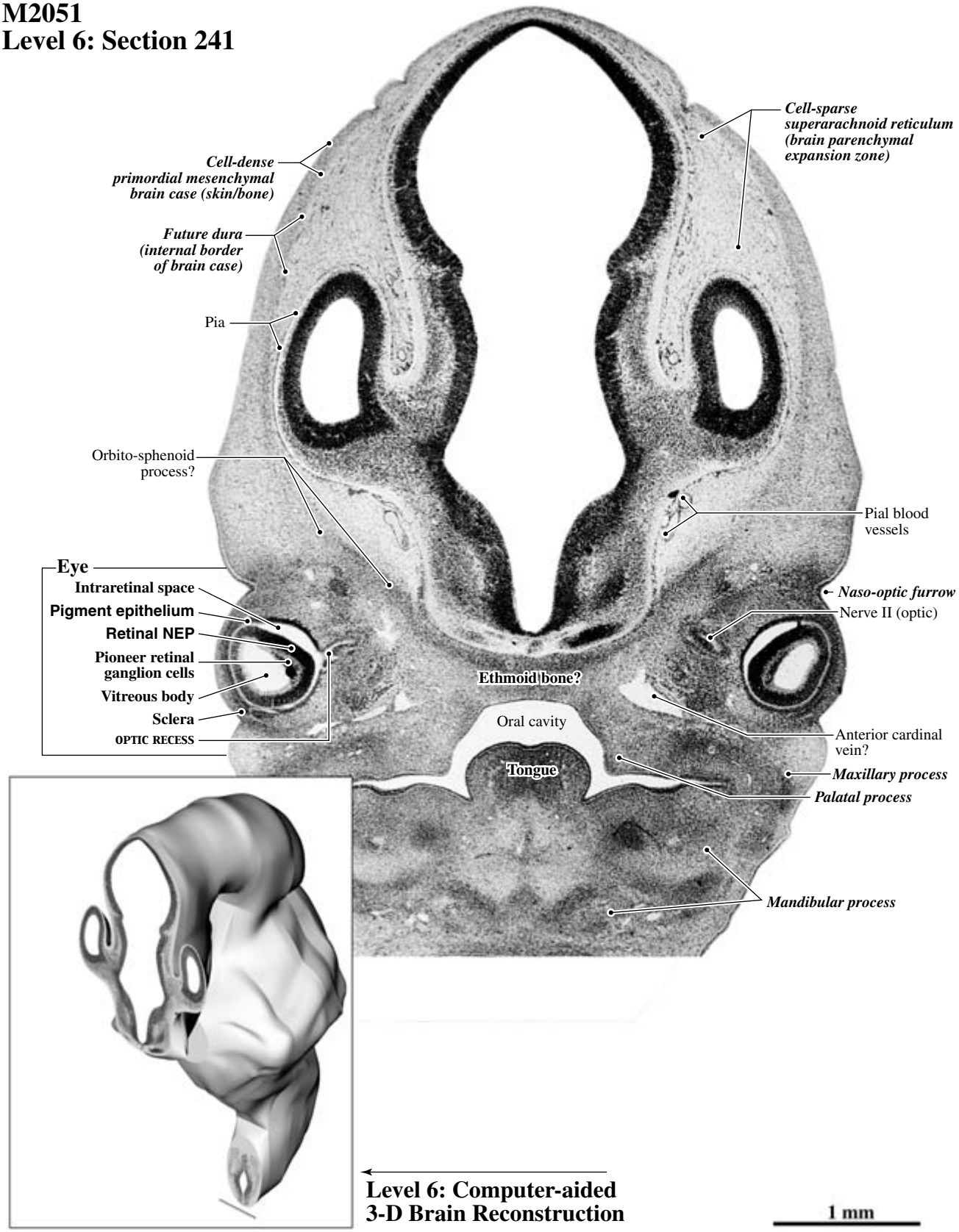
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 51A

Non-neural and peripheral neural structures labeled

GW6.5 Coronal
CR 15.0 mm
M2051
Level 6: Section 241

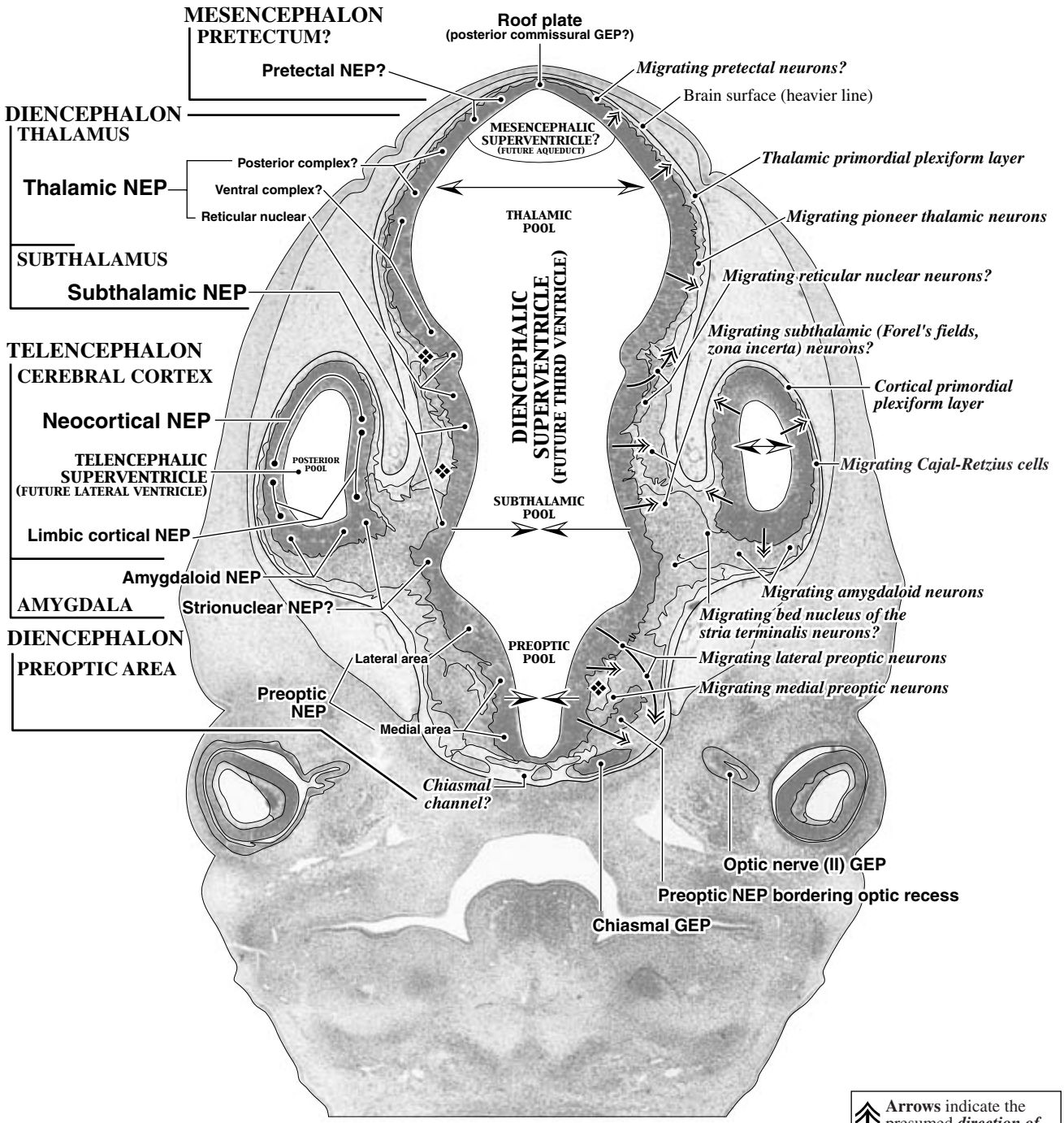


Level 6: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 51B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

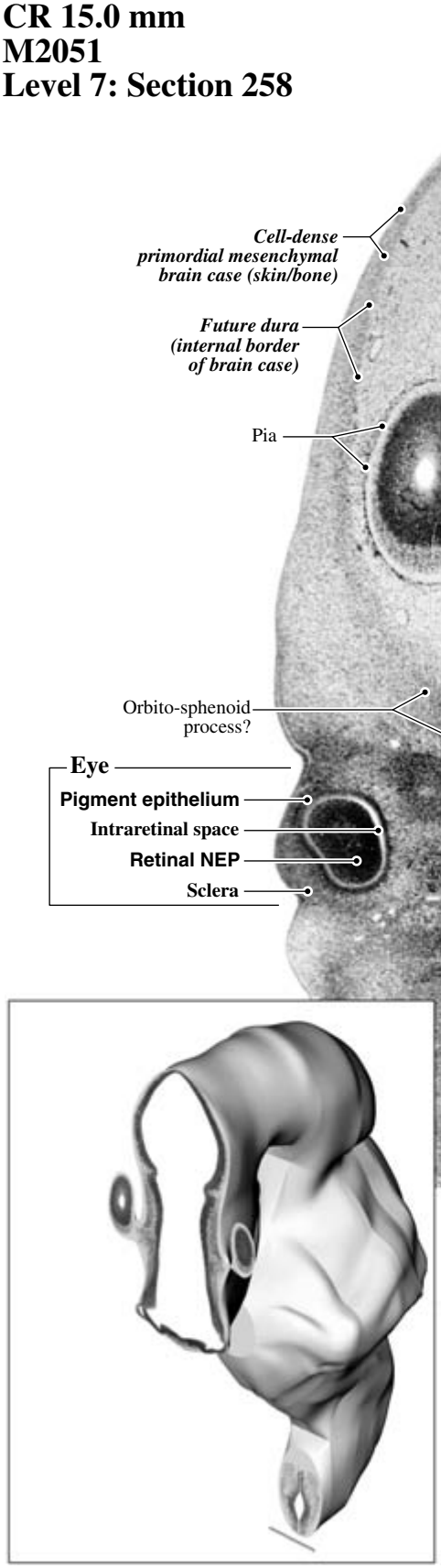
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 52A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 7: Section 258

Non-neural and peripheral neural structures labeled



Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

Cell-dense primordial mesenchymal brain case (skin/bone)

Dural blood vessels

Future dura (internal border of brain case)

Pia

Pial blood vessels

Orbito-sphenoid process?

Eye

Pigment epithelium

Intraretinal space

Retinal NEP

Sclera

Naso-optic furrow

Sphenoid bone?

Anterior cardinal vein?

Oral cavity

Maxillary process

Tongue

Palatal process

Meckel's cartilage

Mandibular process

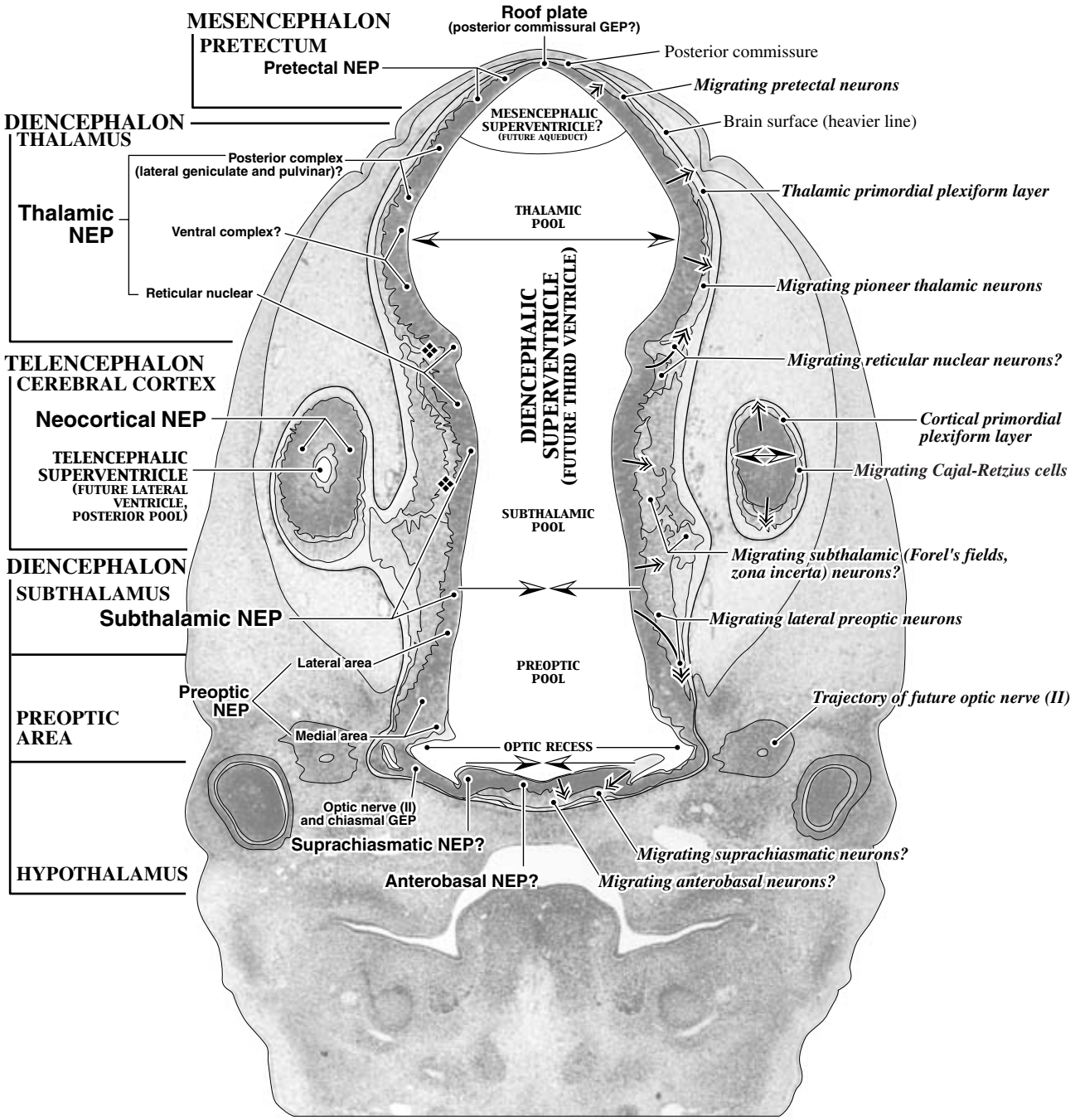
Hypoglossal nerve (XII)?

Level 7: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 52B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

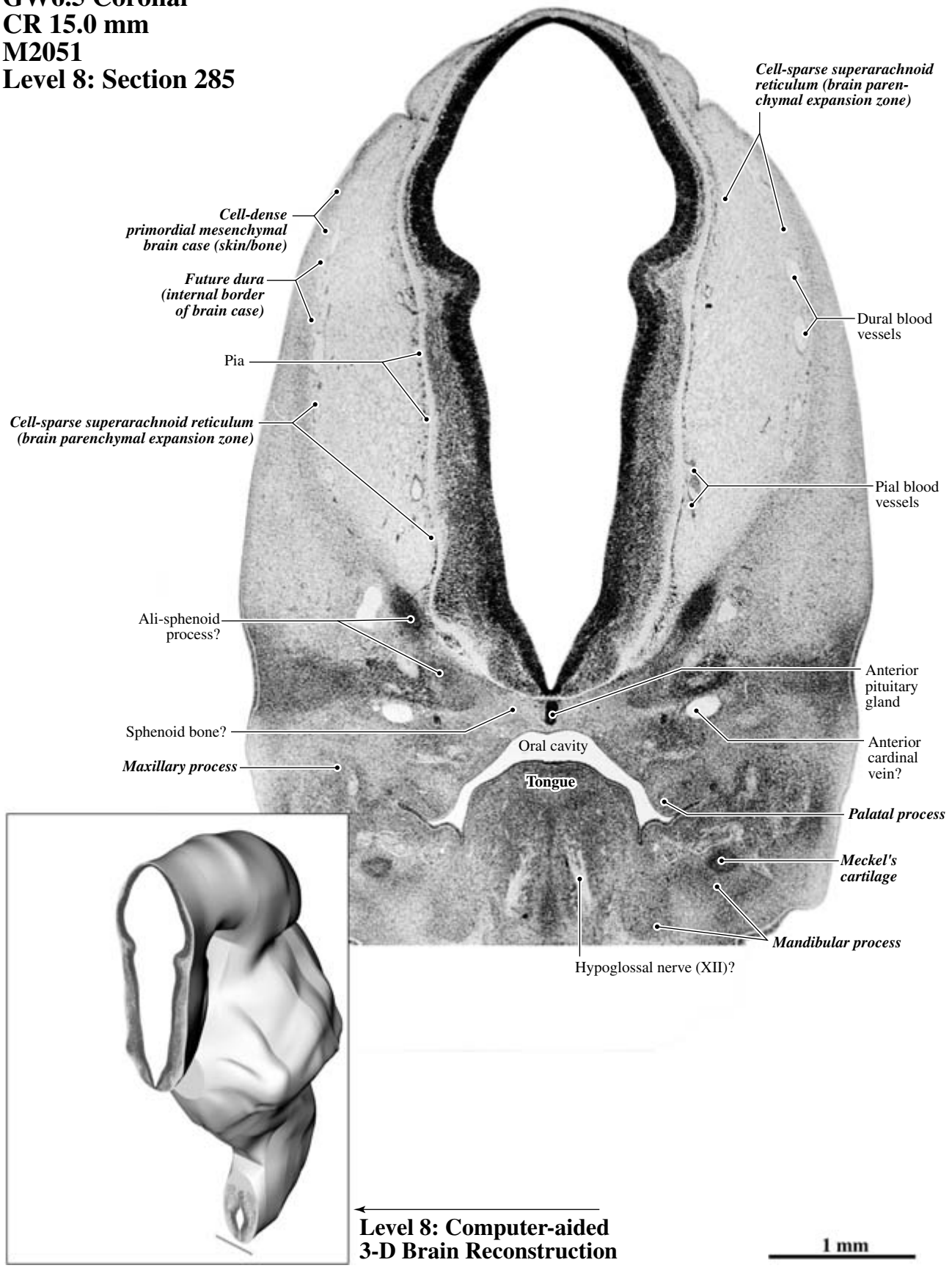
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 53A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 8: Section 285

Non-neural and peripheral neural structures labeled

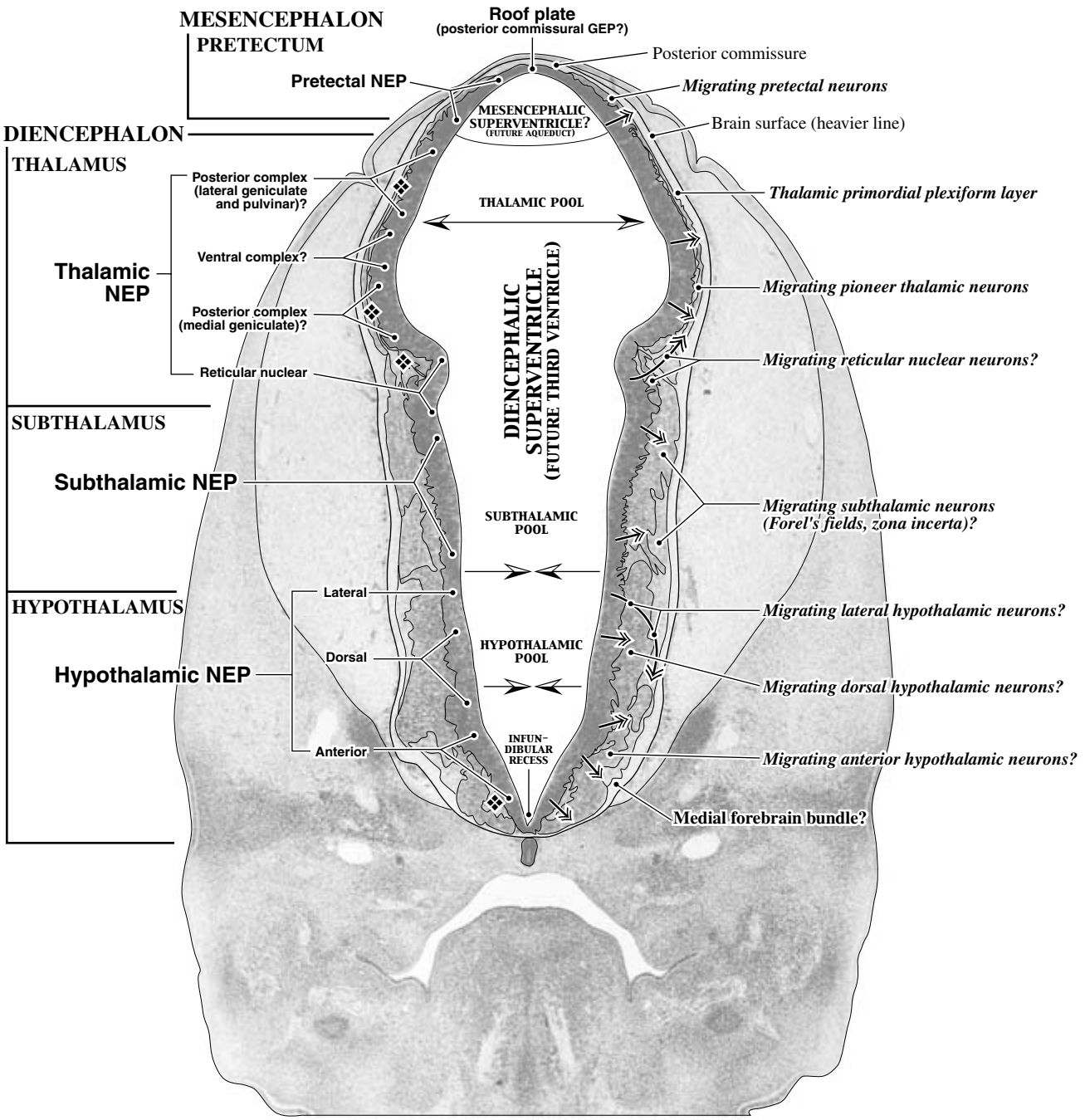


Level 8: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 53B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

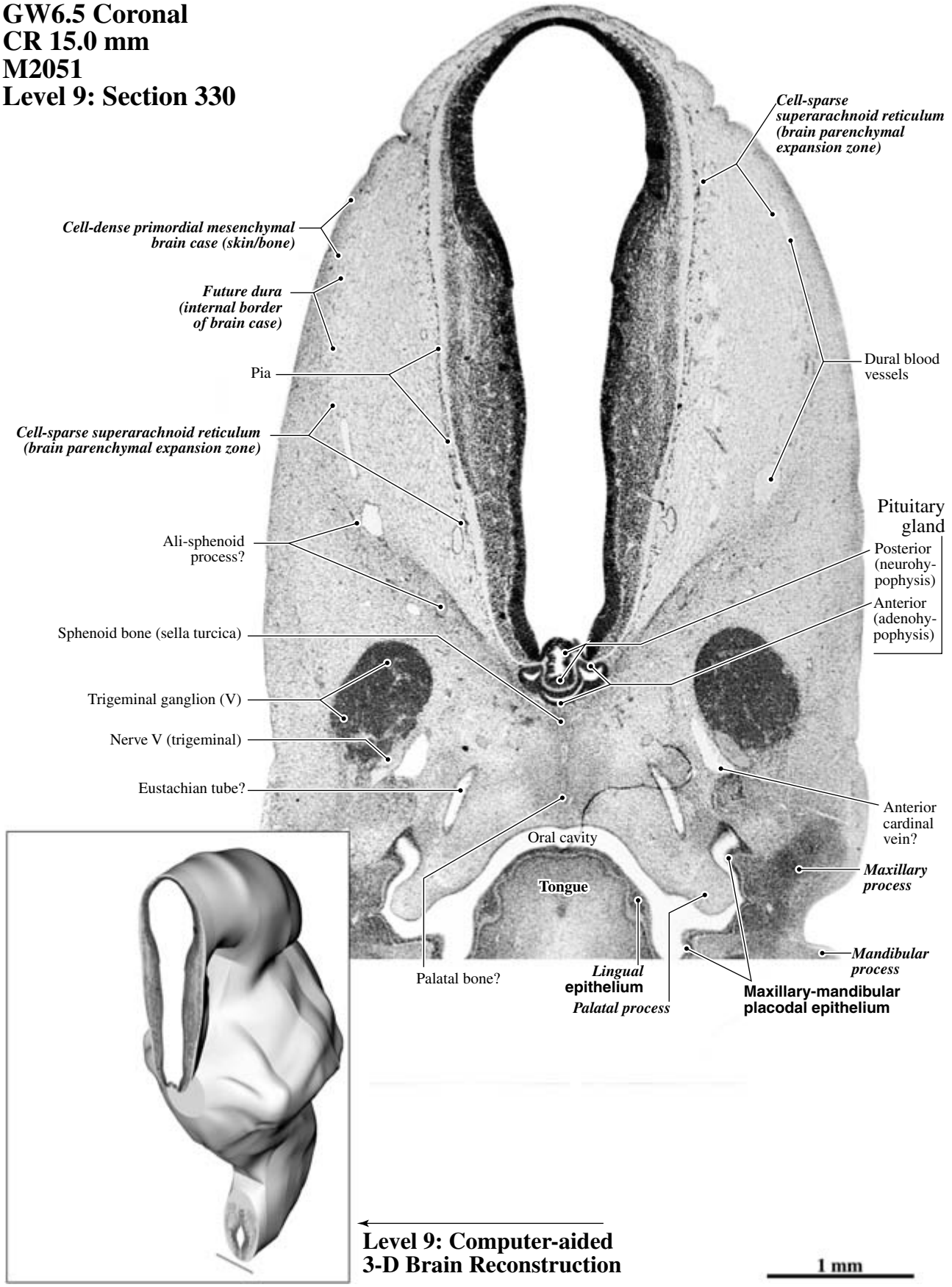
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 54A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 9: Section 330

Non-neural and peripheral neural structures labeled

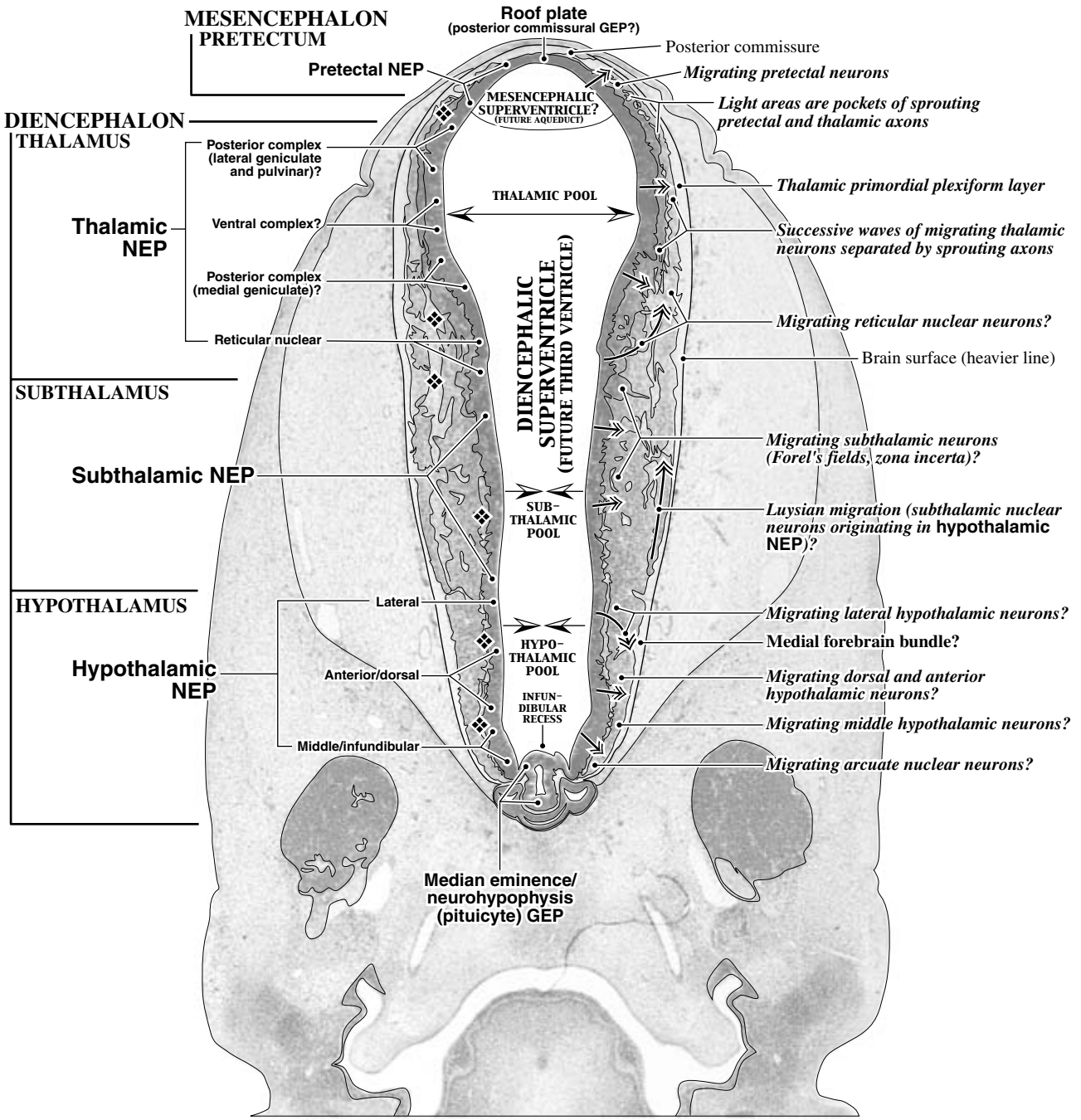


Level 9: Computer-aided 3-D Brain Reconstruction

1 mm

Central neural structures labeled

PLATE 54B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

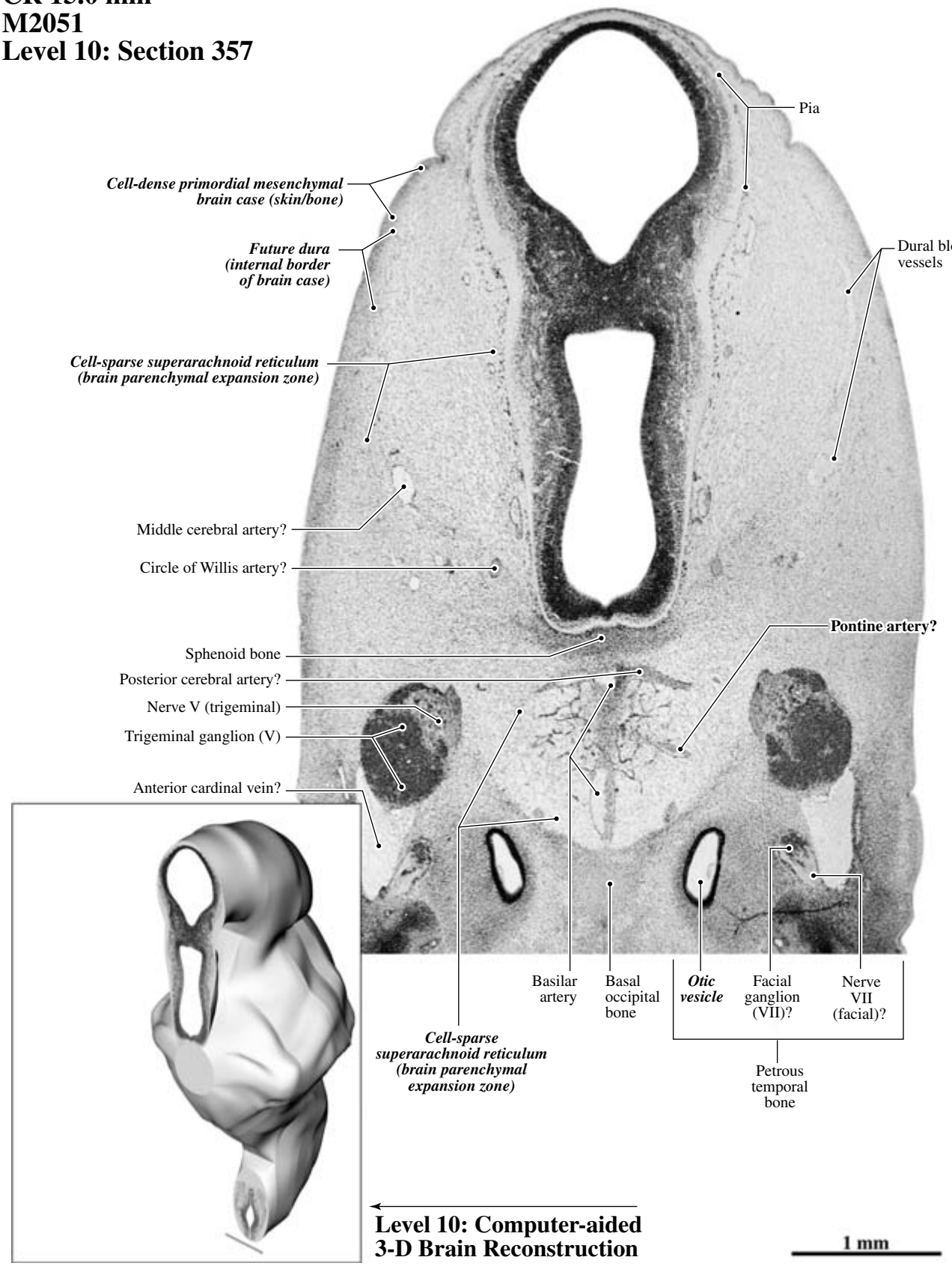
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 55A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 10: Section 357

Non-neural and peripheral neural structures labeled

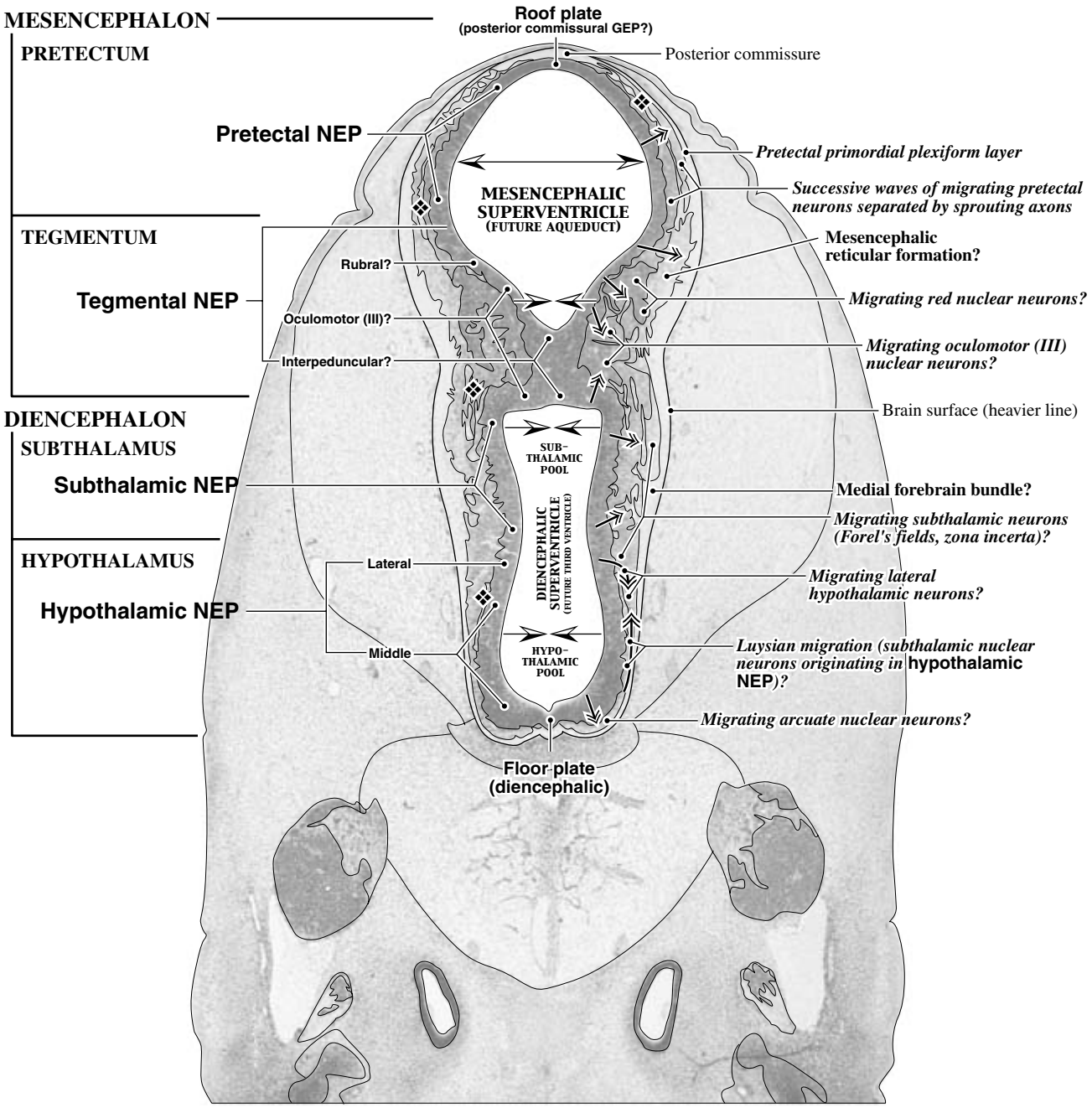


Level 10: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 55B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

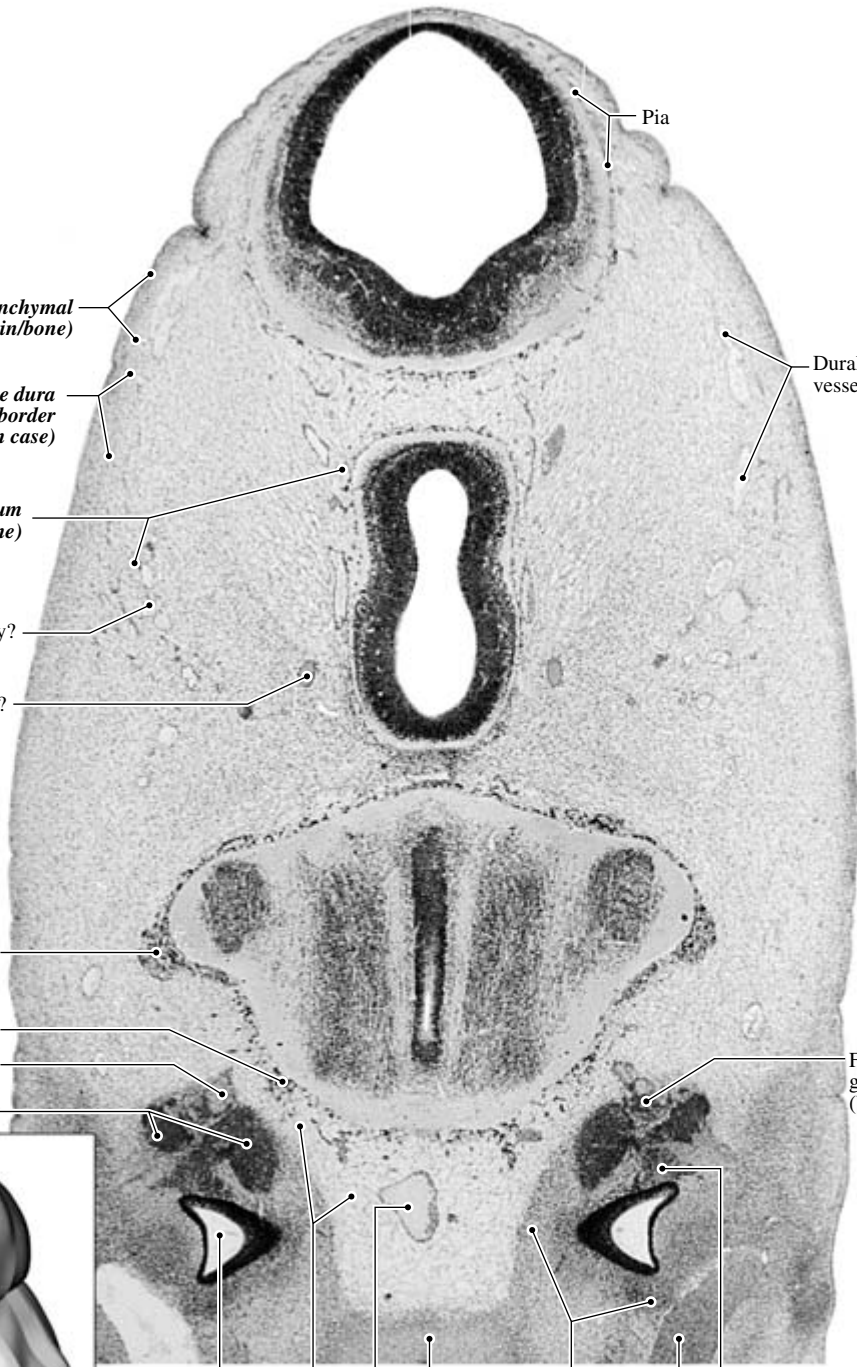
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

PLATE 56A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 11: Section 384

Non-neural and peripheral neural structures labeled



Pia

Cell-dense primordial mesenchymal brain case (skin/bone)

Future dura (internal border of brain case)

Dural blood vessels

Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

Middle cerebral artery?

Circle of Willis artery?

Boundary caps are* **Schwann cell GEPs?

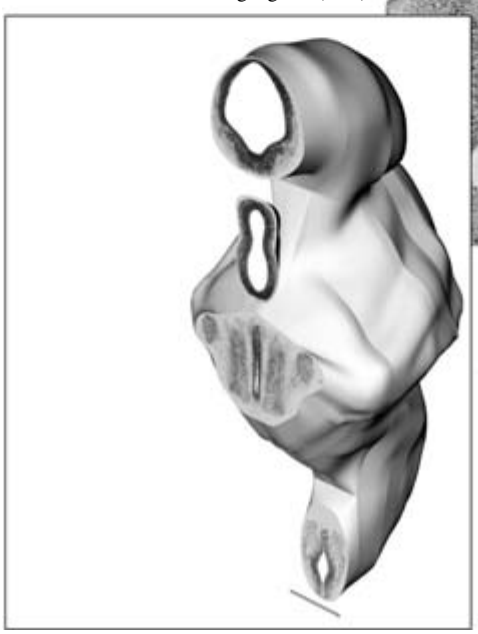
Trigeminal ***boundary cap****

Facial ***boundary cap****

Nerve VII (facial)?

Vestibular ganglion (VIII)

Facial ganglion (VII)?



Temporal bone labyrinth *(otic vesicle)*

Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

Basilar artery

Basal occipital bone

Petrous temporal bone

Anterior cardinal vein?

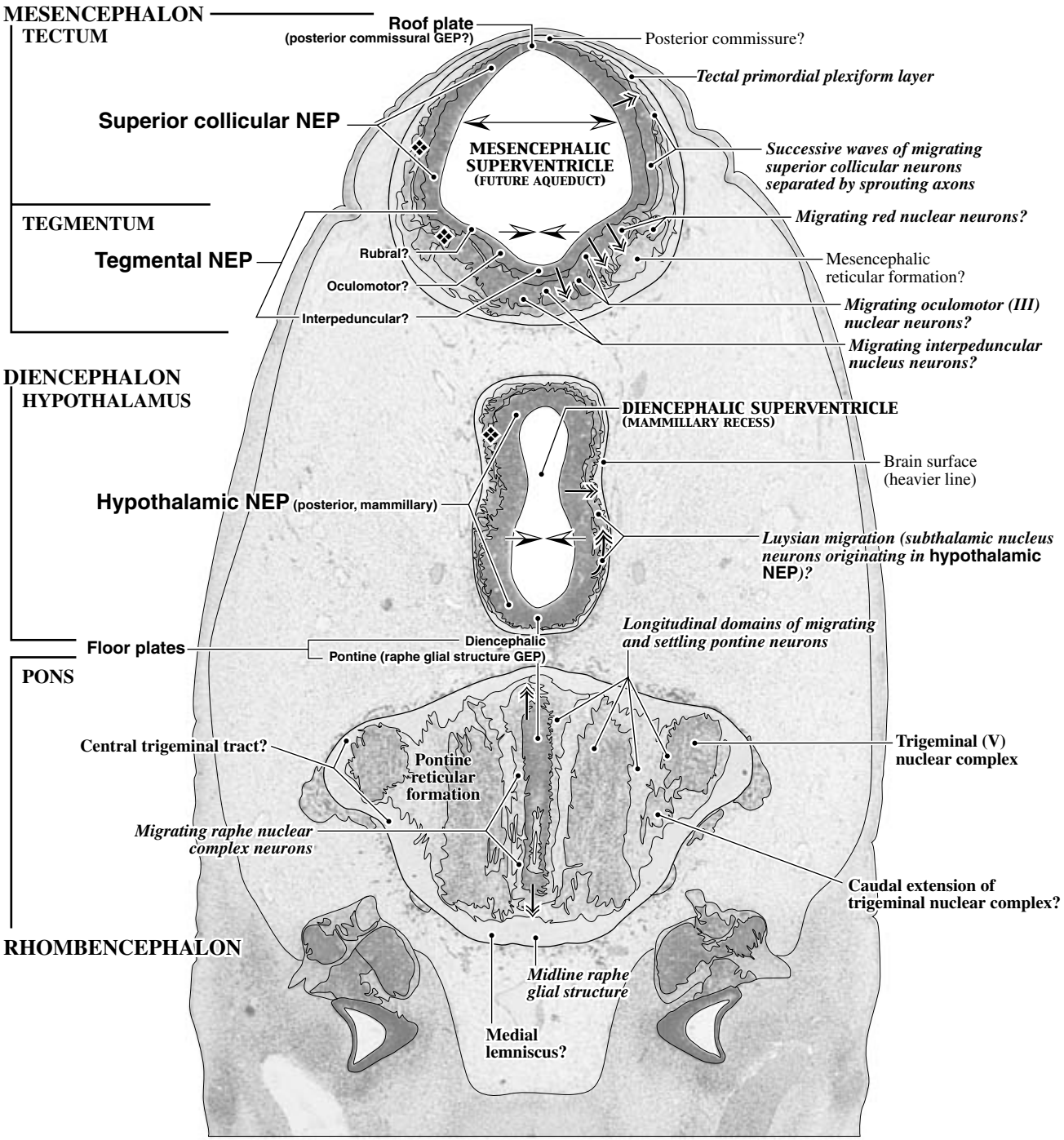
Spiral ganglion (VIII) budding from **otic vesicle epithelium*?***

Level 11: Computer-aided 3-D Brain Reconstruction

1 mm

Central neural structures labeled

PLATE 56B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

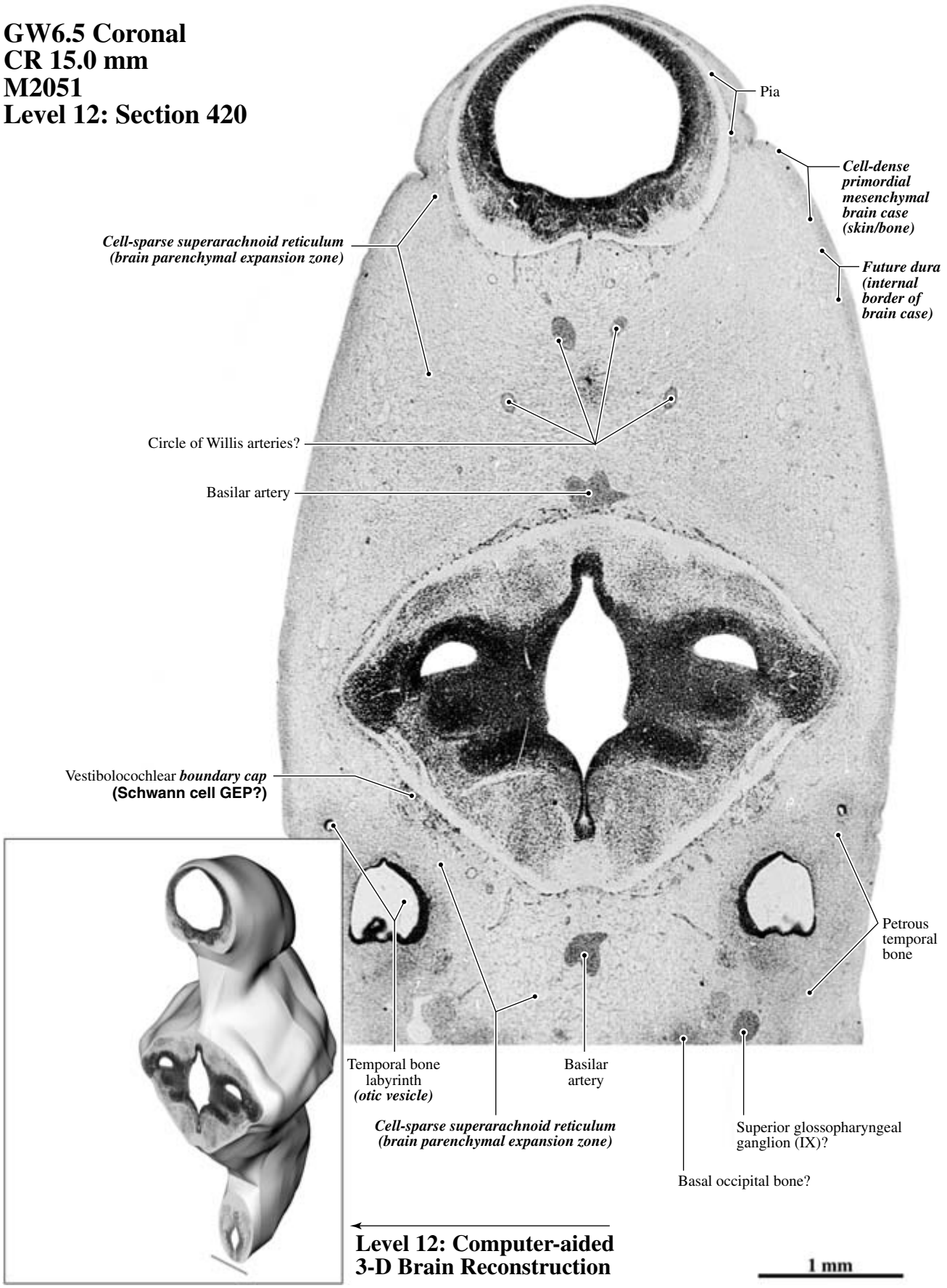
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

PLATE 57A

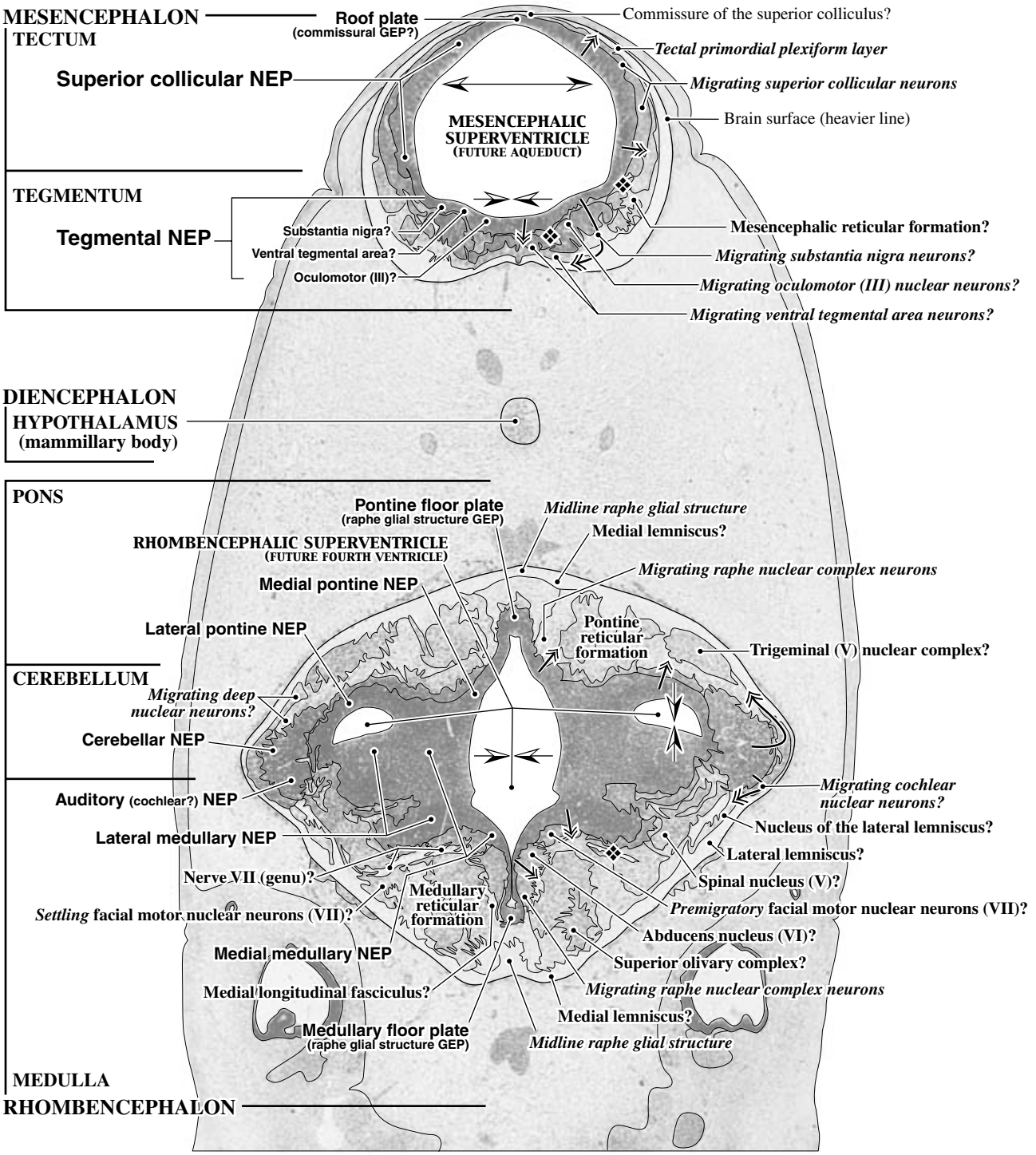
Non-neural and peripheral neural structures labeled

GW6.5 Coronal
CR 15.0 mm
M2051
Level 12: Section 420



Central neural structures labeled

PLATE 57B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 58A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 13: Section 438

Non-neural and peripheral neural structures labeled

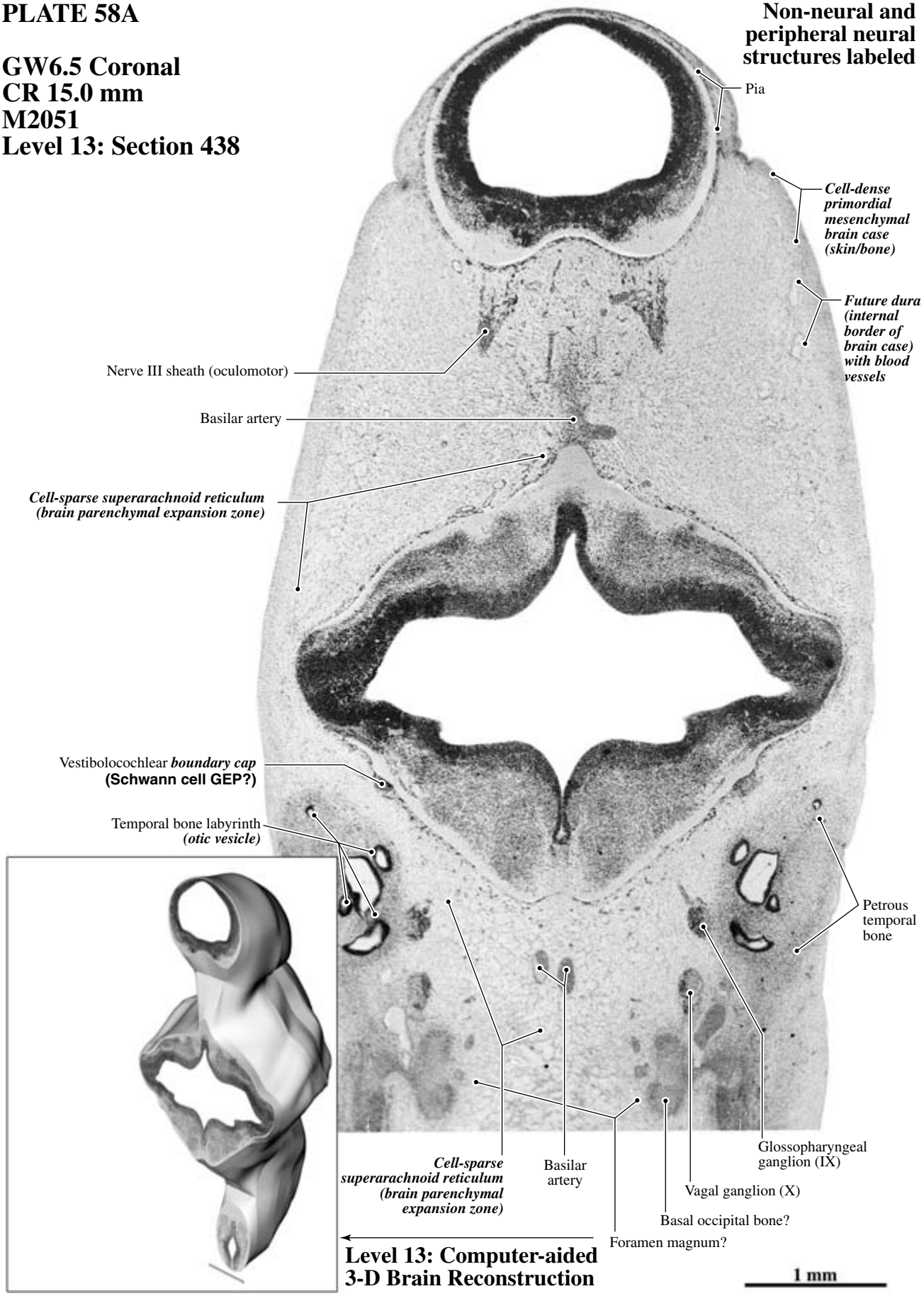
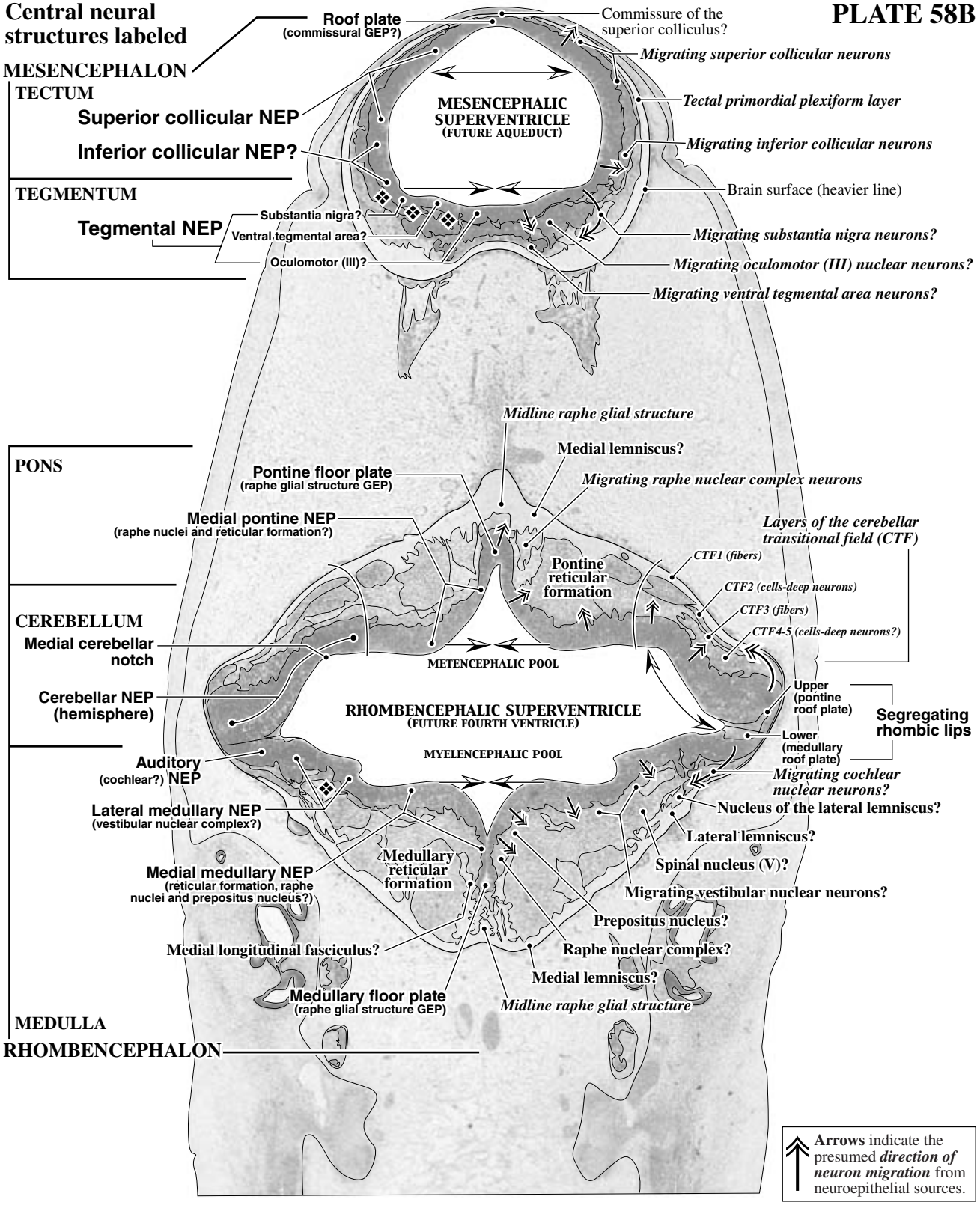


PLATE 58B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

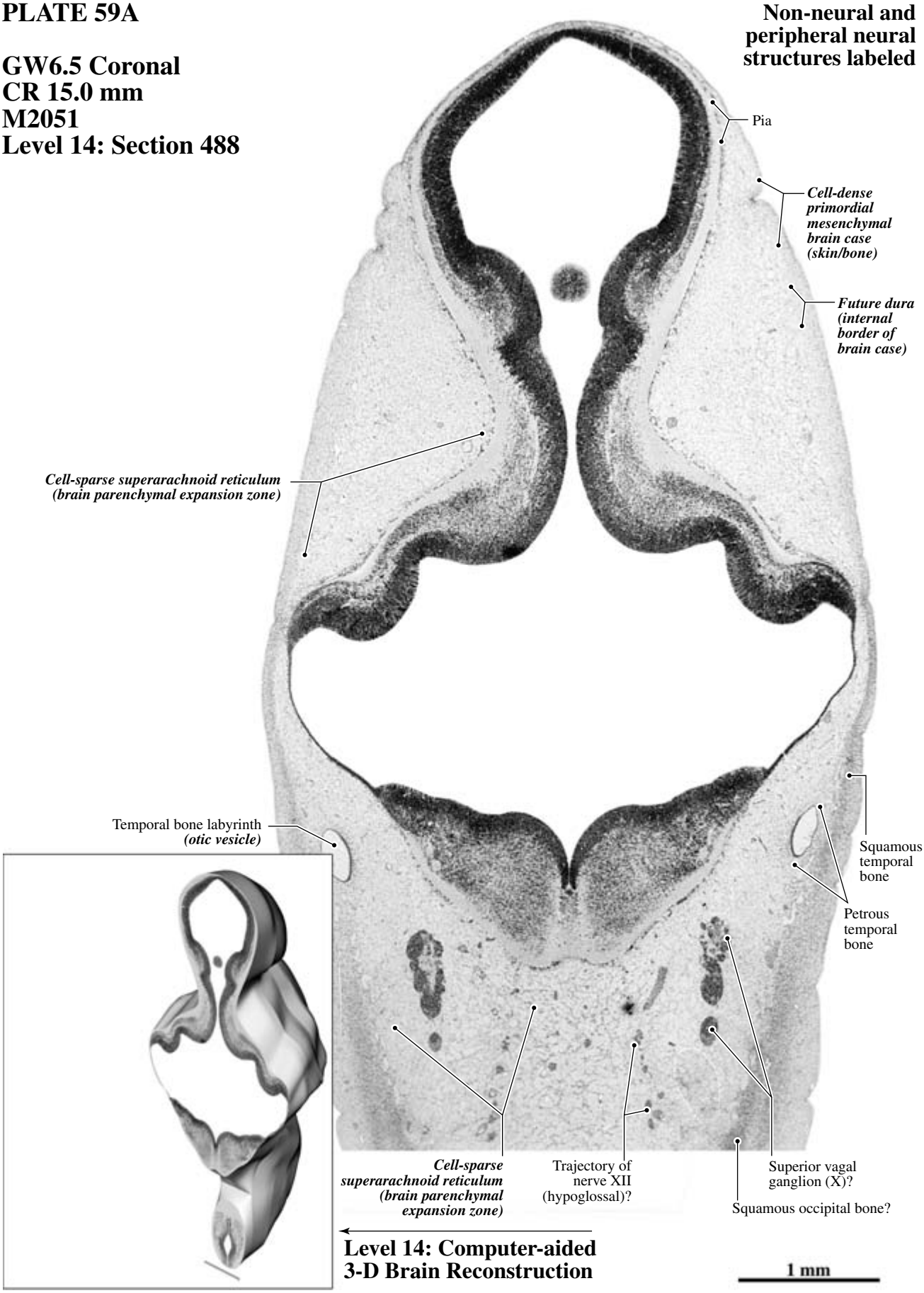
❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 59A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 14: Section 488

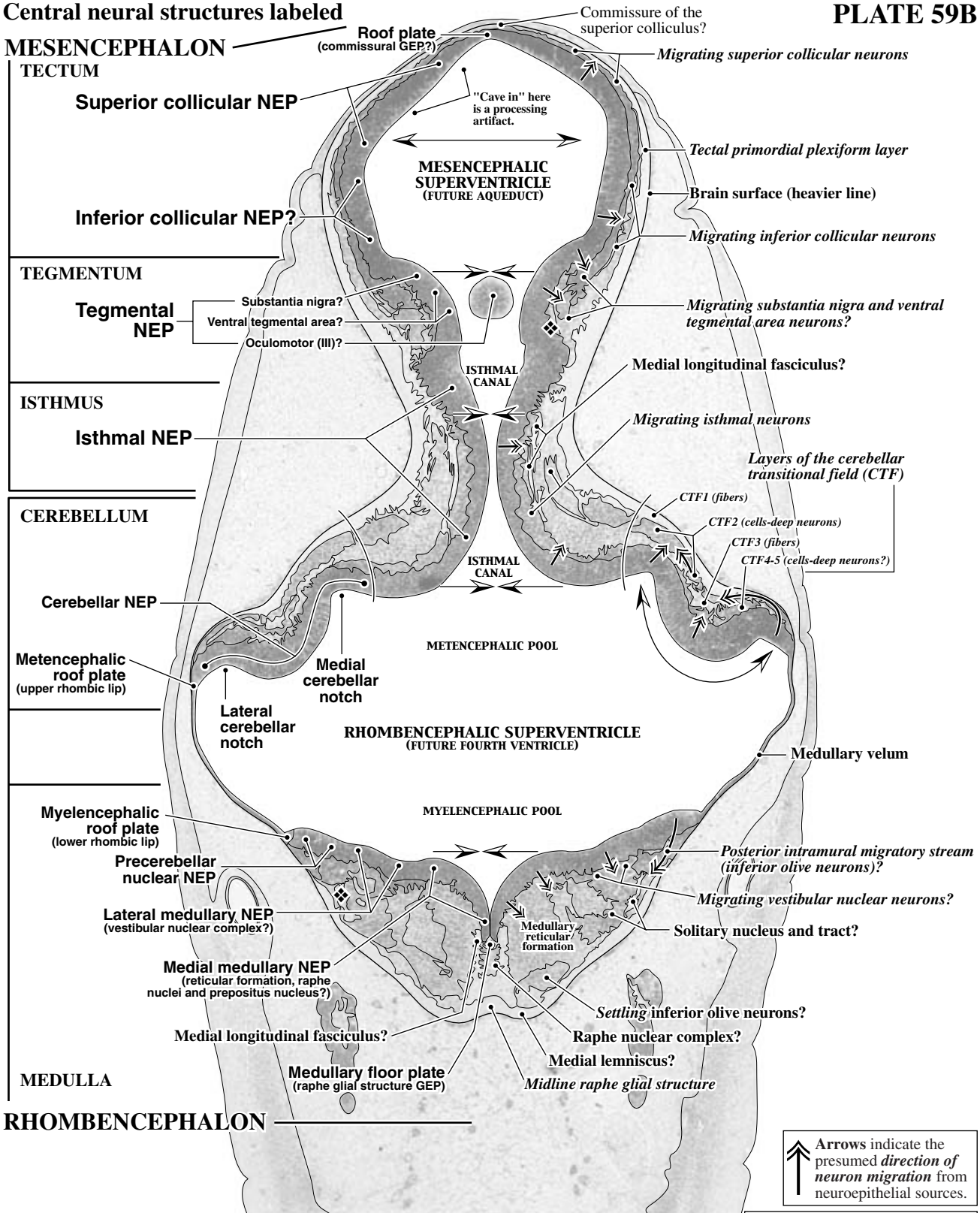
Non-neural and peripheral neural structures labeled



Level 14: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 59B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

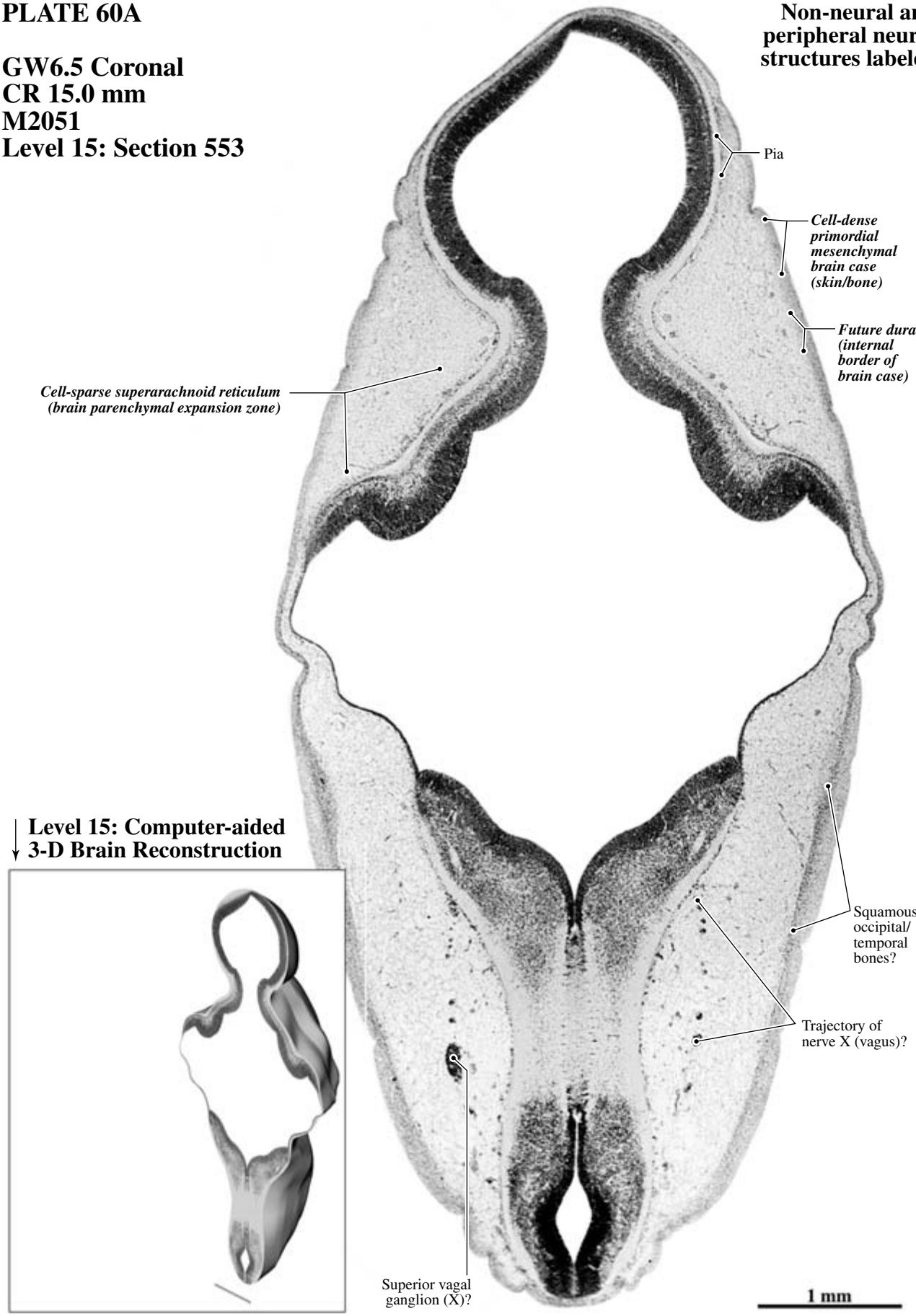
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 60A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 15: Section 553

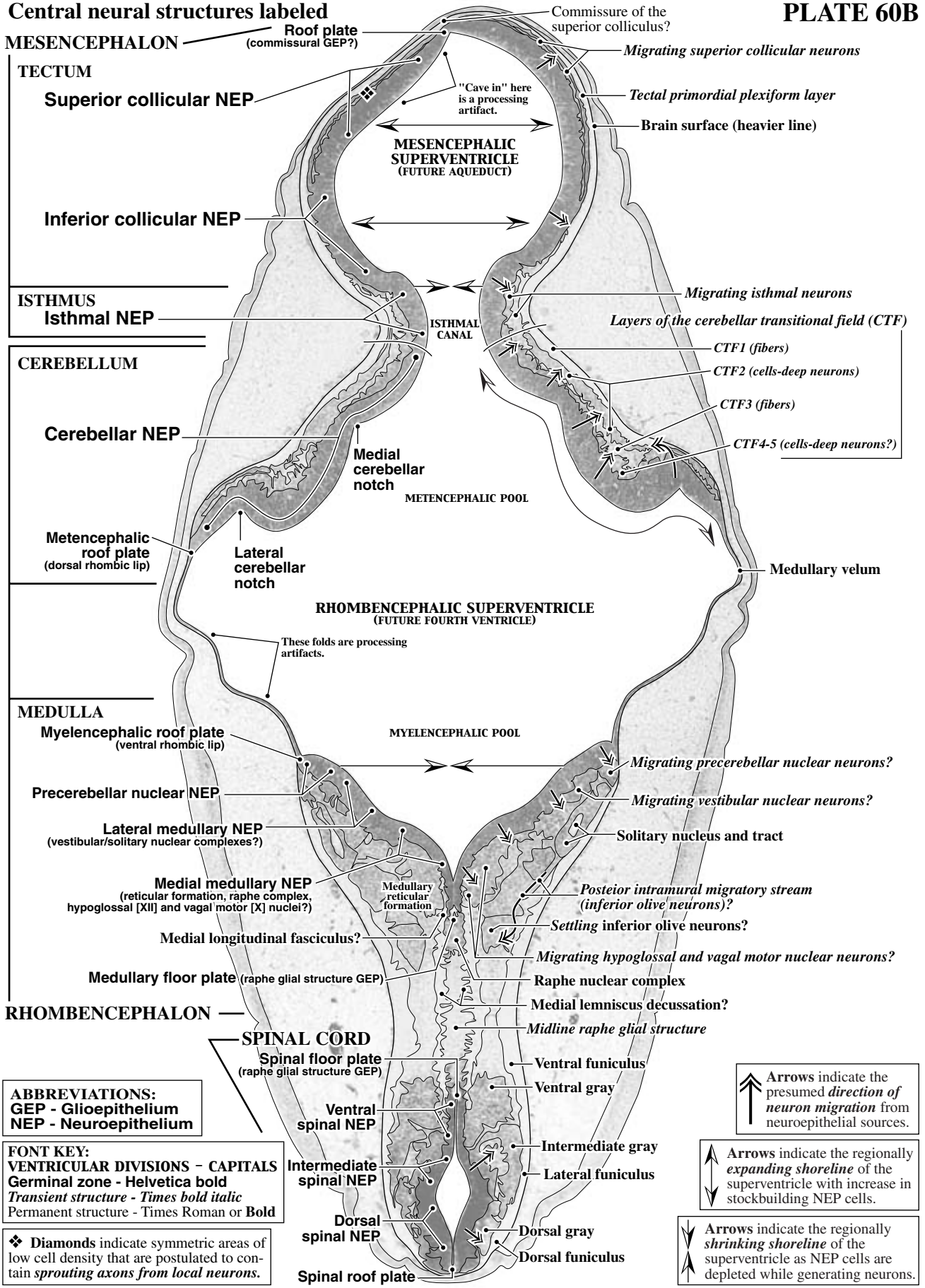
Non-neural and peripheral neural structures labeled



Level 15: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 60B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

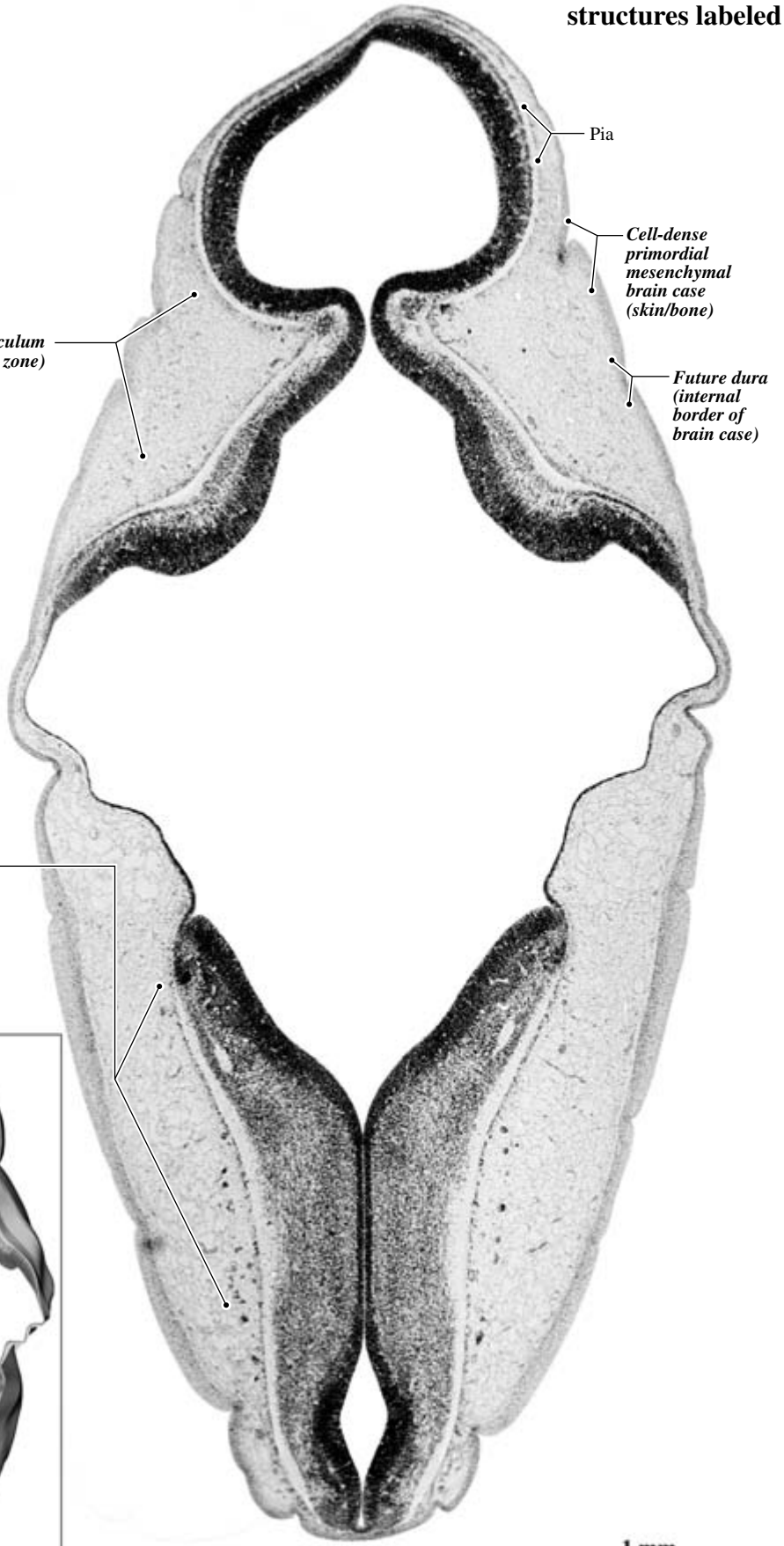
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 61A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 16: Section 583

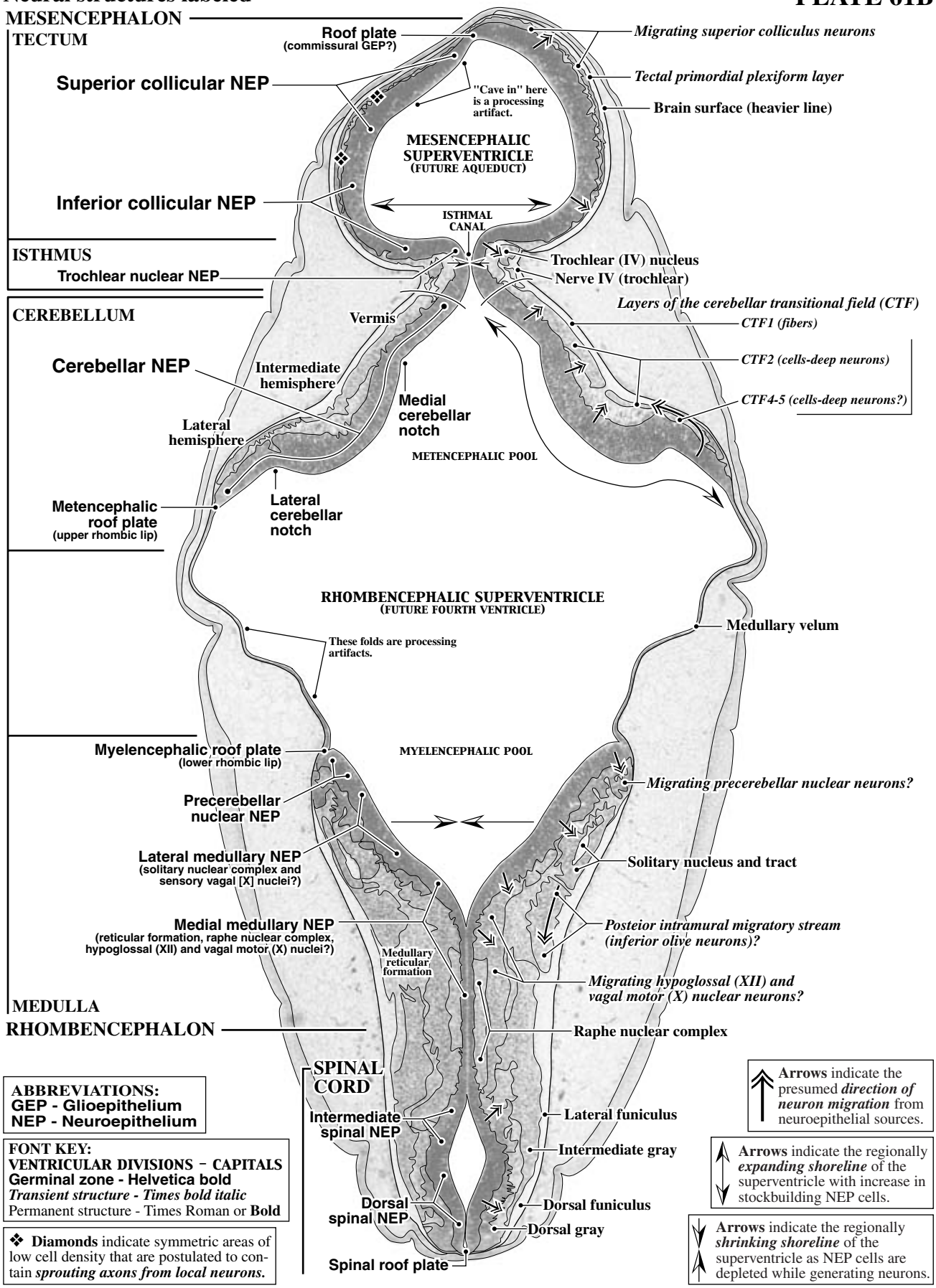
Non-neural structures labeled



Level 16: Computer-aided 3-D Brain Reconstruction

Neural structures labeled

PLATE 61B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

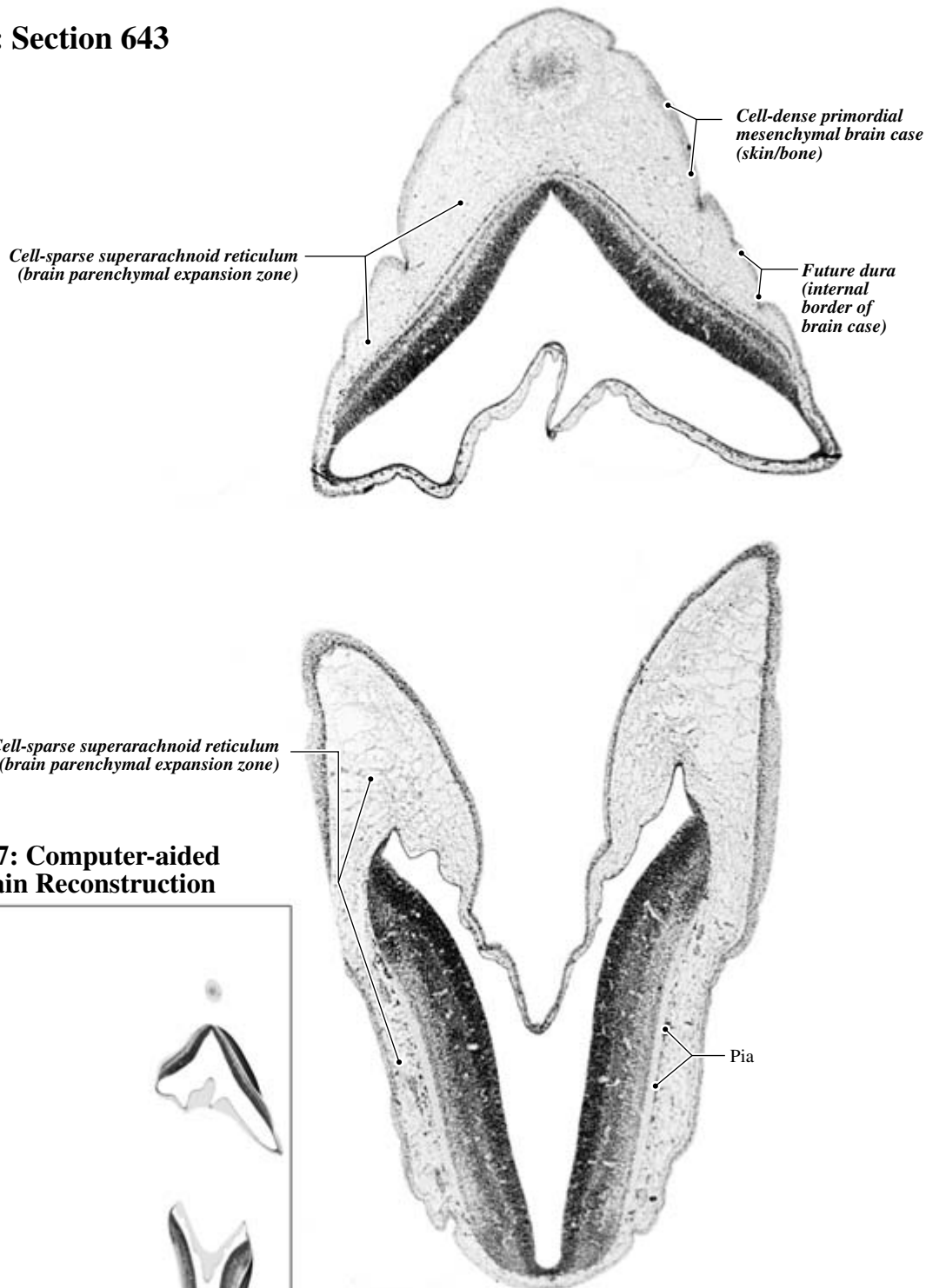
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 62A

GW6.5 Coronal
CR 15.0 mm
M2051
Level 17: Section 643

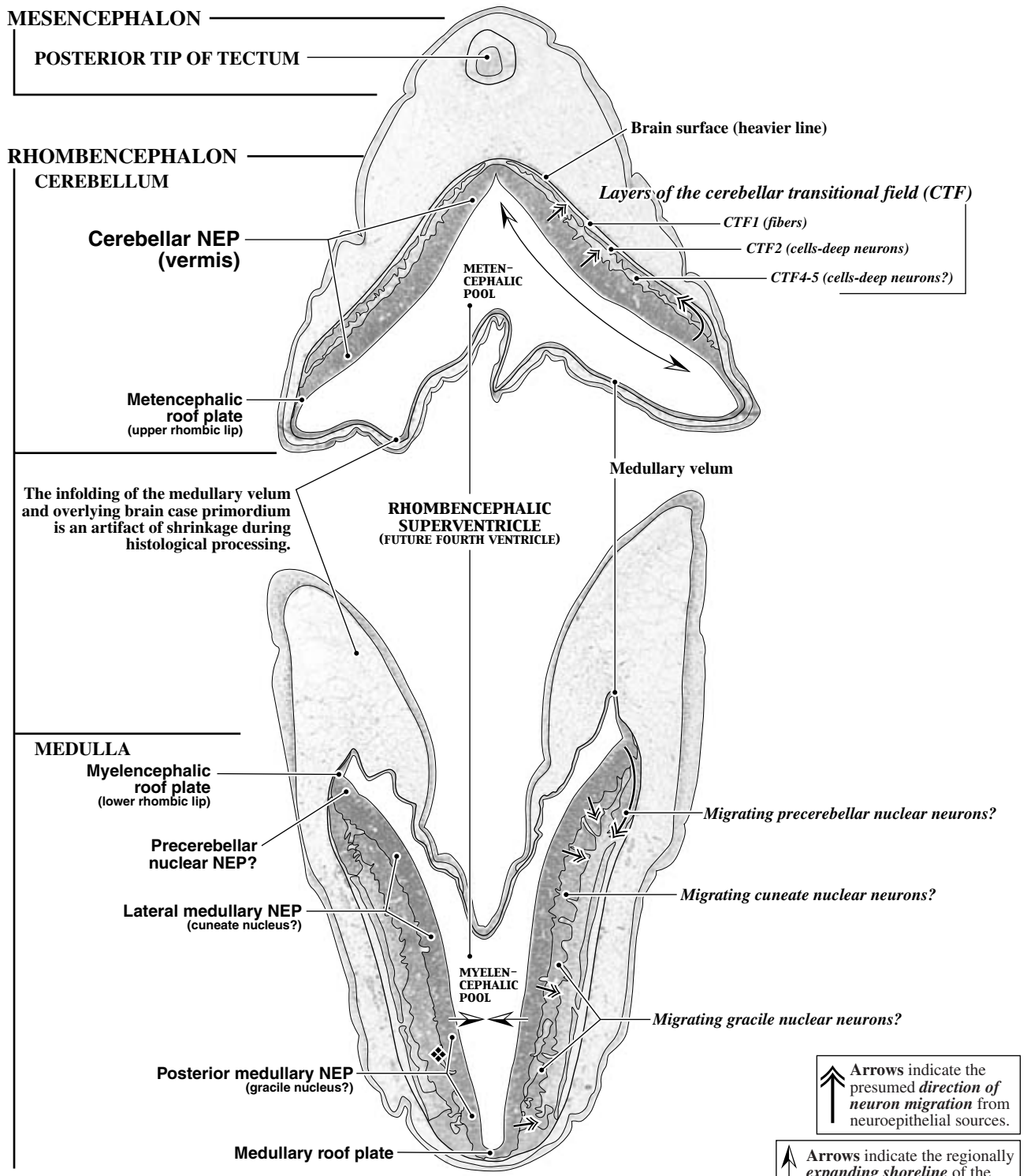
Non-neural structures labeled



Level 17: Computer-aided 3-D Brain Reconstruction

PLATE 62B

Neural structures labeled



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - Neuroepithelium

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

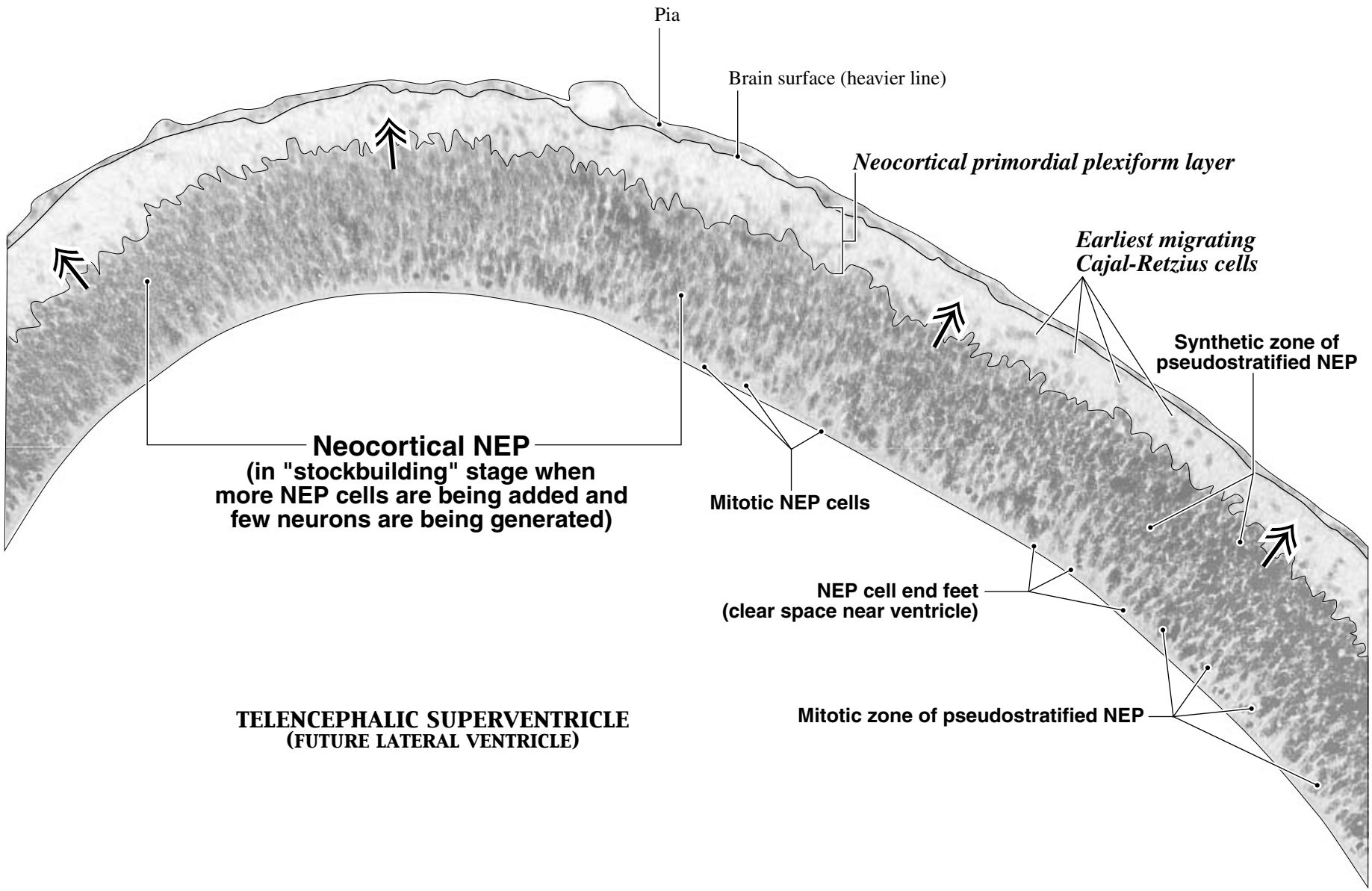
Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 63A
GW6.5 Coronal, CR 15.0 mm, M2051
Near Level 3: Section 122

CEREBRAL CORTEX
FUTURE PARACENTRAL LOBULE

See Level 3 in Plates 48A and B.

PLATE 63B


Pia
Brain surface (heavier line)
Neocortical primordial plexiform layer
Earliest migrating
Cajal-Retzius cells
Synthetic zone of
pseudostratified NEP
Neocortical NEP
(in "stockbuilding" stage when
more NEP cells are being added and
few neurons are being generated)
Mitotic NEP cells
NEP cell end feet
(clear space near ventricle)
Mitotic zone of pseudostratified NEP
TELENCEPHALIC SUPERVENTRICLE
(FUTURE LATERAL VENTRICLE)

PART VI: GW6.5 SAGITTAL

Carnegie Collection specimen #9247 (designated here as C9247) was collected in 1954 from a tubal pregnancy. The crown-rump length (CR) is 15 mm estimated to be at gestational week (GW) 6.5. C9247 was fixed in formalin, embedded in a celloidin/paraffin mix, and was cut in 8-µm sagittal sections that were stained with azan. Various orientations of the computer-aided 3-D reconstruction of M2051's brain are used to show the gross external features of a GW6.5 brain (**Figure 5**). C9247's sections are perfectly aligned in the sagittal plane. Considering all of the specimens in every volume of the Atlas, this is one of the best for quality of histological preservation and adherance to a section plane. Indeed, nearly an entire volume could be dedicated to the analysis of this brain. We photographed 64 sections at low magnification from the left to the right sides of the brain. Seven sections from the left side of the brain are illustrated in **Plates 64AB to 70AB**. Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural structures, peripheral neural structures, and brain ventricular divisions; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 71AB to 84AB** show high-magnification views of all parts of the developing brain. The sagittal plane is ideal to show the relative sizes of major brain subdivisions and the entry zones of sensory nerve fibers.

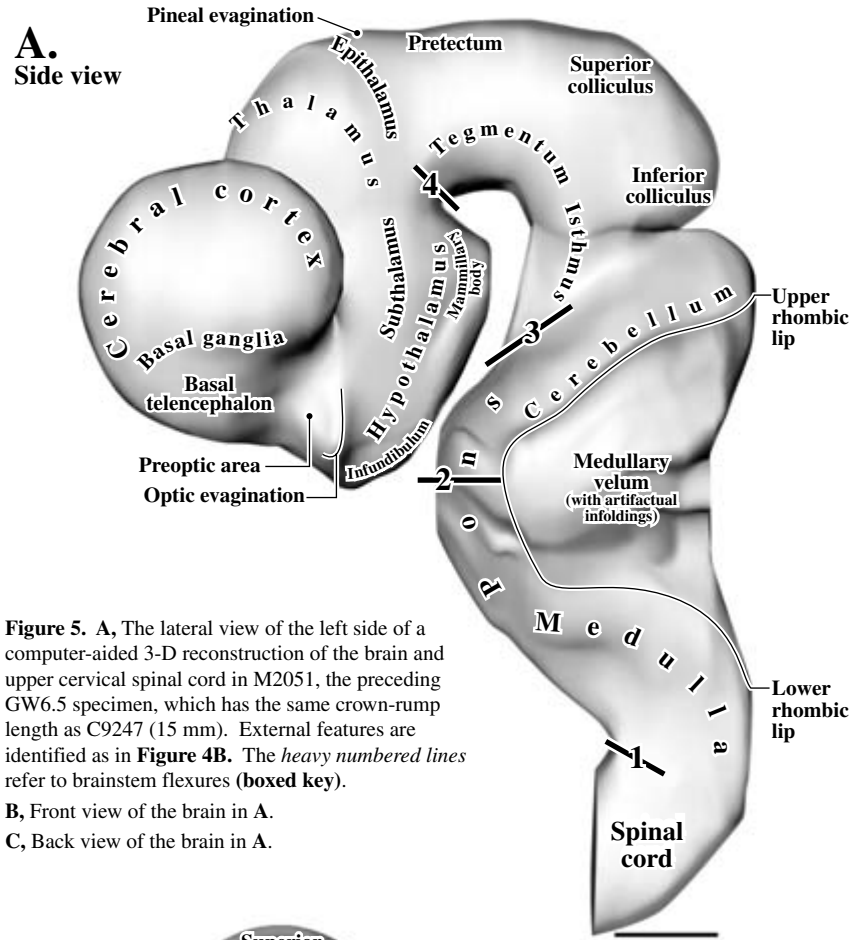
The telencephalon is the smallest overall brain structure, composed mainly of a "stockbuilding" neuroepithelium surrounding an expanding telencephalic superventricle. The primordial plexiform layer adjacent to the cortical neuroepithelium has only scattered Cajal-Retzius cells. Migrating neurons are adjacent to the basal ganglionic and basal telencephalic neuroepithelia forming mounds in the floor of the telencephalon. The olfactory neuroepithelium is indistinct; a few pioneer olfactory nerve fibers get near the brain surface but do not appear to contact it.

The diencephalon is the larger forebrain structure. The "stockbuilding" neuroepithelium surrounds a dorsally expanding superventricle in the future thalamic area. The neuroepithelium is shrinking in the hypothalamic and subthalamic areas where stem cells are depleted as they generate neurons. Migrating and settling young neurons accumulate in a thick band outside the neuroepithelium in the ventral diencephalic parenchyma adjacent to a thin subpial fibrous band.

The mesencephalon is a prominent arch between the mesencephalic and diencephalic flexures. The roof (tectum and pretectum) of the mesencephalon contains a stockbuilding neuroepithelium adjacent to a very thin layer of pioneer migrating neurons. In comparison to the GW7 specimens, bundles of fibers in the posterior commissure are distinct but smaller. The tegmental and isthmal neuroepithelia are rapidly unloading their neuronal progeny in dense bands in the adjacent parenchyma. The outermost clumps of young neurons appear to interact with axons in the thick subpial fiber band.

The rhombencephalon is the largest brain structure. Both the pons and medulla have neuroepithelia that are still relatively thick as stem cells unload their neuronal and glial progeny into an expanding parenchyma at a faster rate than the addition of new stem cells. The pons and medulla contain longitudinal bands of migrating cells, more dense just outside the neuroepithelium, less dense in the core, and again more dense adjacent to the subpial fiber band. The genu of the facial motor nerve forms fascicles adjacent to the neuroepithelium in both medial and lateral sections; these fascicles never reach the pial surface. What is presumed to be the solitary tract is the most prominent internal fiber tract in the medulla. Lateral sections show large peripheral sensory nerves contacting the brain. The mesencephalic nuclear neurons associated with the trigeminal nerve are migrating into the brain. The subpial fiber band is thicker where the axons from sensory ganglia enter the brain and appear to mingle with migrating neurons at the entry zones. As in the GW7 specimens, peripheral nerves have dense glia (Schwann cells), while central fiber tracts are clear. The cerebellum stands out as the most immature part of the rhombencephalon. All parts of the cerebellar neuroepithelium are stockbuilding neuronal and glial stem cells. Relatively indistinct layers are in the cerebellar transitional field.

EXTERNAL FEATURES OF THE GW6.5 BRAIN



A perfect sagittal cut through the brain is parallel to the midline in both horizontal and vertical directions. C9247 is a rare perfectly cut sagittal specimen.

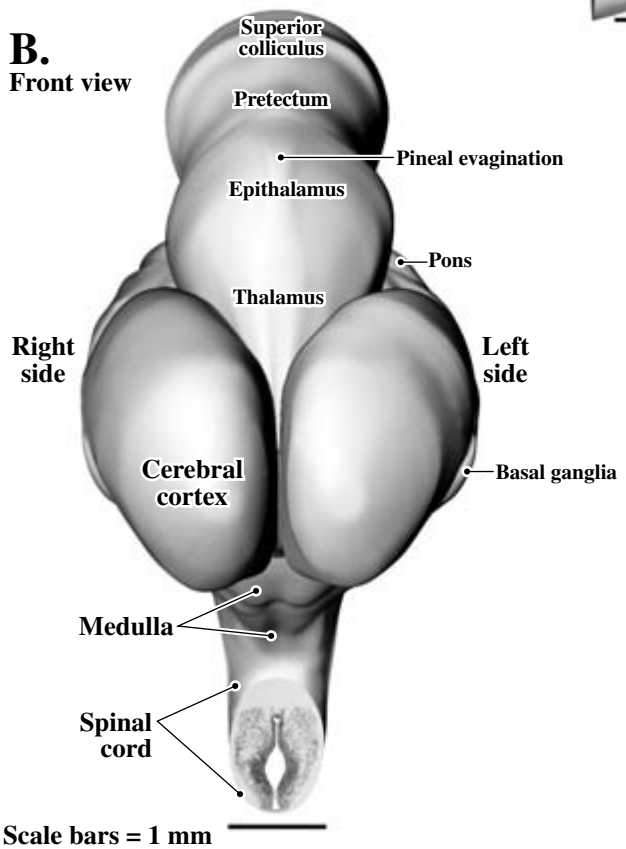
BRAINSTEM FLEXURES

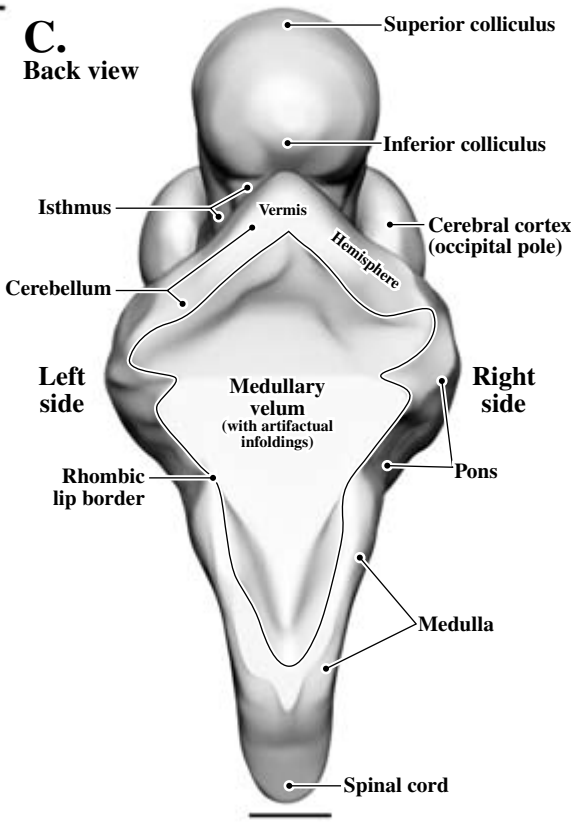
1. Medullary
2. Pontine
3. Mesencephalic
4. Diencephalic

Figure 5. A, The lateral view of the left side of a computer-aided 3-D reconstruction of the brain and upper cervical spinal cord in M2051, the preceding GW6.5 specimen, which has the same crown-rump length as C9247 (15 mm). External features are identified as in **Figure 4B.** The *heavy numbered lines* refer to brainstem flexures **(boxed key)**.

B, Front view of the brain in **A**.

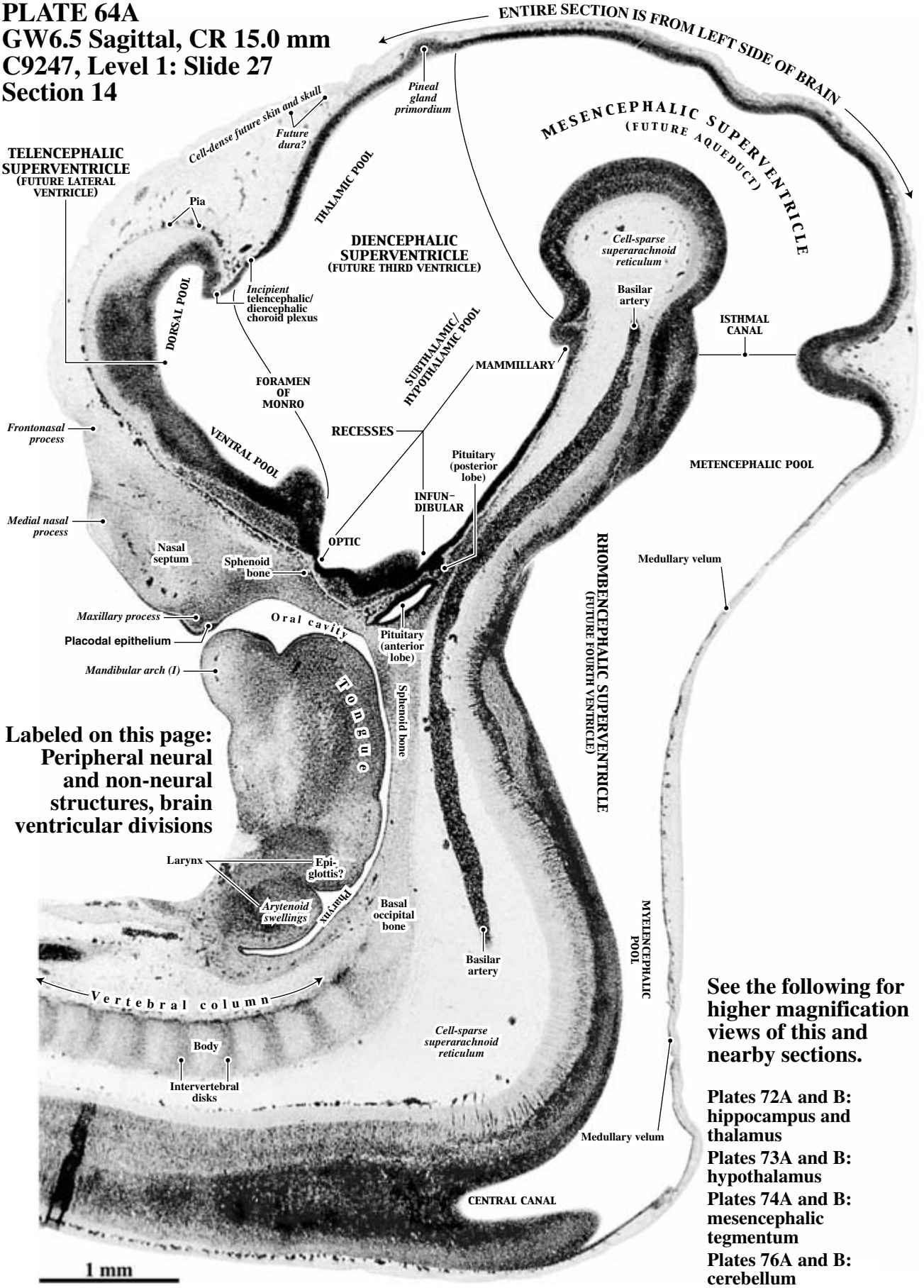
C, Back view of the brain in **A**.





Scale bars = 1 mm

PLATE 64A
GW6.5 Sagittal, CR 15.0 mm
C9247, Level 1: Slide 27
Section 14



Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

See the following for higher magnification views of this and nearby sections.

Plates 72A and B: hippocampus and thalamus

Plates 73A and B: hypothalamus

Plates 74A and B: mesencephalic tegmentum

Plates 76A and B: cerebellum

PLATE 64B

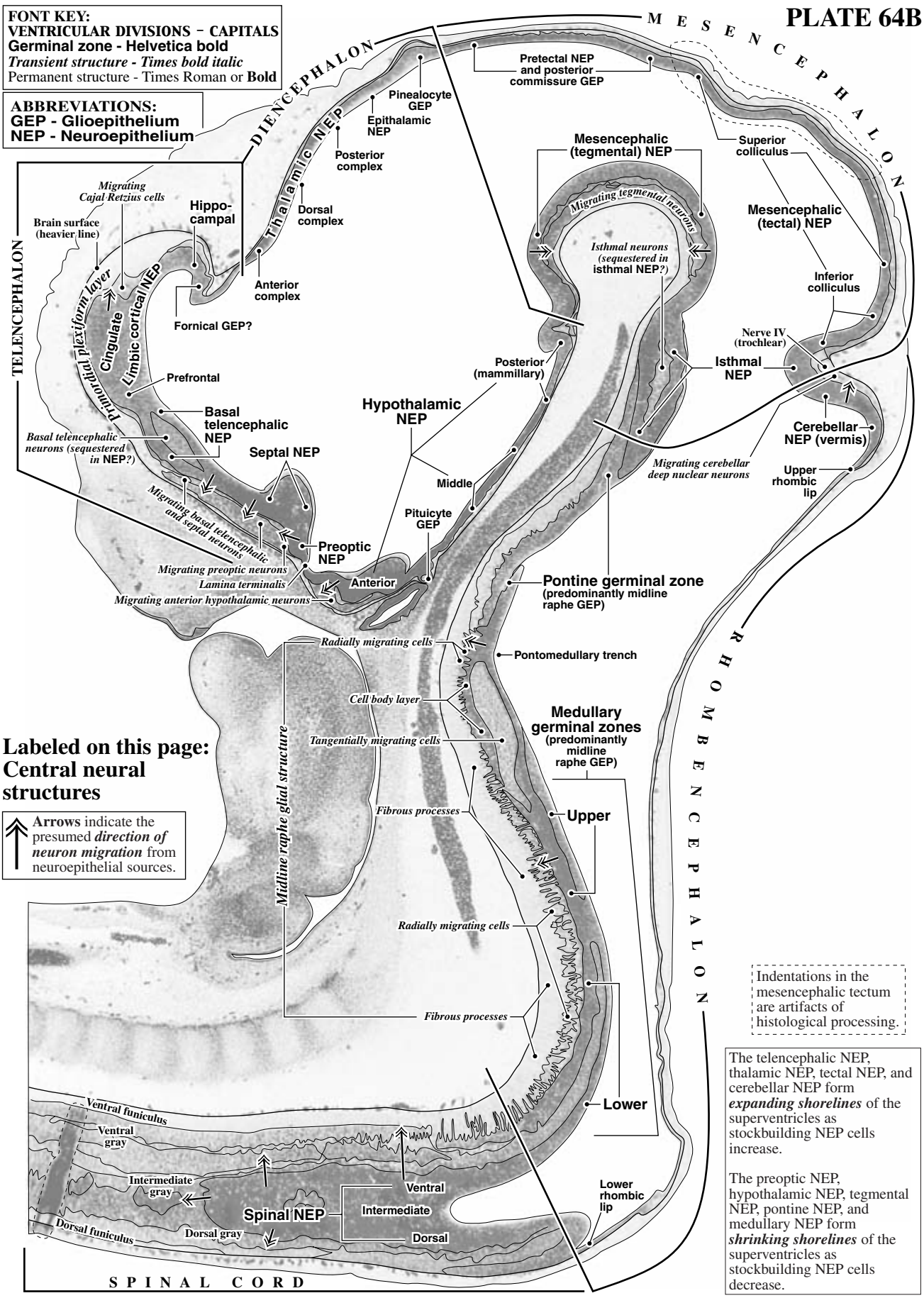
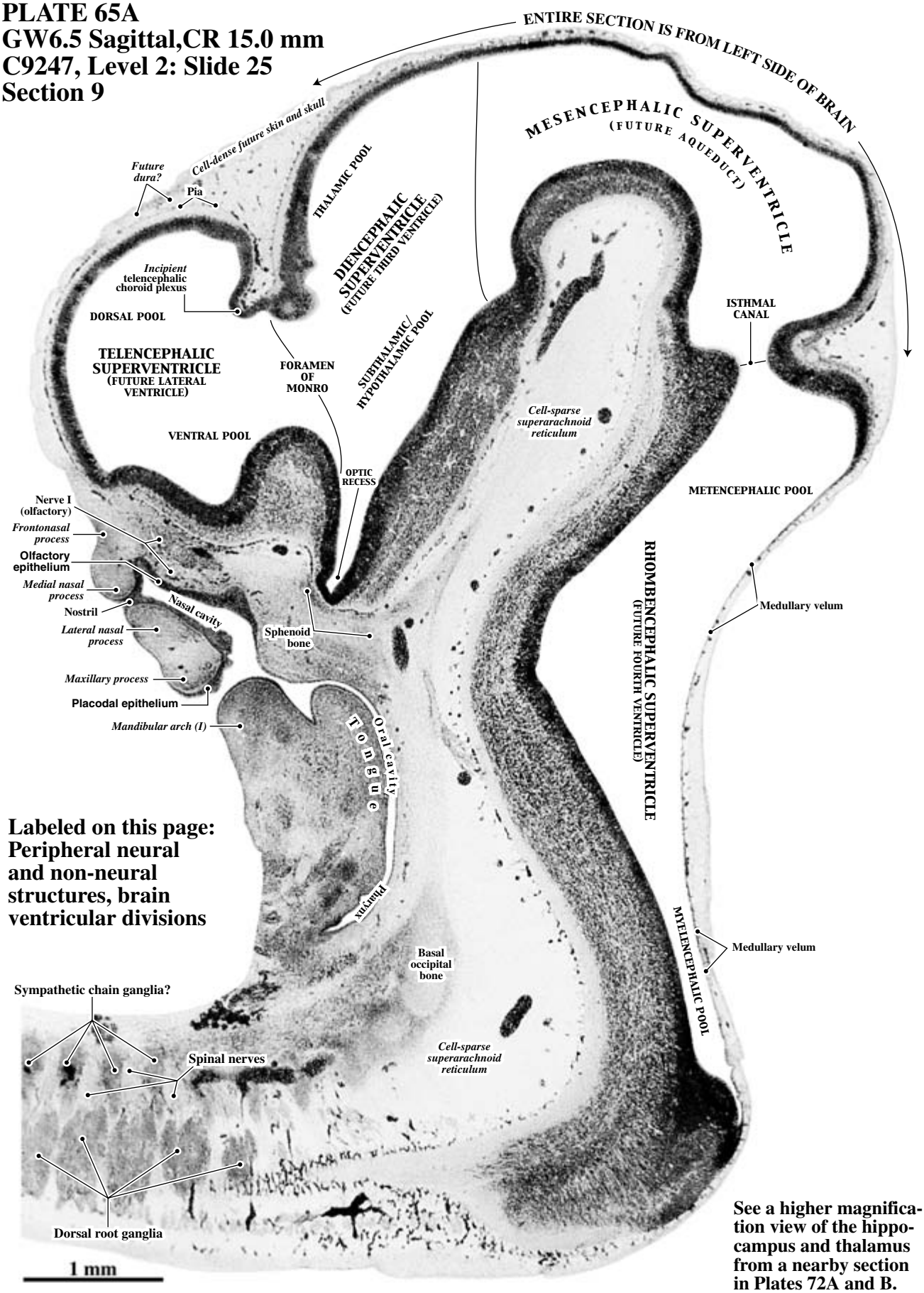

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
MESENCEPHALON
DIENCEPHALON
TELENCEPHALON
RHOMBENCEPHALON
SPINAL CORD
Pretectal NEP and posterior commissure GEP
Pinealocyte GEP
Epithalamic NEP
Posterior complex
Thalamic NEP
Dorsal complex
Anterior complex
Fornical GEP?
Migrating Cajal Retzius cells
Brain surface (heavier line)
Hippo-campal
Primordial plexiform layer
Cingulate
Limbic cortical NEP
Prefrontal
Basal telencephalic NEP
Basal telencephalic neurons (sequestered in NEP?)
Septal NEP
Migrating basal telencephalic and septal neurons
Preoptic NEP
Migrating preoptic neurons
Lamina terminalis
Migrating anterior hypothalamic neurons
Anterior
Hypothalamic NEP
Middle
Posterior (mammillary)
Pituicyte GEP
Mesencephalic (tegmental) NEP
Migrating tegmental neurons
Isthmal neurons (sequestered in isthmal NEP?)
Superior colliculus
Mesencephalic (tectal) NEP
Inferior colliculus
Nerve IV (trochlear)
Isthmal NEP
Cerebellar NEP (vermis)
Upper rhombic lip
Migrating cerebellar deep nuclear neurons
Pontine germinal zone (predominantly midline raphe GEP)
Radially migrating cells
Pontomedullary trench
Cell body layer
Tangentially migrating cells
Medullary germinal zones (predominantly midline raphe GEP)
Midline raphe glial structure
Fibrous processes
Upper
Radially migrating cells
Fibrous processes
Lower
Lower rhombic lip
Ventral funiculus
Ventral gray
Intermediate gray
Dorsal funiculus
Dorsal gray
Spinal NEP
Ventral
Intermediate
Dorsal
Labeled on this page: Central neural structures
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Indentations in the mesencephalic tectum are artifacts of histological processing.
The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form expanding shorelines of the superventricles as stockbuilding NEP cells increase.
The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form shrinking shorelines of the superventricles as stockbuilding NEP cells decrease.

PLATE 65A
GW6.5 Sagittal,CR 15.0 mm
C9247, Level 2: Slide 25
Section 9



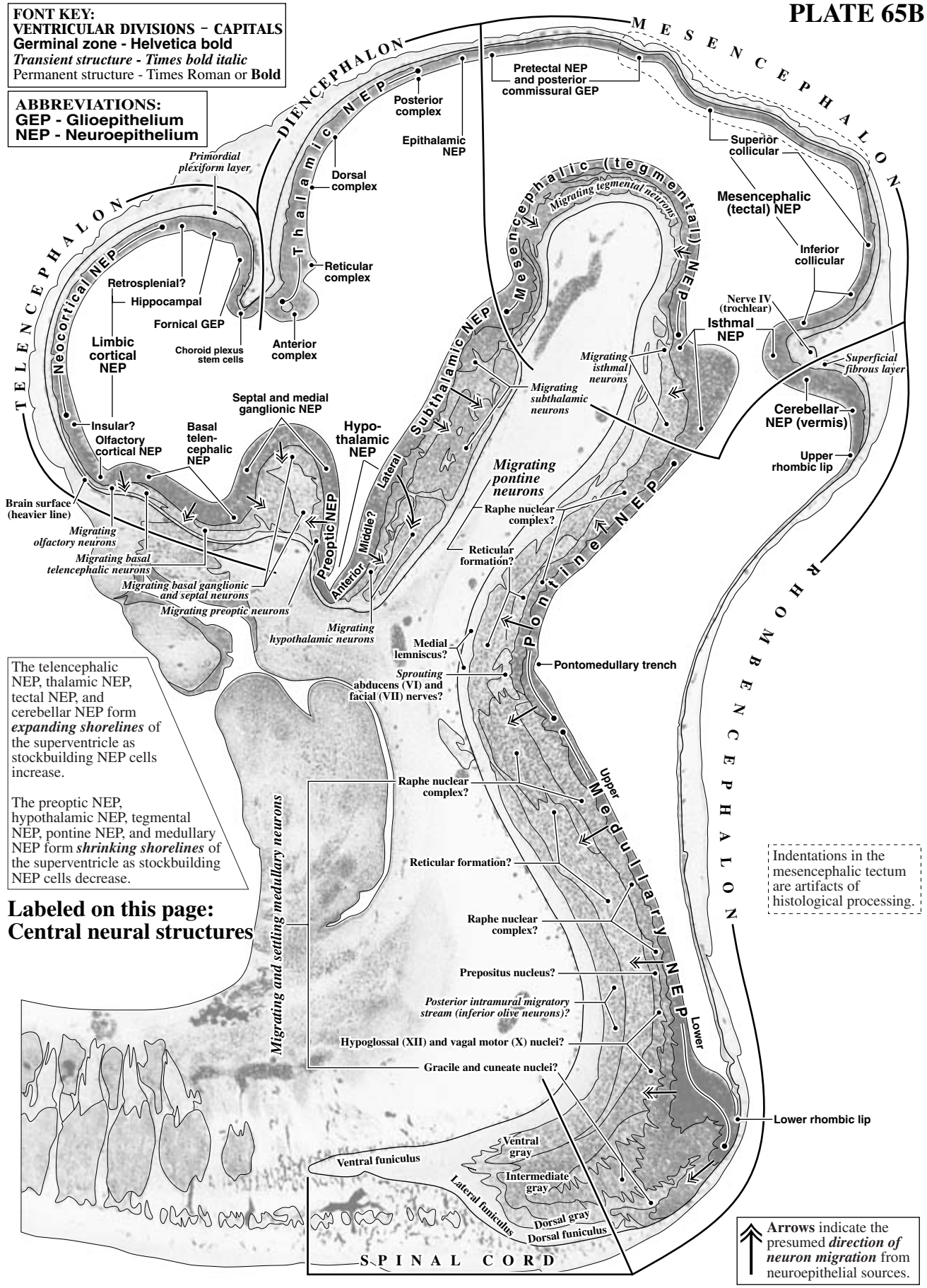
Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

See a higher magnification view of the hippocampus and thalamus from a nearby section in Plates 72A and B.

PLATE 65B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

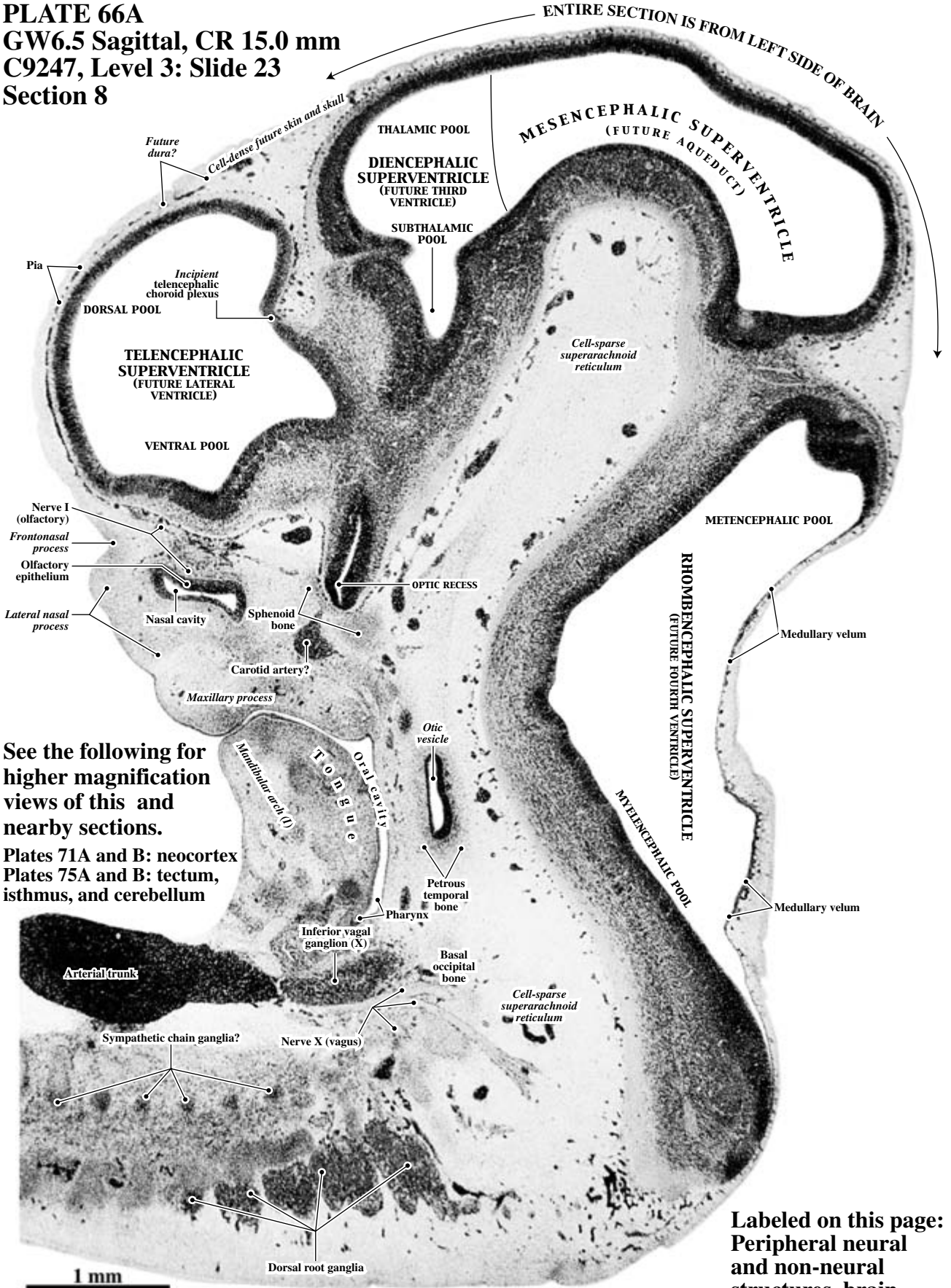
The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Labeled on this page: Central neural structures

Indentations in the mesencephalic tectum are artifacts of histological processing.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 66A
GW6.5 Sagittal, CR 15.0 mm
C9247, Level 3: Slide 23
Section 8



See the following for higher magnification views of this and nearby sections.

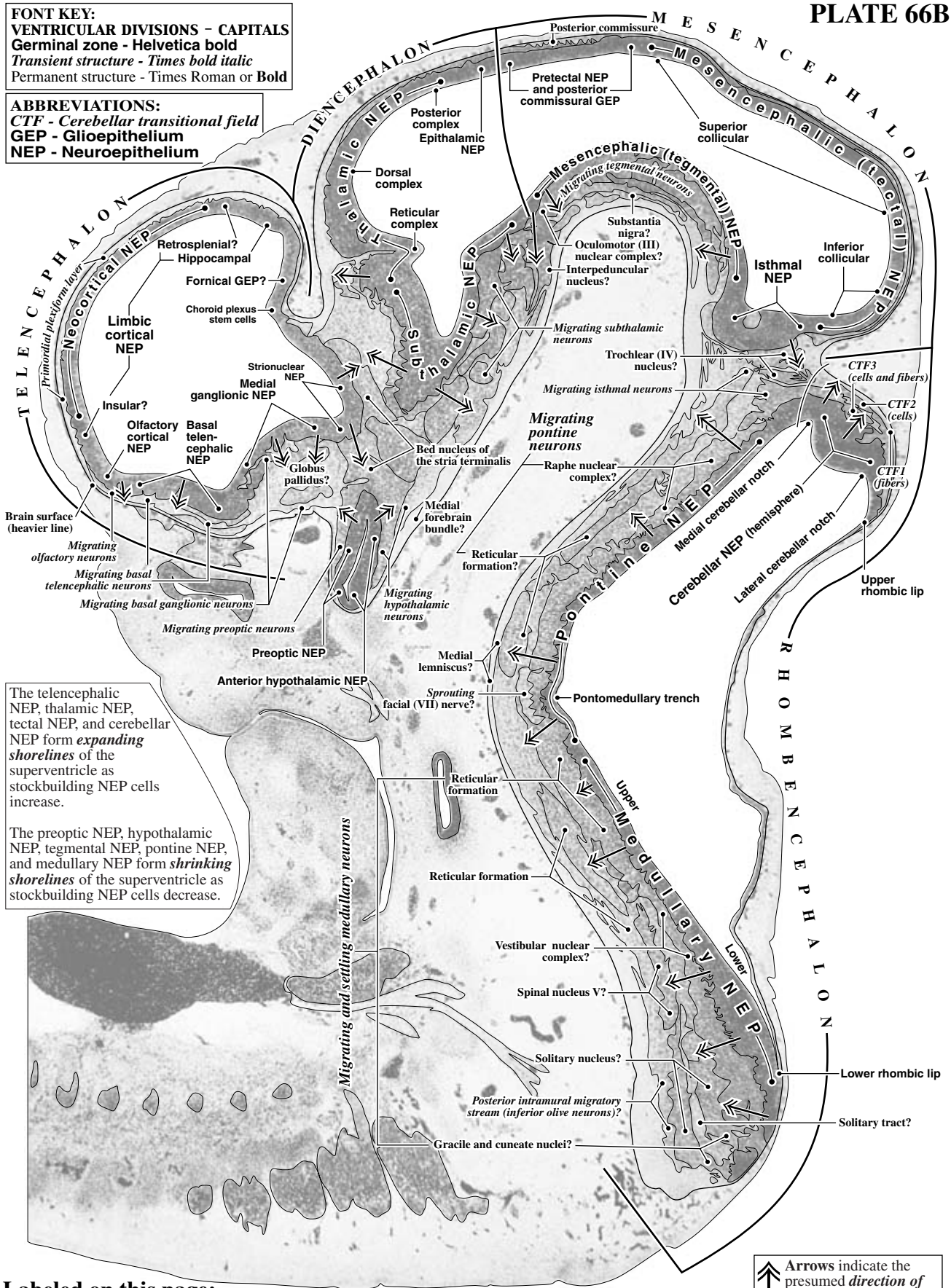
Plates 71A and B: neocortex
Plates 75A and B: tectum, isthmus, and cerebellum

Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 66B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium



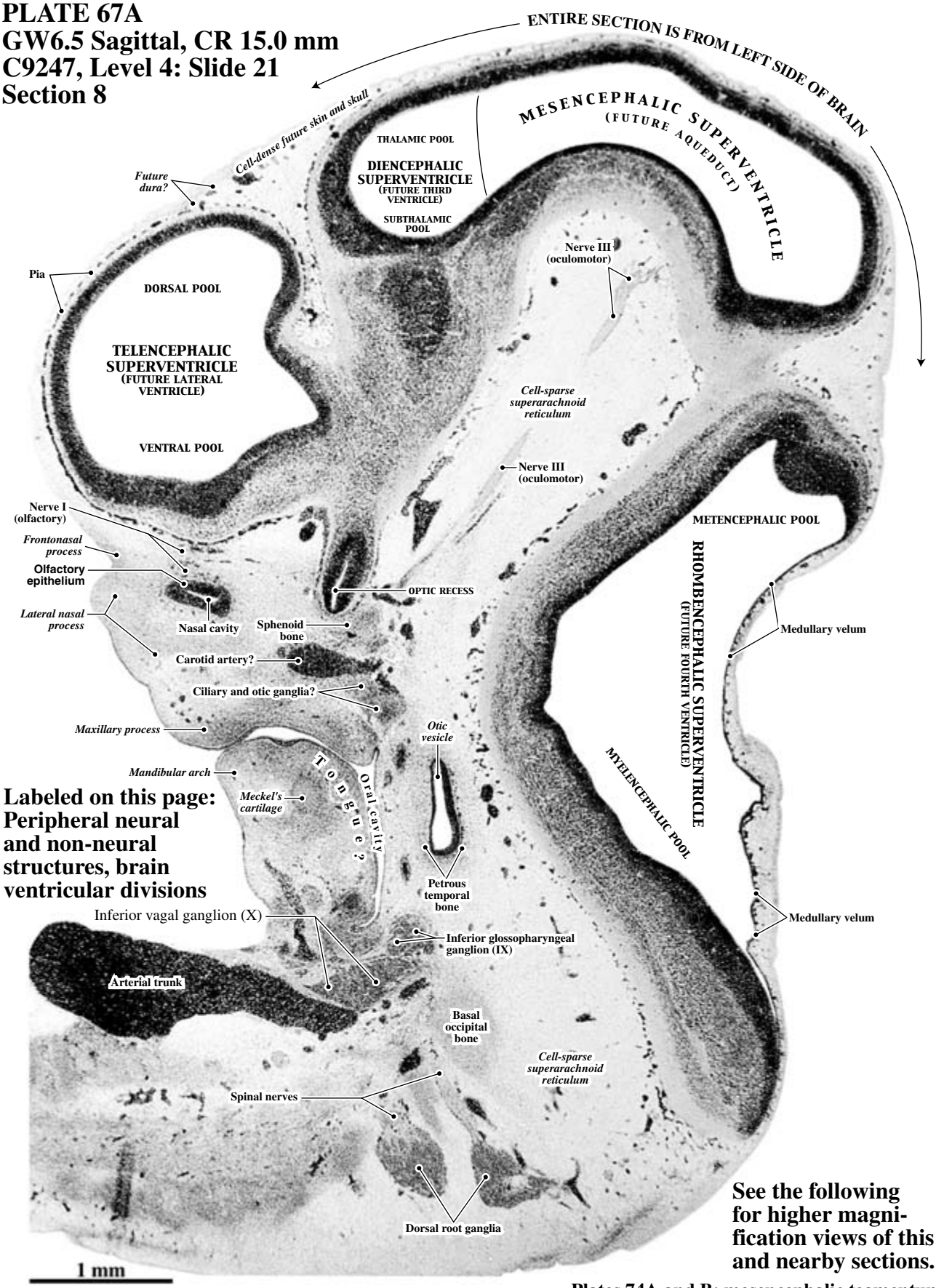
The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Labeled on this page:
Central neural structures

PLATE 67A
GW6.5 Sagittal, CR 15.0 mm
C9247, Level 4: Slide 21
Section 8



Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

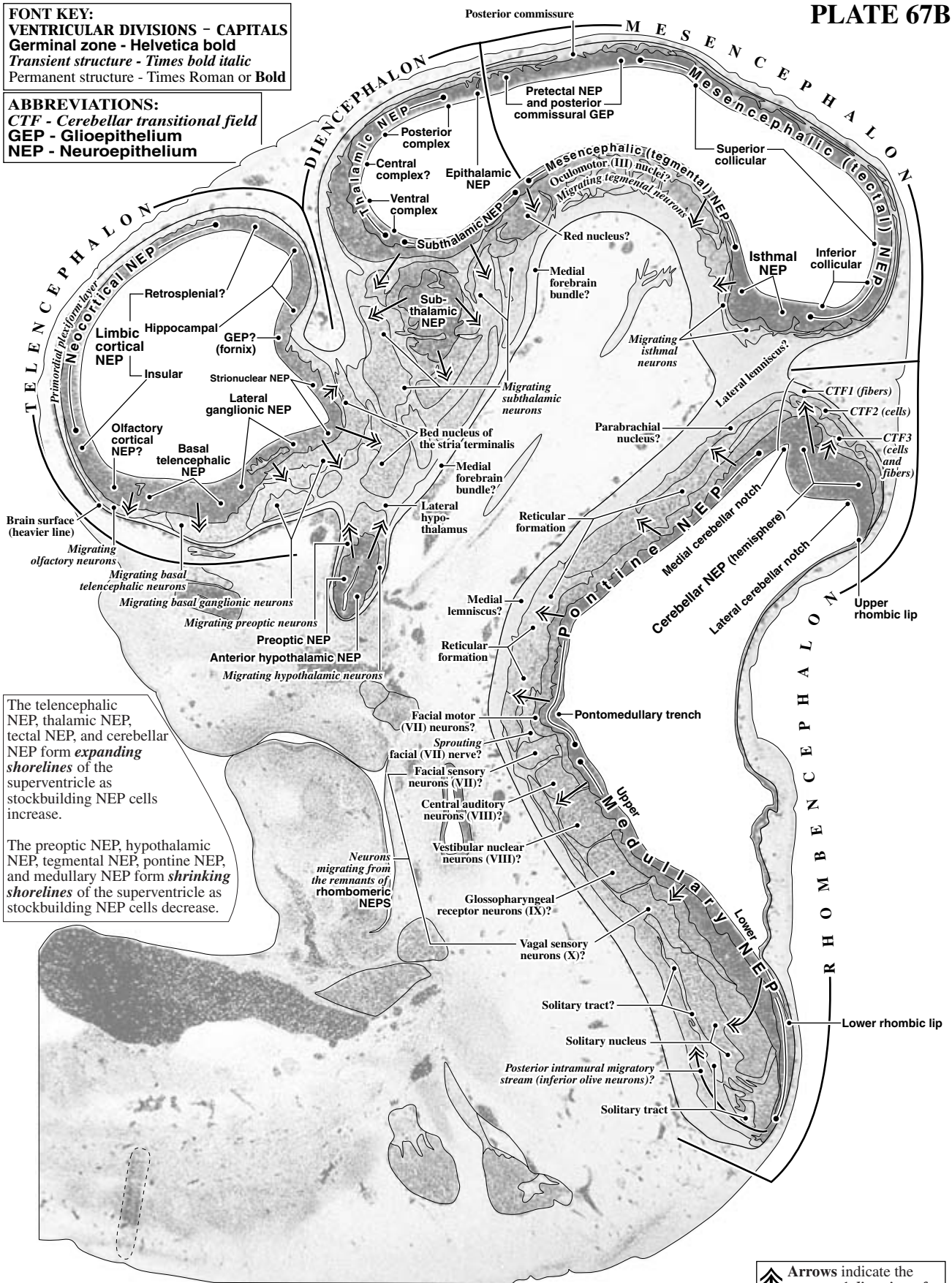
See the following for higher magnification views of this and nearby sections.

Plates 74A and B: mesencephalic tegmentum
Plates 81A and B: pons and upper medulla

PLATE 67B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

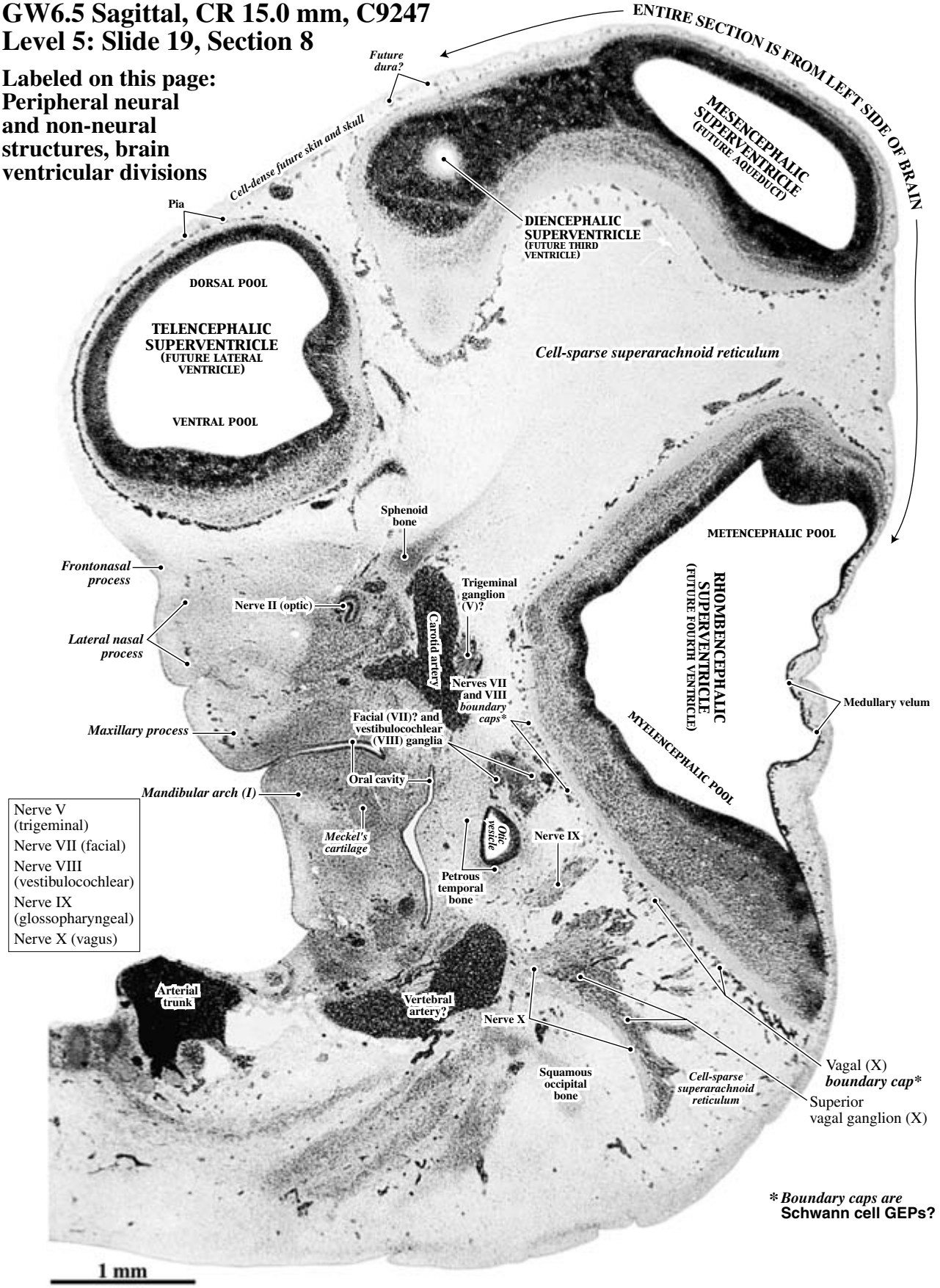
The preoptic NEP, hypothalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Labeled on this page:
Central neural structures

PLATE 68A
GW6.5 Sagittal, CR 15.0 mm, C9247
Level 5: Slide 19, Section 8

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



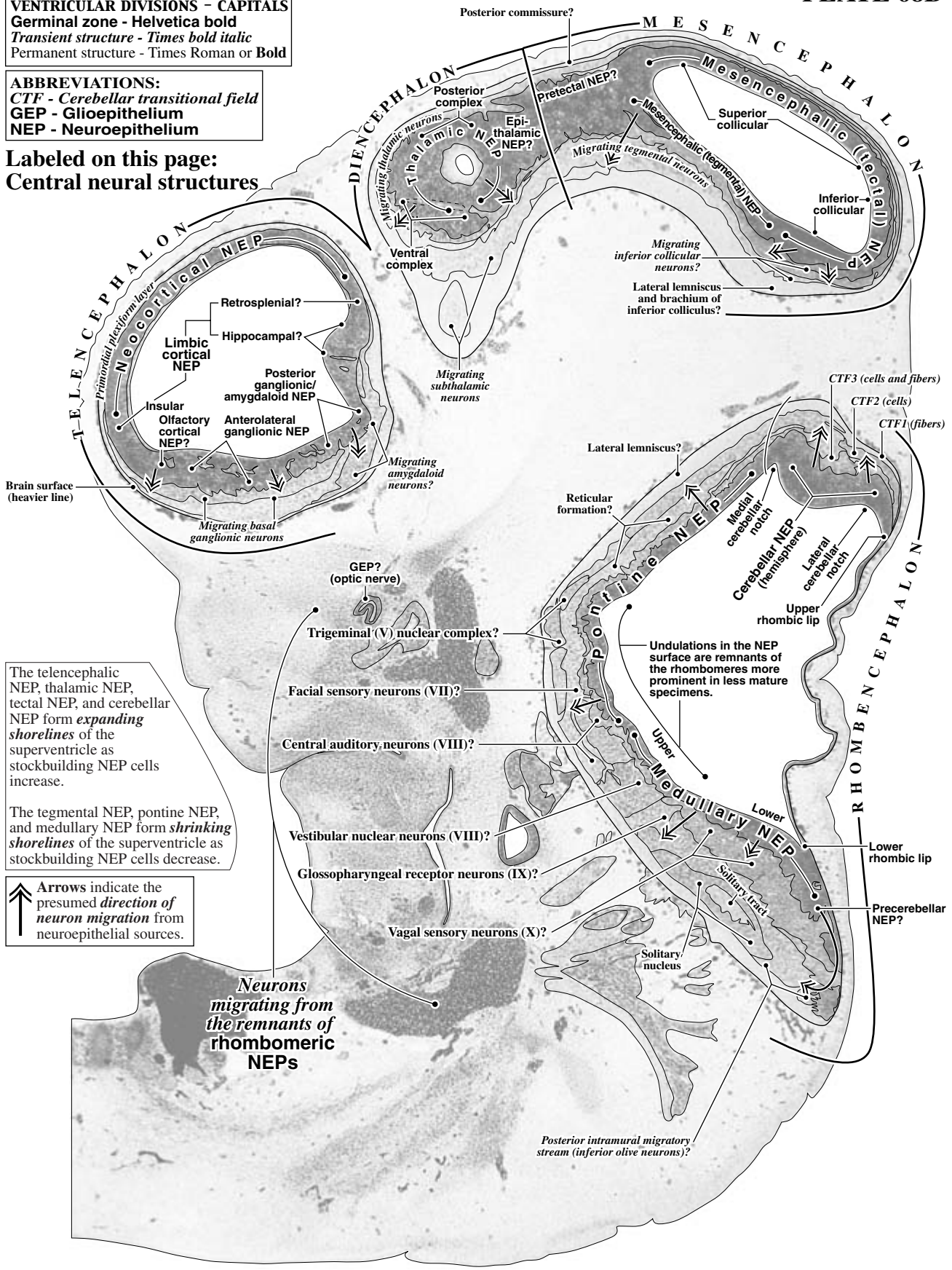
* *Boundary caps are* **Schwann cell GEPs?**

PLATE 68B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

Labeled on this page:
Central neural structures



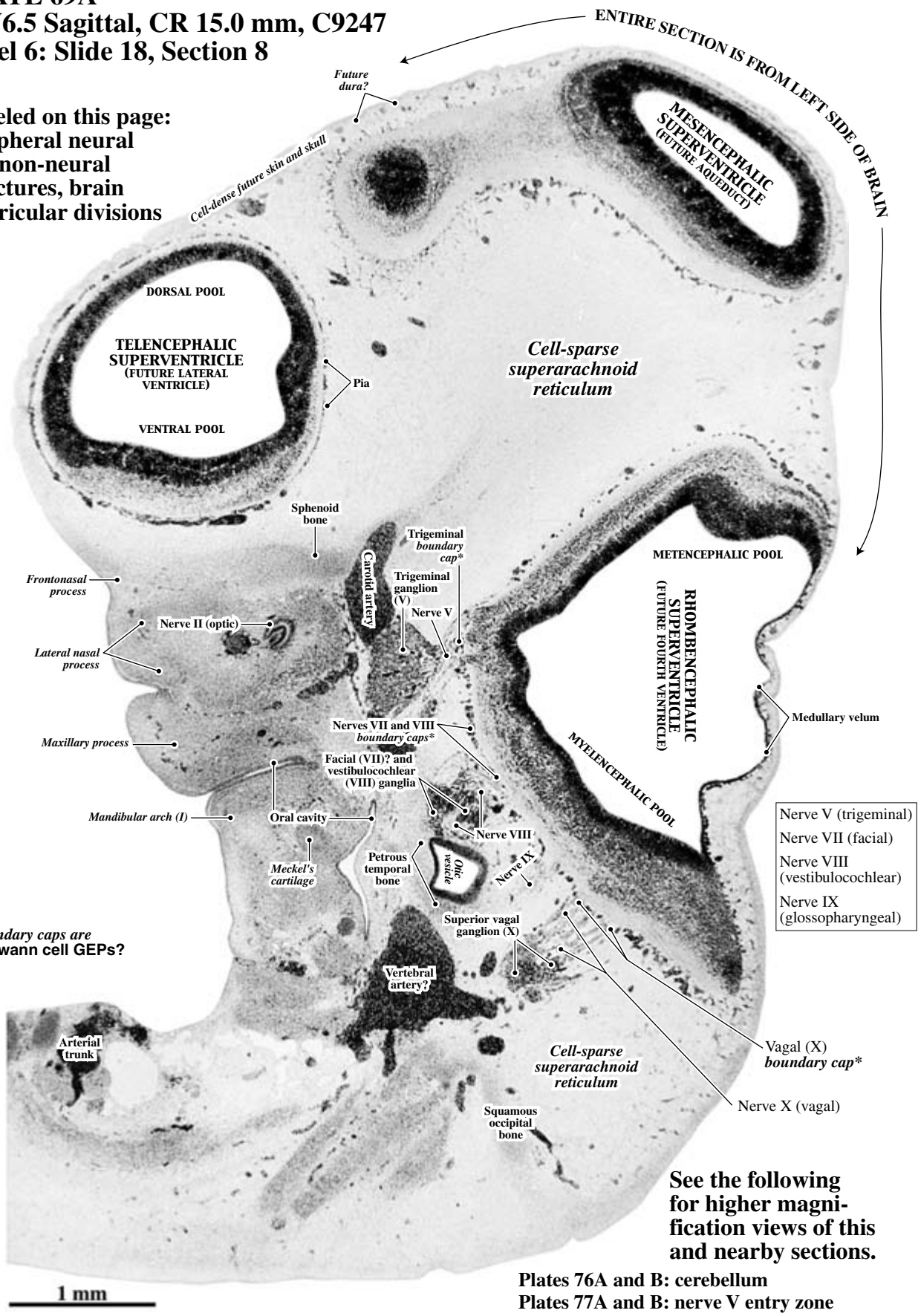
The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 69A
GW6.5 Sagittal, CR 15.0 mm, C9247
Level 6: Slide 18, Section 8

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)

* *Boundary caps are* **Schwann cell GEPs?**

See the following for higher magnification views of this and nearby sections.

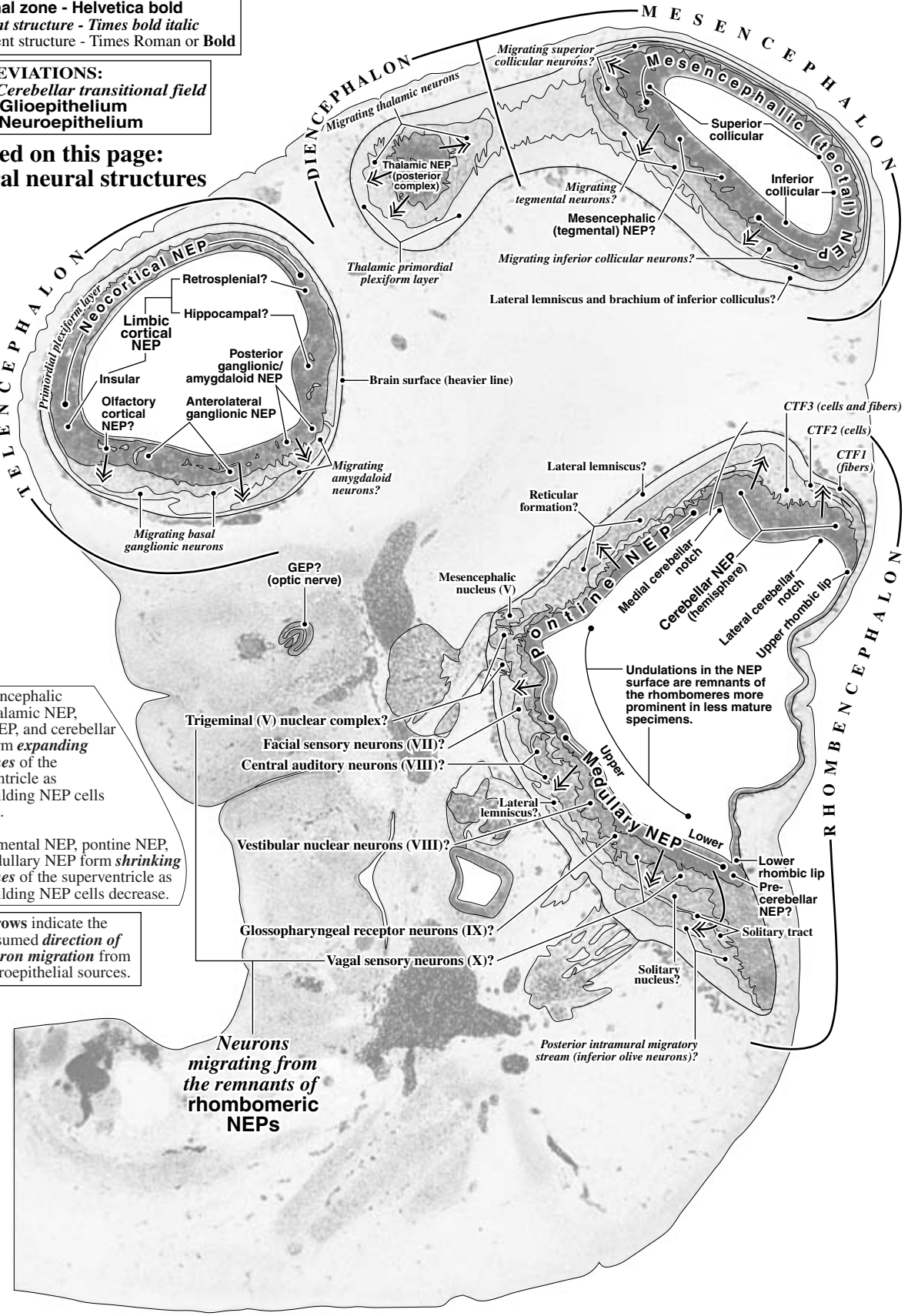
Plates 76A and B: cerebellum
Plates 77A and B: nerve V entry zone
Plates 80A and B: nerves IX and X entry zones

PLATE 69B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

Labeled on this page:
Central neural structures



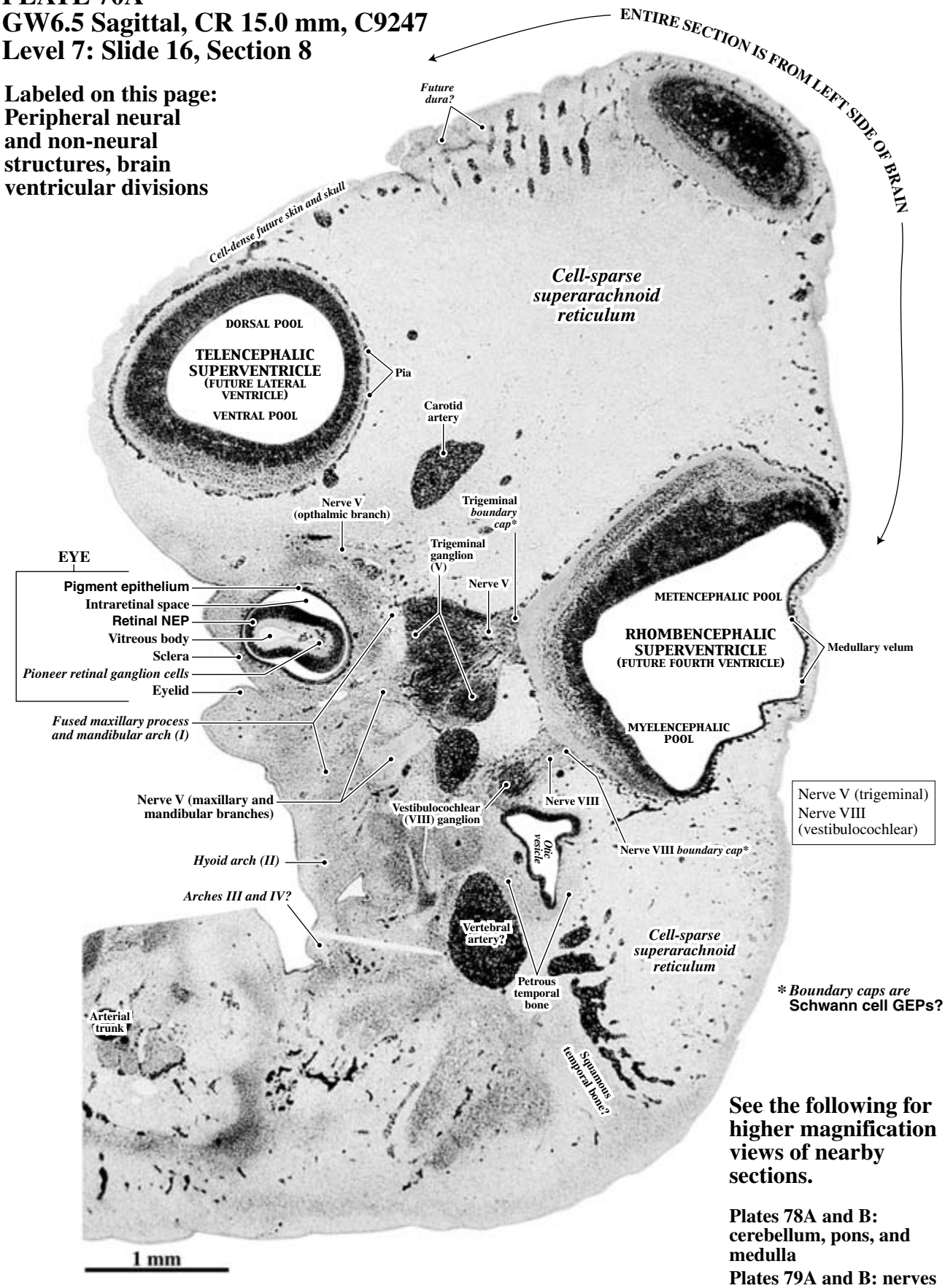
The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 70A
GW6.5 Sagittal, CR 15.0 mm, C9247
Level 7: Slide 16, Section 8

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



Nerve V (trigeminal)
Nerve VIII (vestibulocochlear)

* *Boundary caps are* Schwann cell GEPs?

See the following for higher magnification views of nearby sections.

Plates 78A and B: cerebellum, pons, and medulla

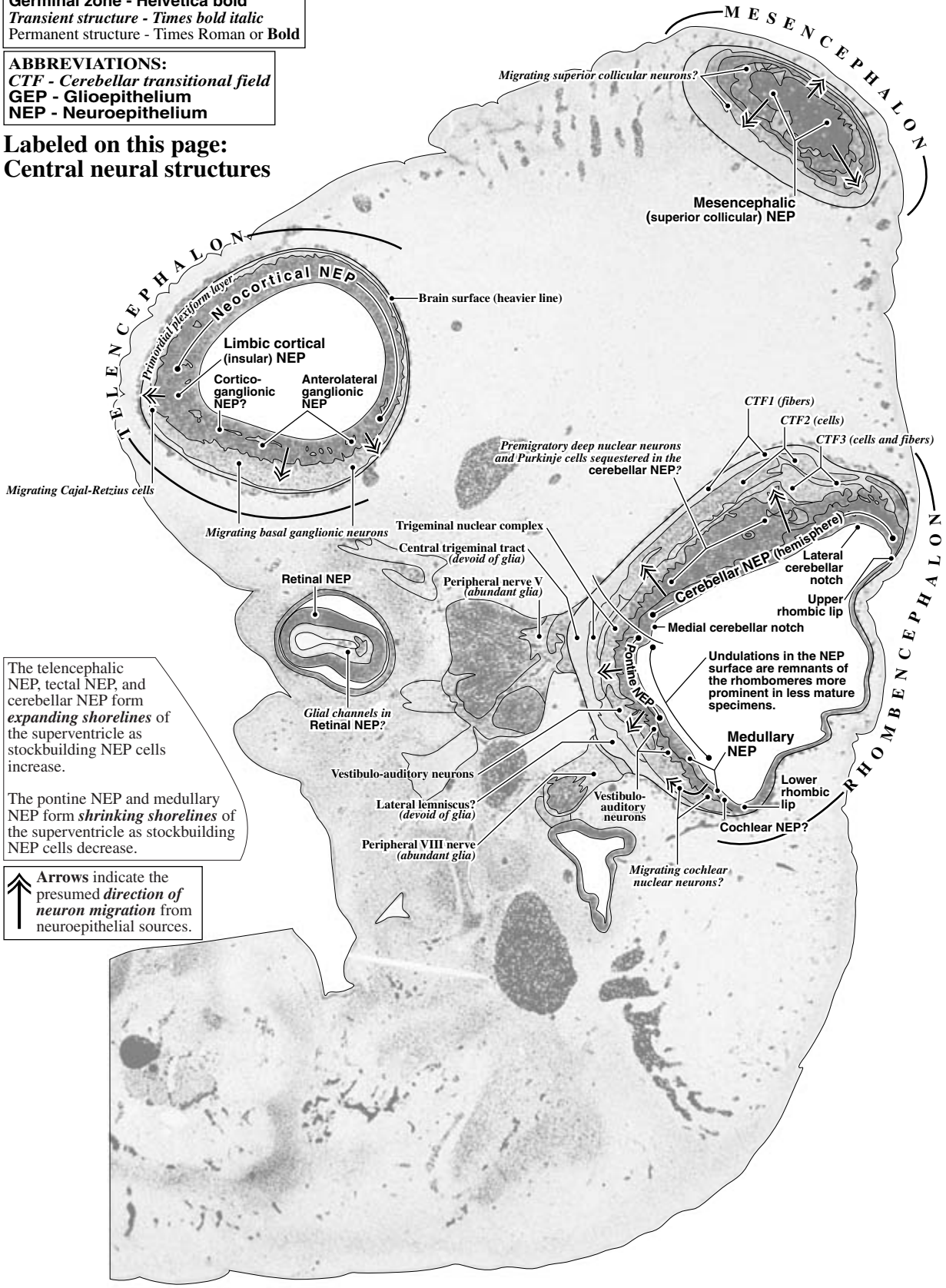
Plates 79A and B: nerves V and VIII entry zones

PLATE 70B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

Labeled on this page:
Central neural structures



The telencephalic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The pontine NEP and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 71A **DORSAL NEOCORTEX**

GW6.5 Sagittal, CR 15.0 mm, C9247
Level 3: Slide 23, Section 8

See Level 3 in Plates 66A and B.

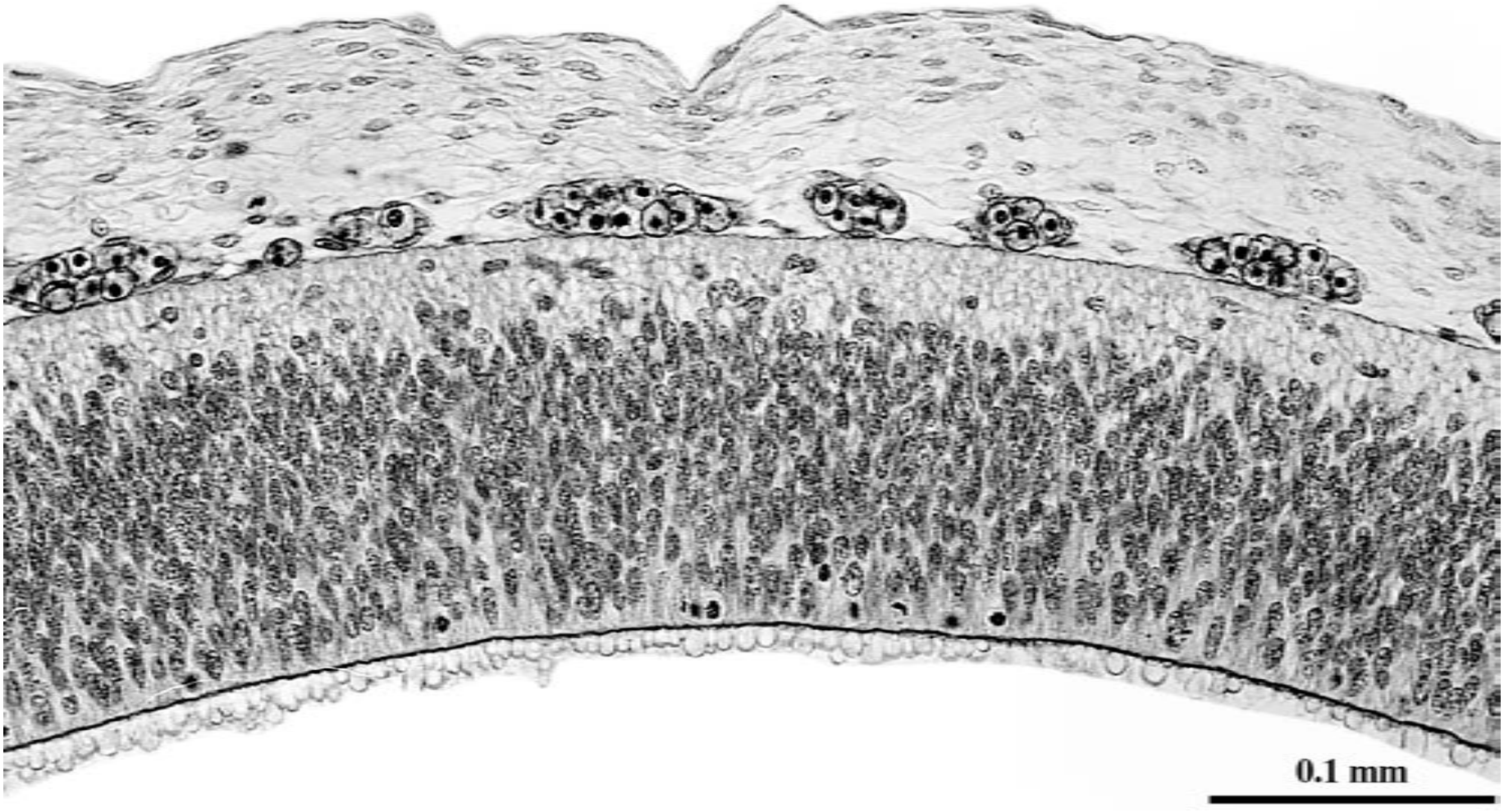
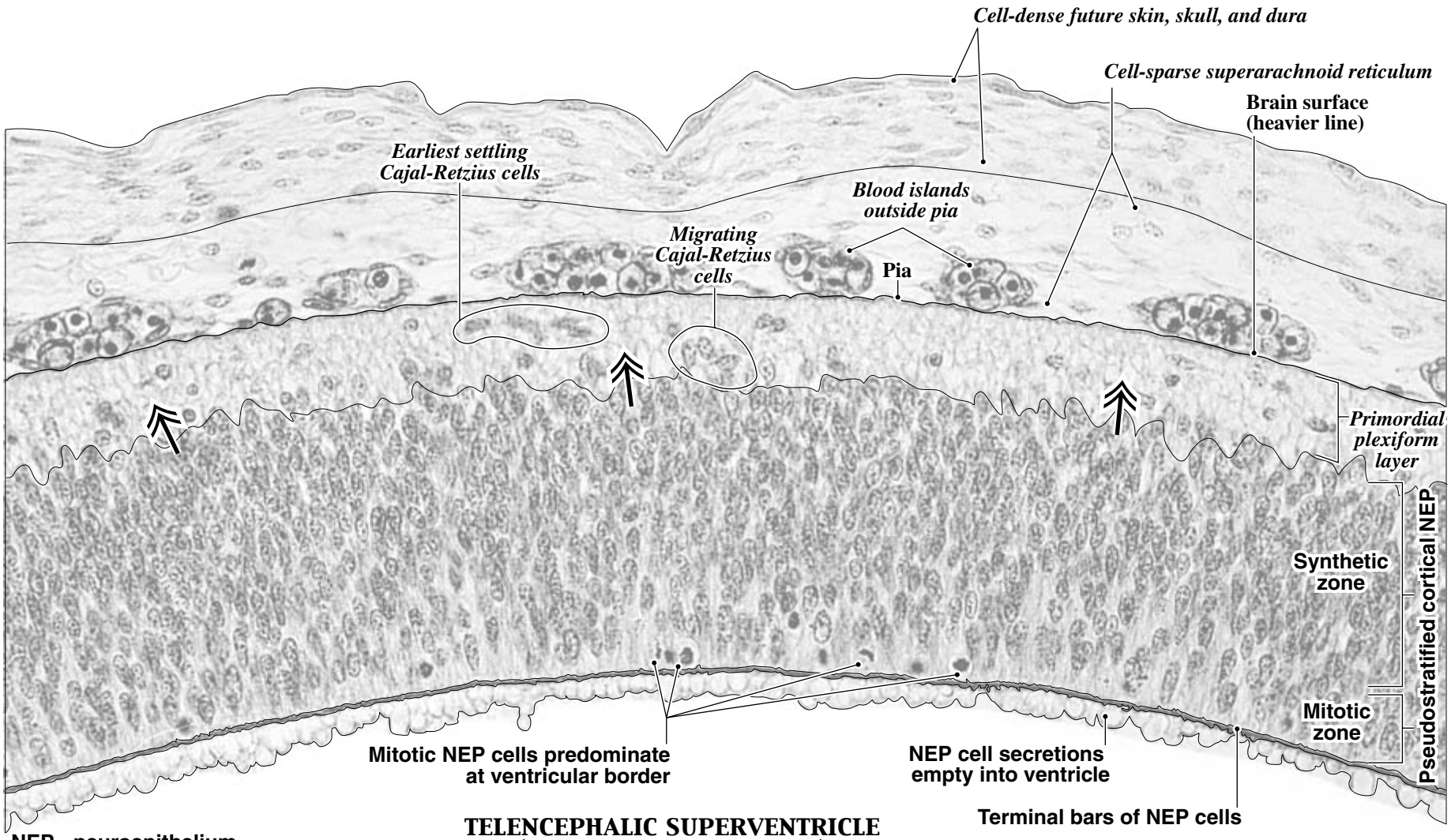


PLATE 71B



TELENCEPHALIC SUPERVENTRICLE
(FUTURE LATERAL VENTRICLE)

NEP - neuroepithelium

The **cortical NEP** is in the "stockbuilding" phase when neural stem cells are increasing while few neurons (mainly Cajal-Retzius cells) are being generated.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 72A

HIPPOCAMPUS AND THALAMUS

GW6.5 Sagittal
CR 15.0 mm
C9247
Between
Levels 1 and 2:
Slide 26
Section 9

See Level 1 in Plates 64A and B; Level 2 in Plates 65A and B.

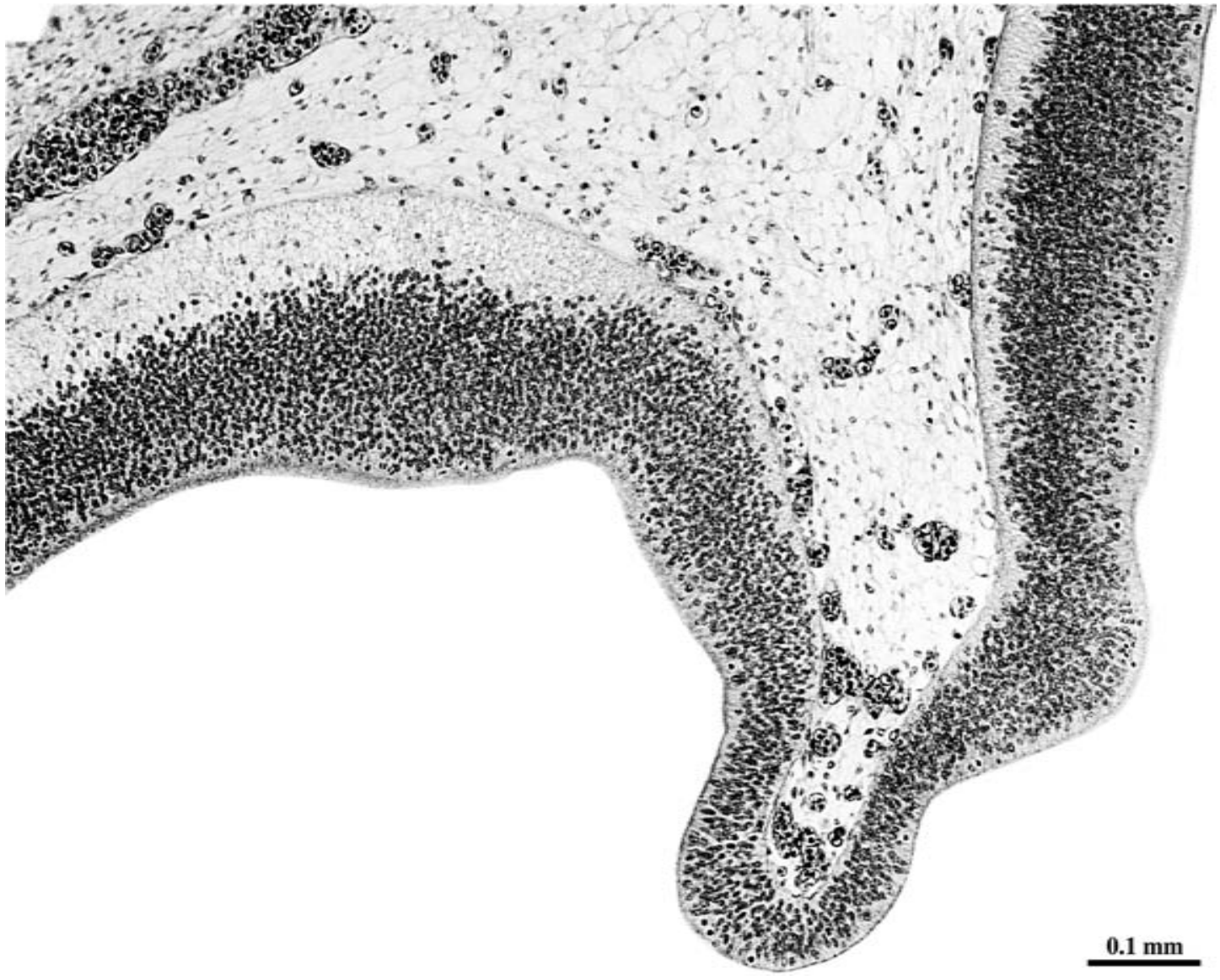
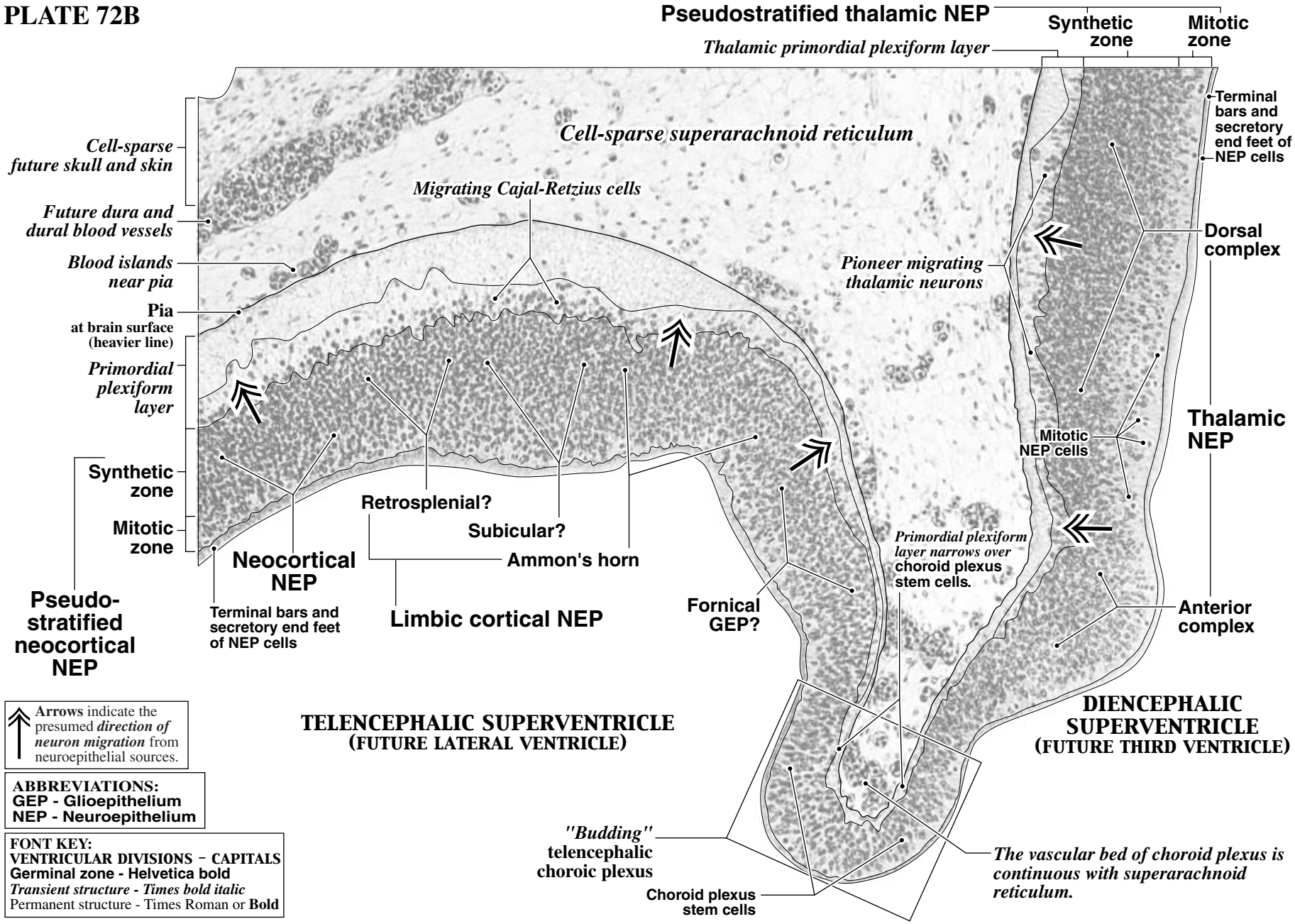


PLATE 72B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 73A

GW6.5 Sagittal, CR 15.0 mm, C9247
Level 1: Slide 27, Section 14

HYPOTHALAMUS
See Level 1 in Plates 64A and B.

A. Anterior hypothalamus and infundibular recess

B. Posterior hypothalamus and mammillary recess

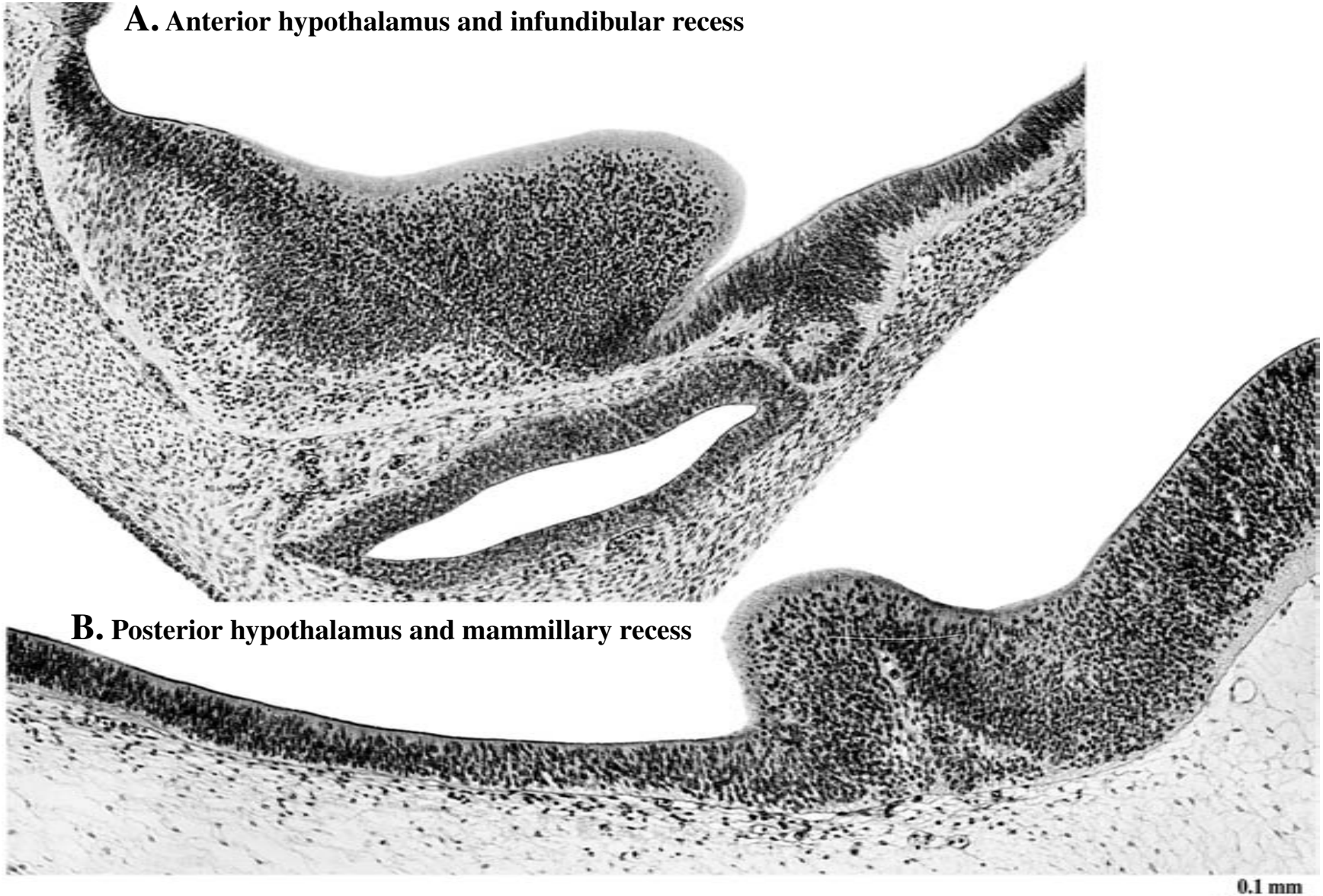


PLATE 73B

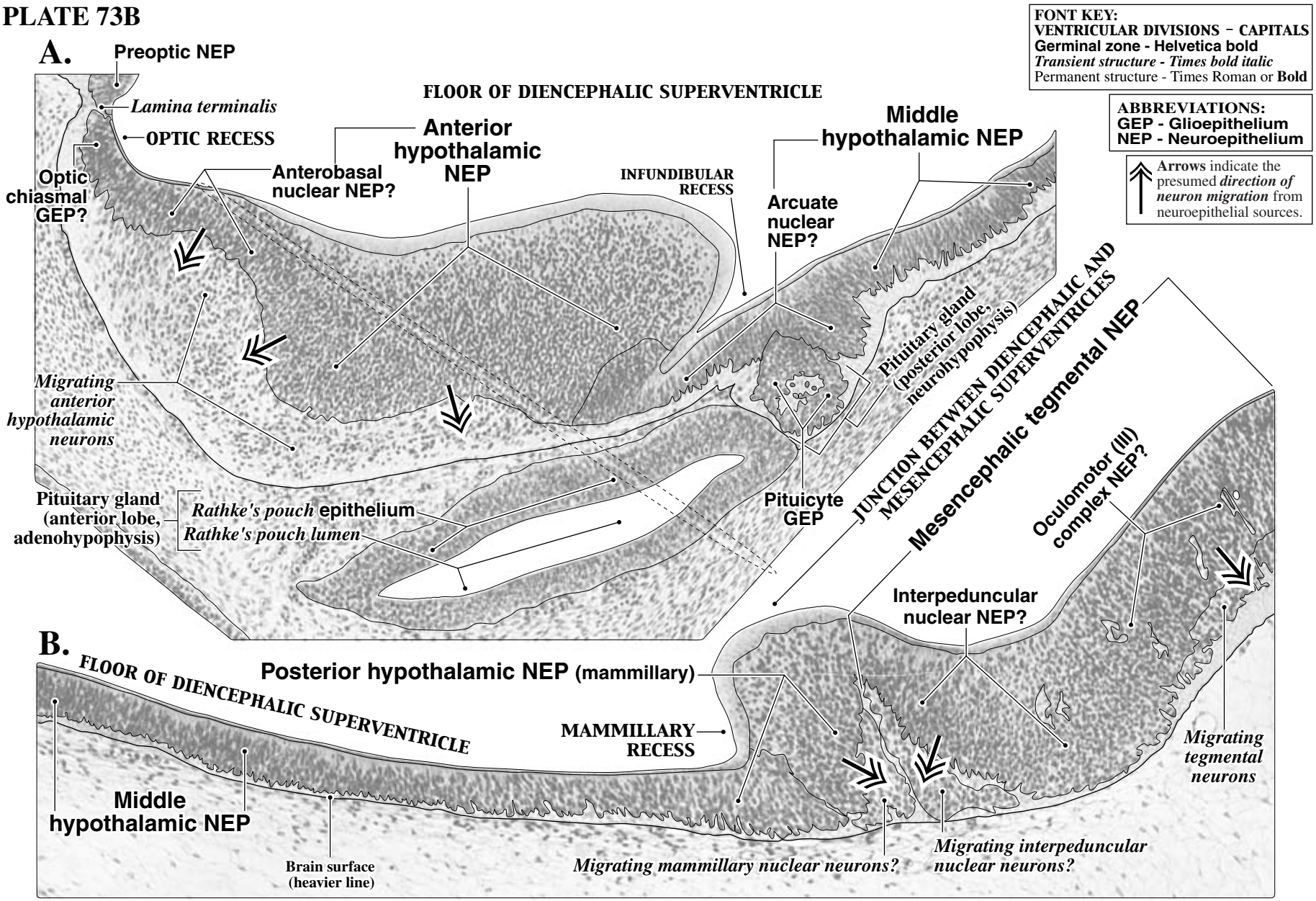
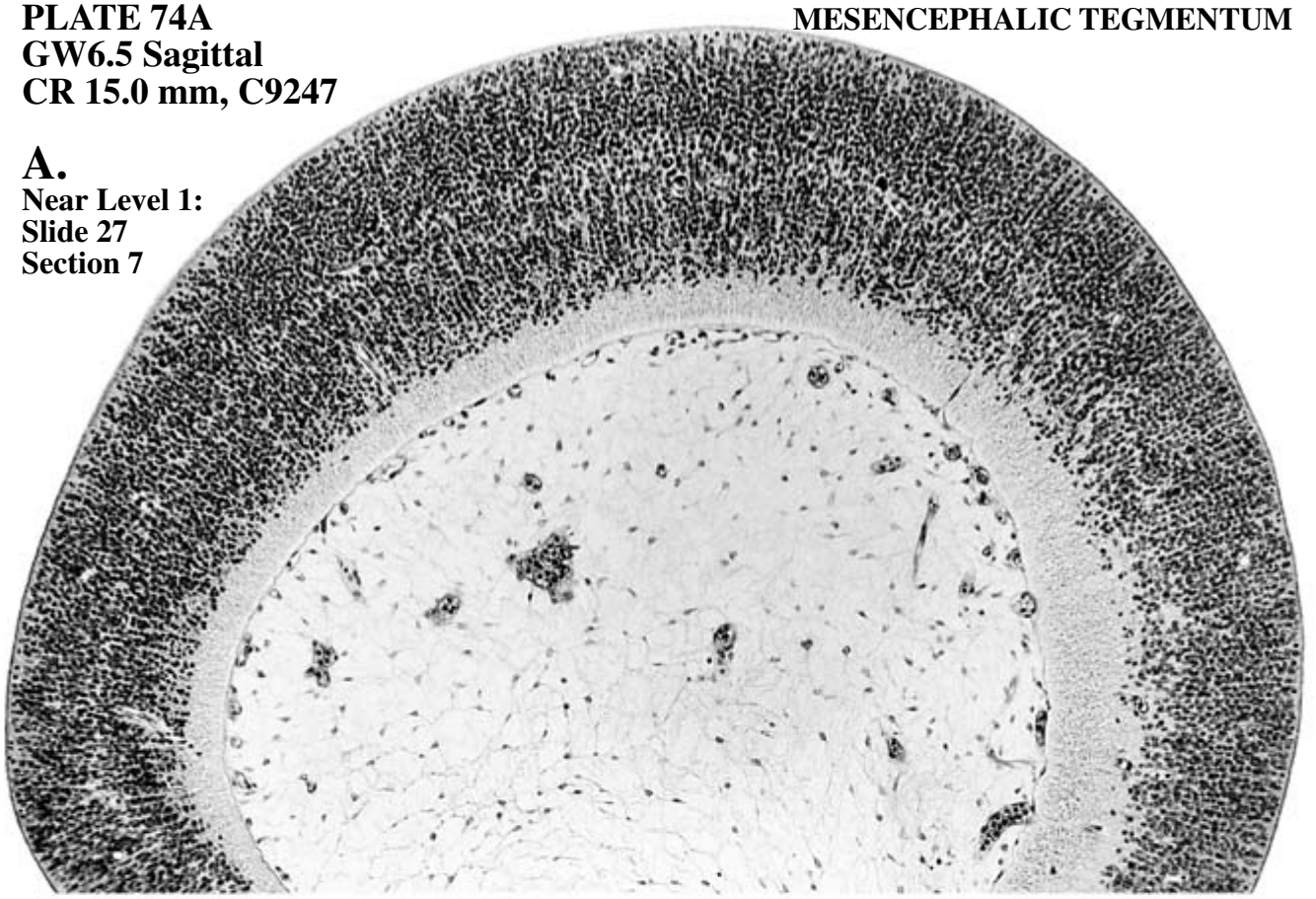
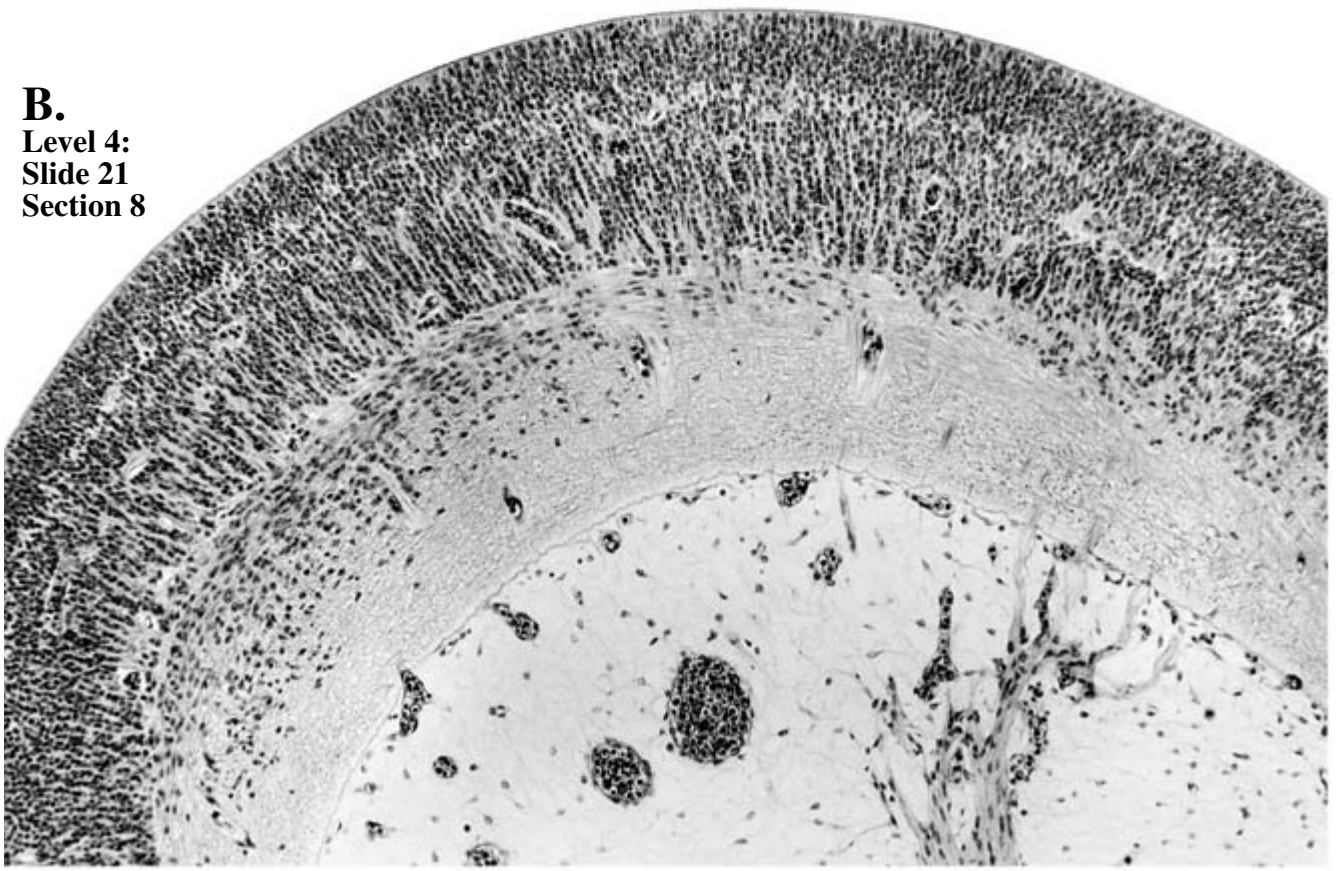

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
A.
Preoptic NEP
Lamina terminalis
OPTIC RECESS
FLOOR OF DIENCEPHALIC SUPERVENTRICLE
Optic chiasmal GEP?
Anterobasal nuclear NEP?
Anterior hypothalamic NEP
INFUNDIBULAR RECESS
Middle hypothalamic NEP
Arcuate nuclear NEP?
Pituitary gland (posterior lobe, neurohypophysis)
JUNCTION BETWEEN DIENCEPHALIC AND MESENCEPHALIC SUPERVENTRICLES
Mesencephalic tegmental NEP
Migrating anterior hypothalamic neurons
Pituitary gland (anterior lobe, adenohypophysis)
Rathke's pouch epithelium
Rathke's pouch lumen
Pituicyte GEP
Oculomotor (III) complex NEP?
Interpeduncular nuclear NEP?
B.
FLOOR OF DIENCEPHALIC SUPERVENTRICLE
Posterior hypothalamic NEP (mammillary)
MAMMILLARY RECESS
Migrating tegmental neurons
Middle hypothalamic NEP
Brain surface (heavier line)
Migrating mammillary nuclear neurons?
Migrating interpeduncular nuclear neurons?

PLATE 74A
GW6.5 Sagittal
CR 15.0 mm, C9247

A.
Near Level 1:
Slide 27
Section 7



B.
Level 4:
Slide 21
Section 8



See level 1 in Plates 64A and B; level 4 in Plates 67A and B.

0.1 mm

PLATE 74B

FONT KEY:
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

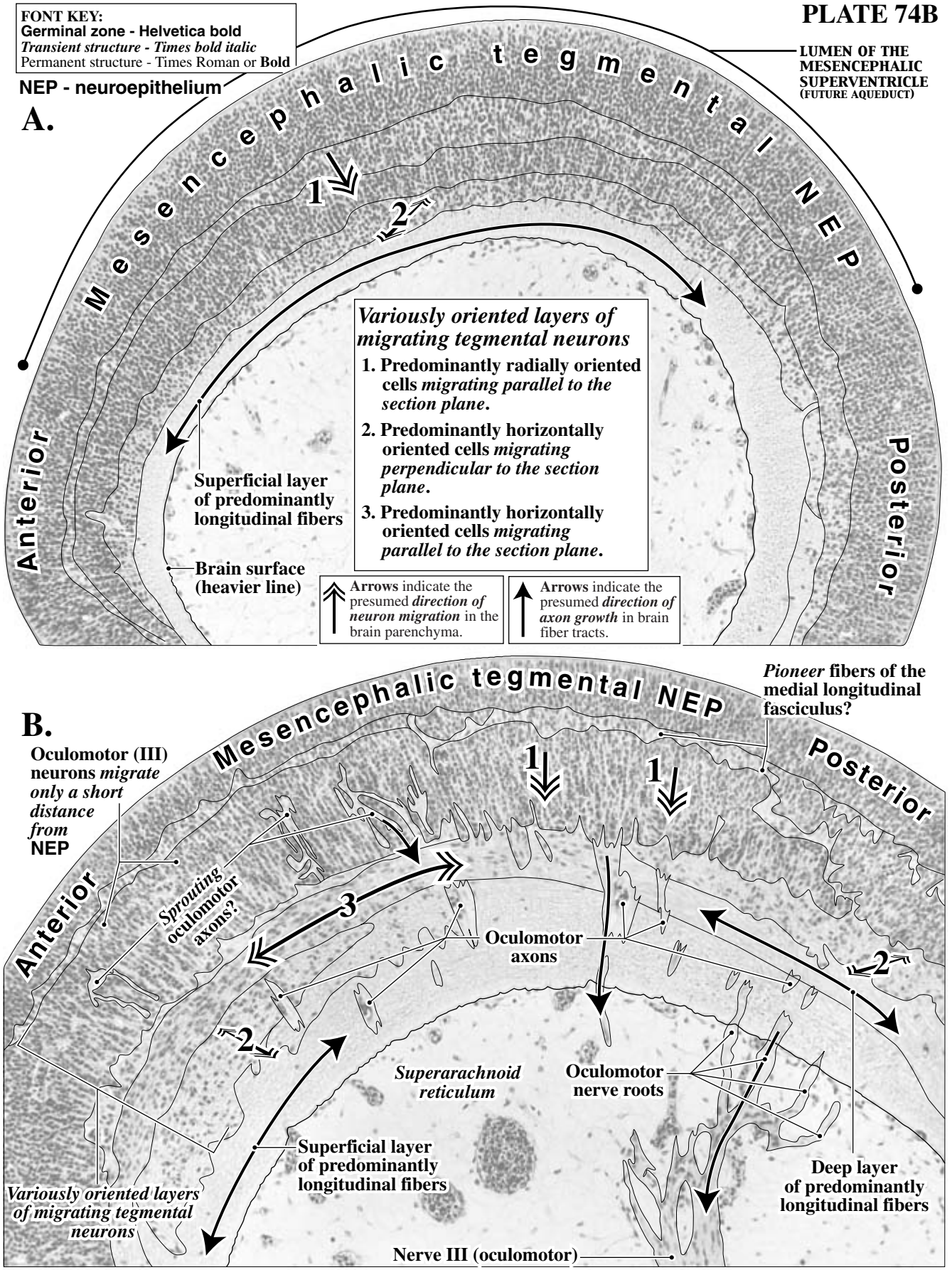


PLATE 75A

MESENCEPHALIC TECTUM, ISTHMUS, AND CEREBELLUM

GW6.5 Sagittal
CR 15.0 mm
C9247
Near Level 3:
Slide 24, Section 8

See Level 3 in Plates 66A and B.

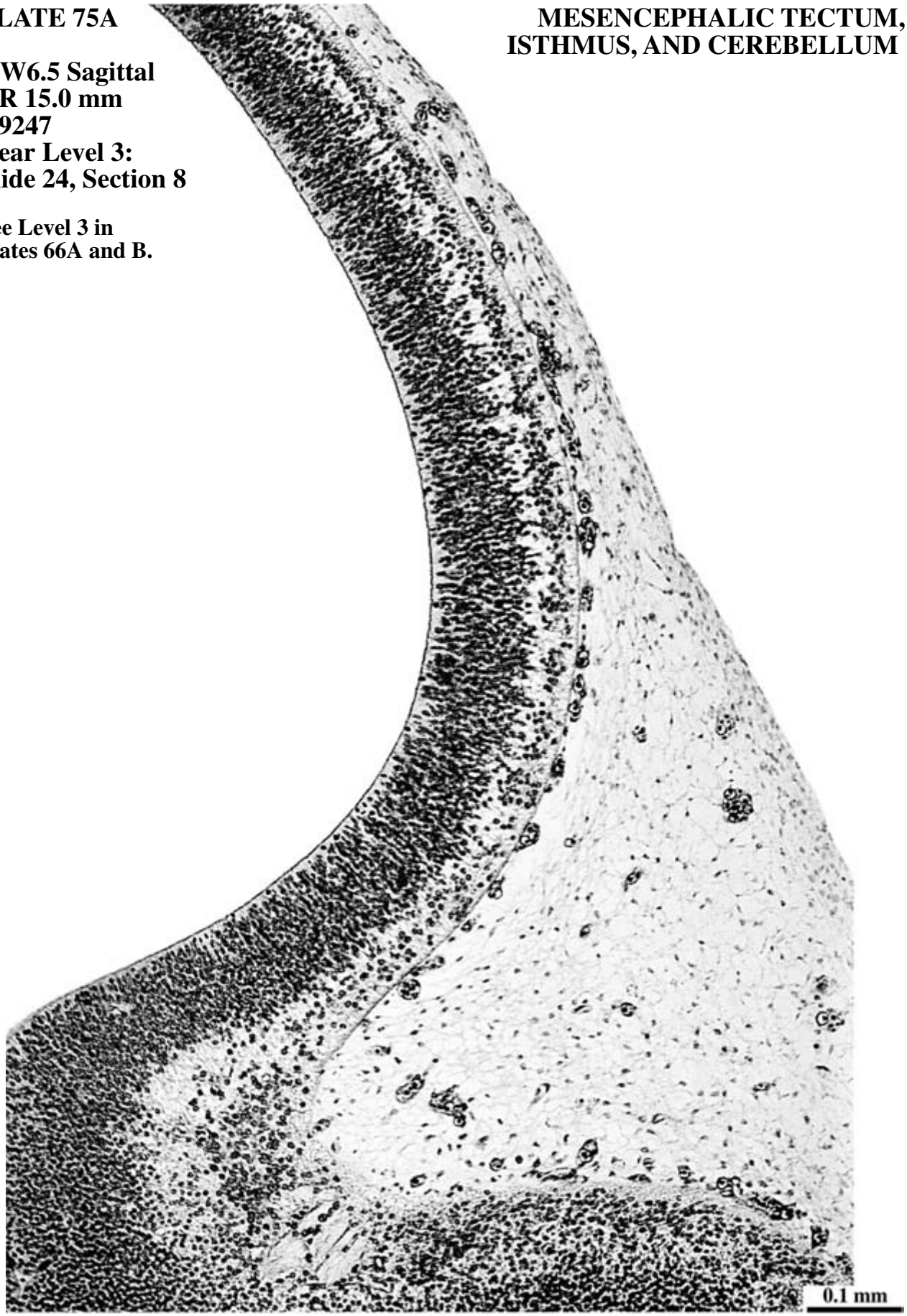


PLATE 75B

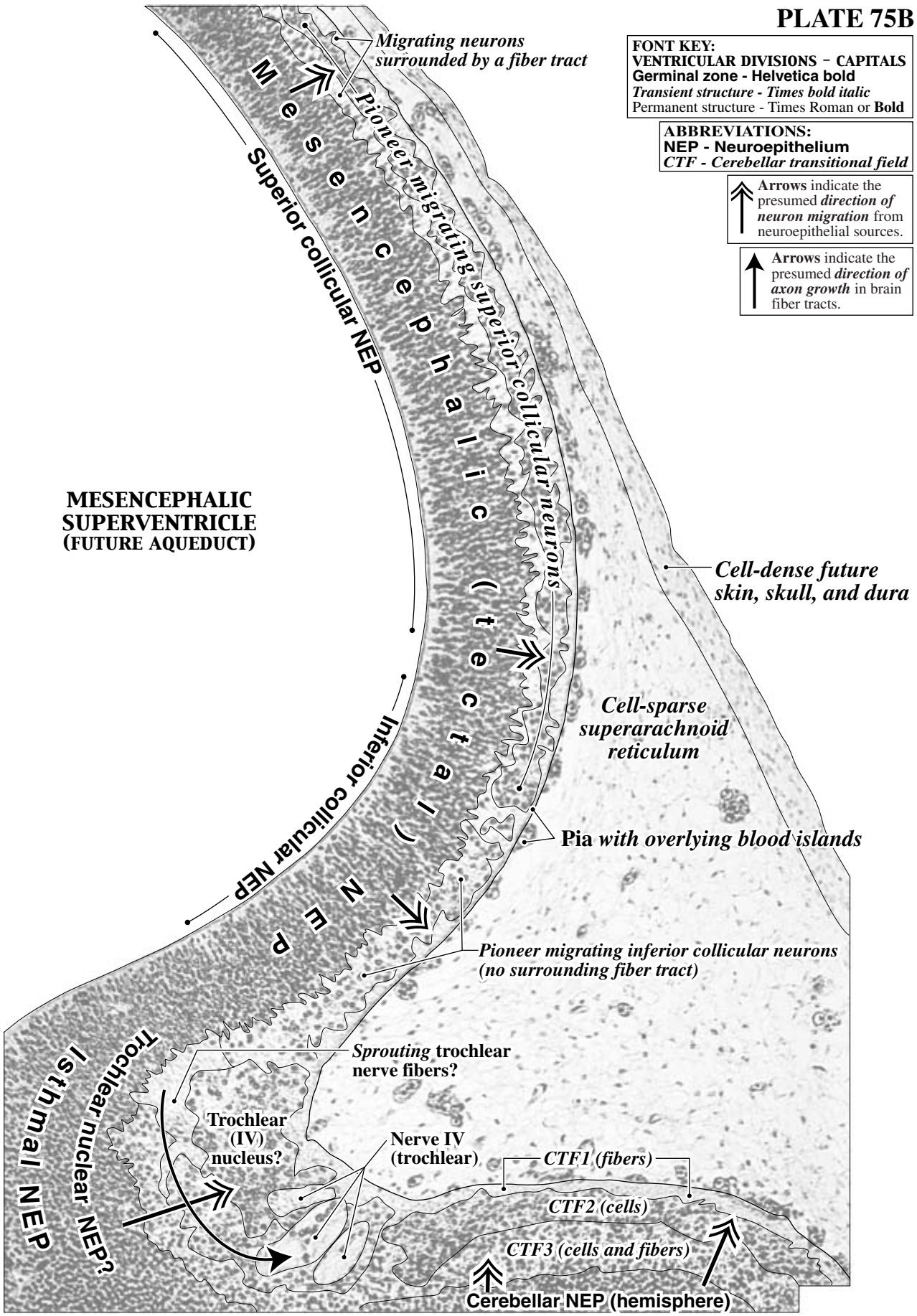
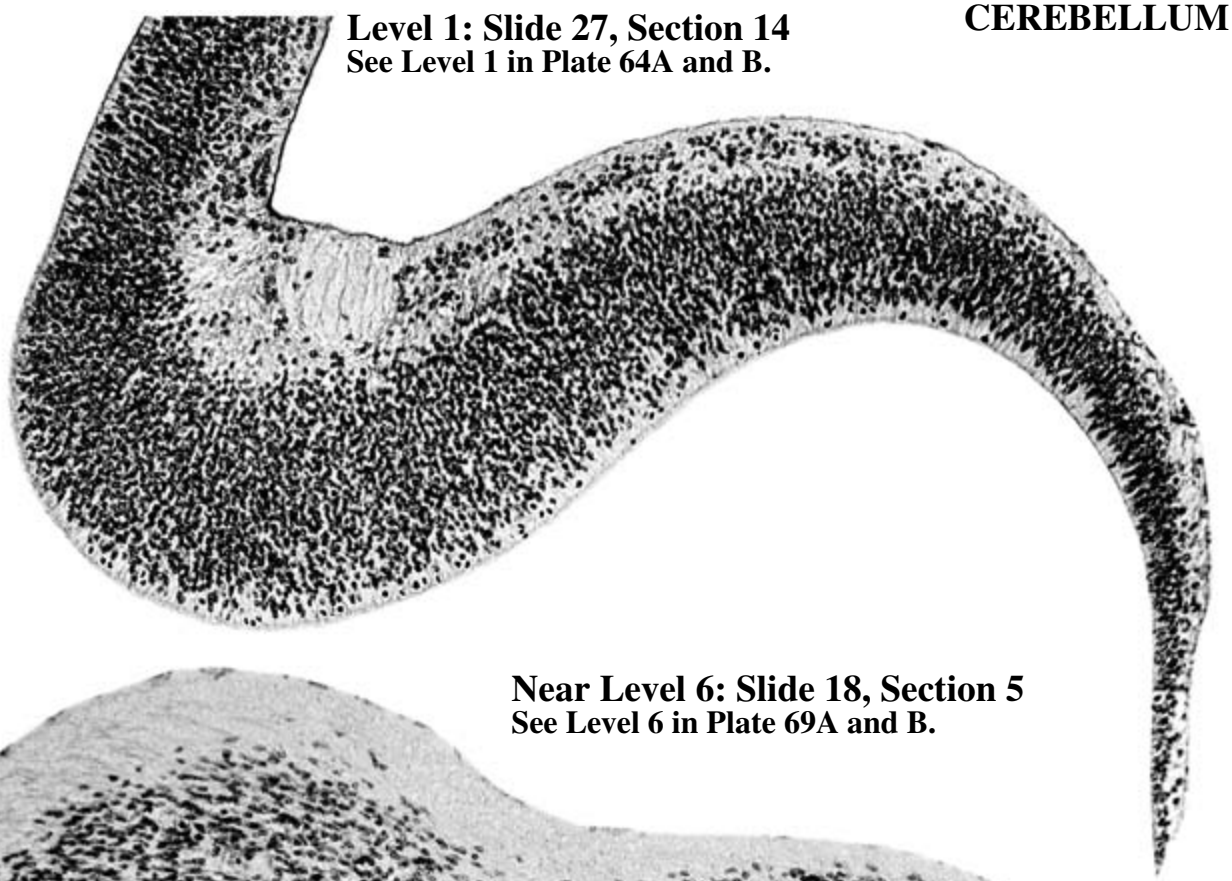

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
NEP - Neuroepithelium
CTF - Cerebellar transitional field
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the presumed direction of axon growth in brain fiber tracts.
Migrating neurons surrounded by a fiber tract
Pioneer migrating superior collicular neurons
Superior collicular NEP
MESENCEPHALIC (tectal) NEP
Inferior collicular NEP
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Cell-dense future skin, skull, and dura
Cell-sparse superarachnoid reticulum
Pia with overlying blood islands
Pioneer migrating inferior collicular neurons (no surrounding fiber tract)
Sprouting trochlear nerve fibers?
Trochlear (IV) nucleus?
Nerve IV (trochlear)
CTF1 (fibers)
CTF2 (cells)
CTF3 (cells and fibers)
Cerebellar NEP (hemisphere)
Isthmal NEP
Trochlear nuclear NEP?

PLATE 76A

GW6.5 Sagittal, CR 15.0 mm, C9247
CEREBELLUM

A.

Level 1: Slide 27, Section 14
See Level 1 in Plate 64A and B.



B.

Near Level 6: Slide 18, Section 5
See Level 6 in Plate 69A and B.

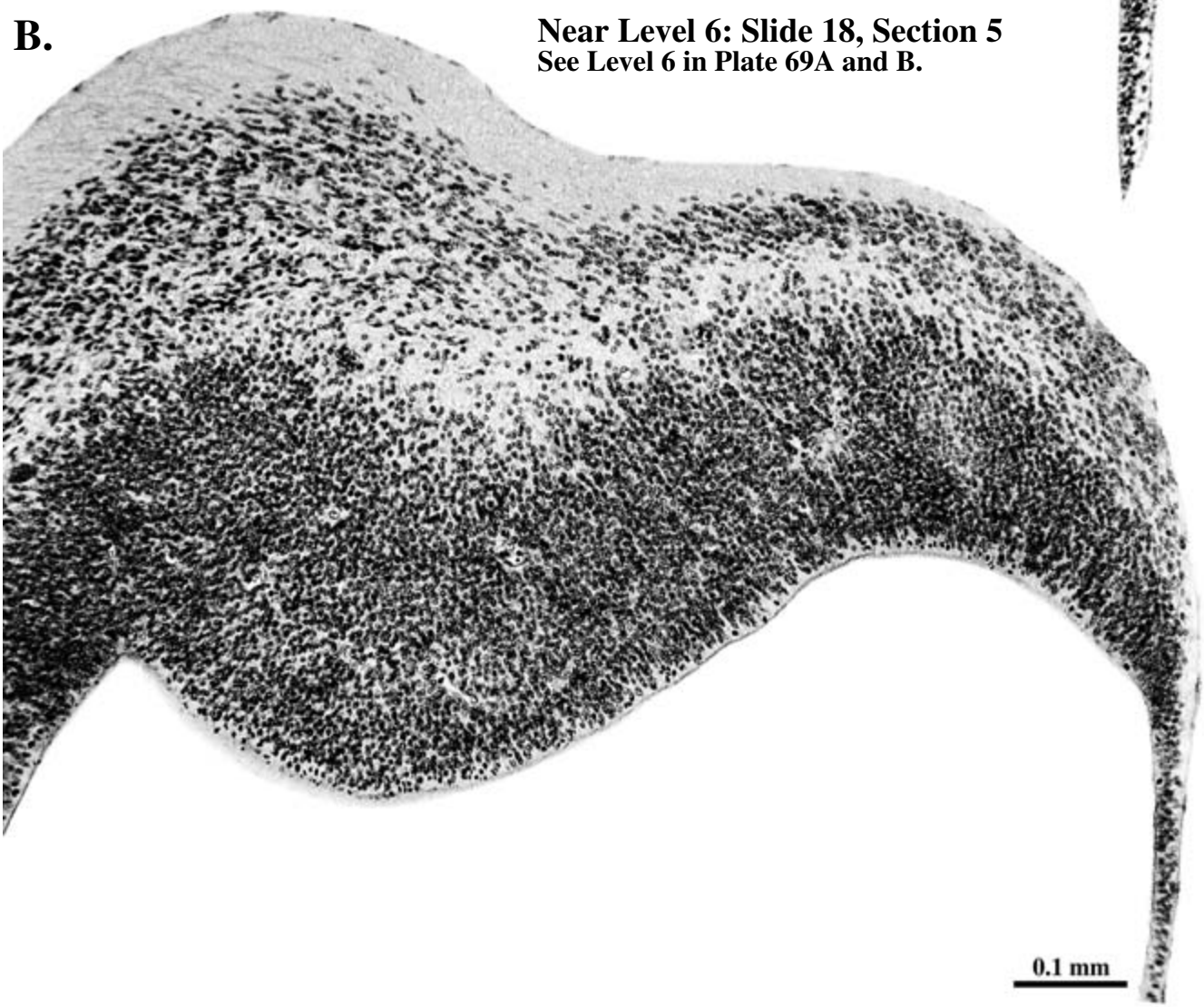


PLATE 76B

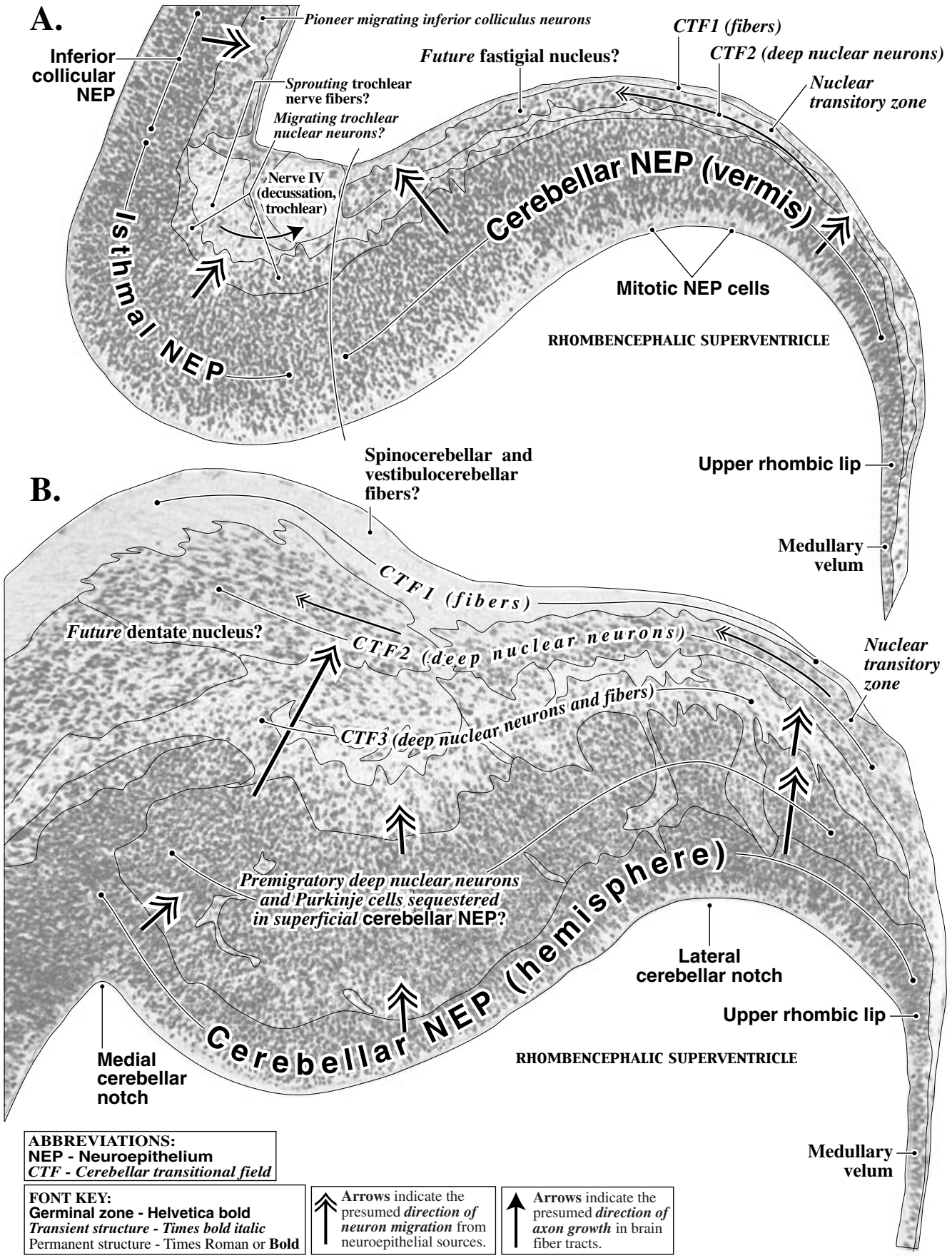
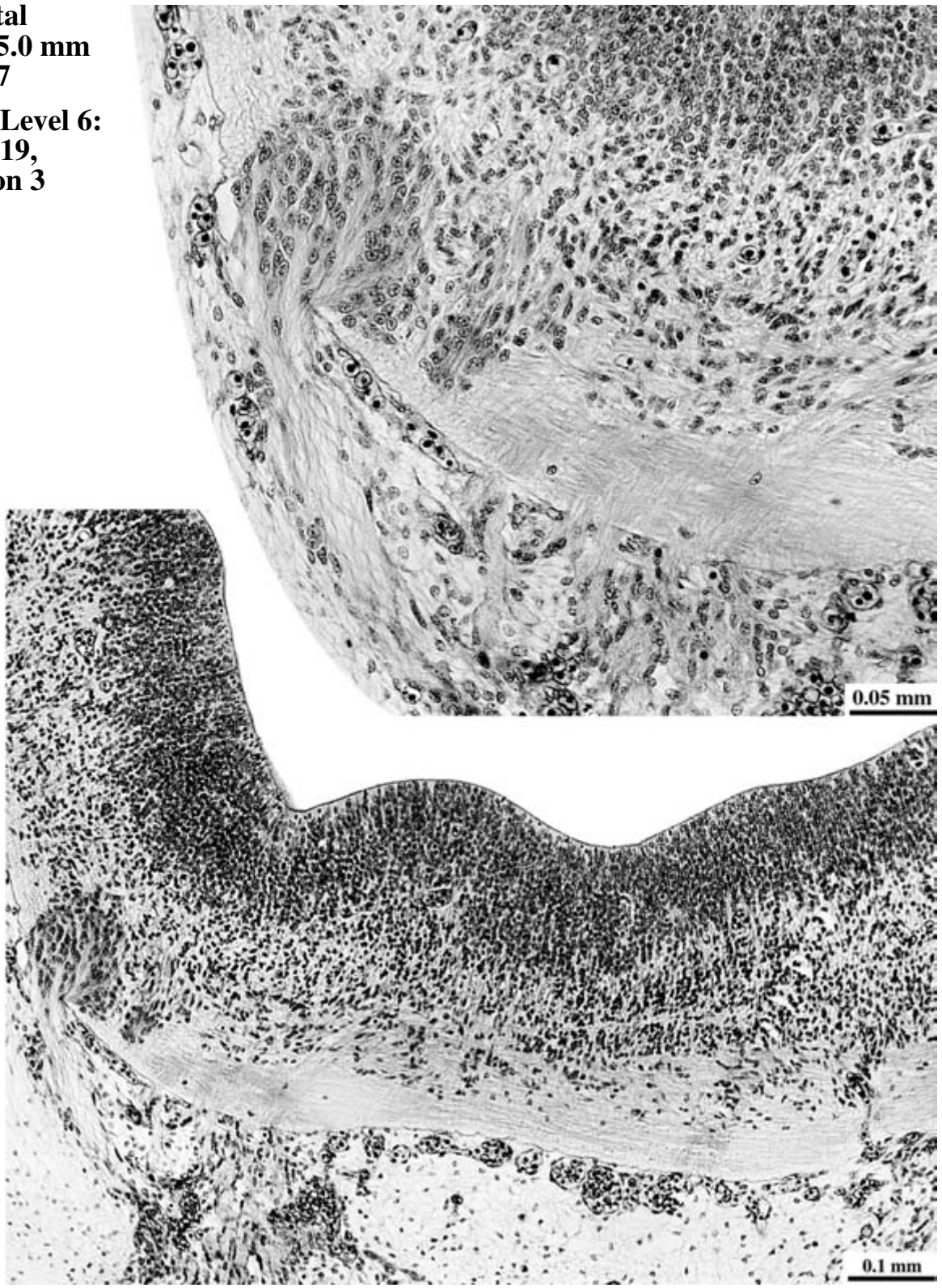

A.
Pioneer migrating inferior colliculus neurons
CTF1 (fibers)
CTF2 (deep nuclear neurons)
Inferior collicular NEP
Future fastigial nucleus?
Sprouting trochlear nerve fibers?
Migrating trochlear nuclear neurons?
Nuclear transitory zone
Nerve IV (decussation, trochlear)
Cerebellar NEP (vermis)
Isthmal NEP
Mitotic NEP cells
RHOMBENCEPHALIC SUPERVENTRICLE
Spinocerebellar and vestibulocerebellar fibers?
Upper rhombic lip
B.
Medullary velum
CTF1 (fibers)
Future dentate nucleus?
CTF2 (deep nuclear neurons)
Nuclear transitory zone
CTF3 (deep nuclear neurons and fibers)
Premigratory deep nuclear neurons and Purkinje cells sequestered in superficial cerebellar NEP?
Lateral cerebellar notch
Cerebellar NEP (hemisphere)
Upper rhombic lip
Medial cerebellar notch
RHOMBENCEPHALIC SUPERVENTRICLE
Medullary velum
ABBREVIATIONS:
NEP - Neuroepithelium
CTF - Cerebellar transitional field
FONT KEY:
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the presumed direction of axon growth in brain fiber tracts.

PLATE 77A **TRIGEMINAL NERVE ENTRY ZONE**

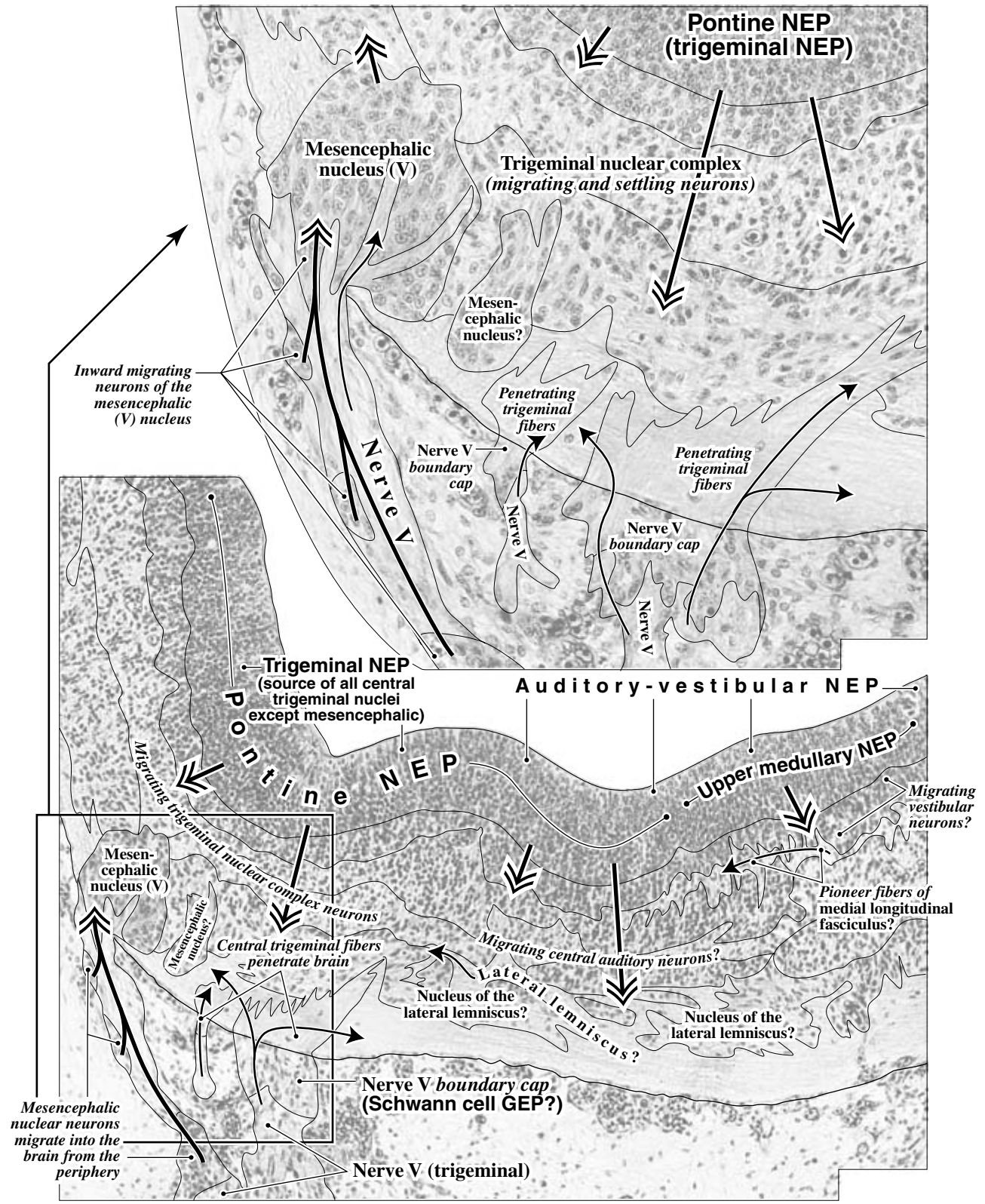
GW6.5
Sagittal
CR 15.0 mm
C9247

Near Level 6:
Slide 19,
Section 3



See Level 5 in Plate 68A and B; Level 6 in Plate 69A and B.

PLATE 77B



FONT KEY:
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

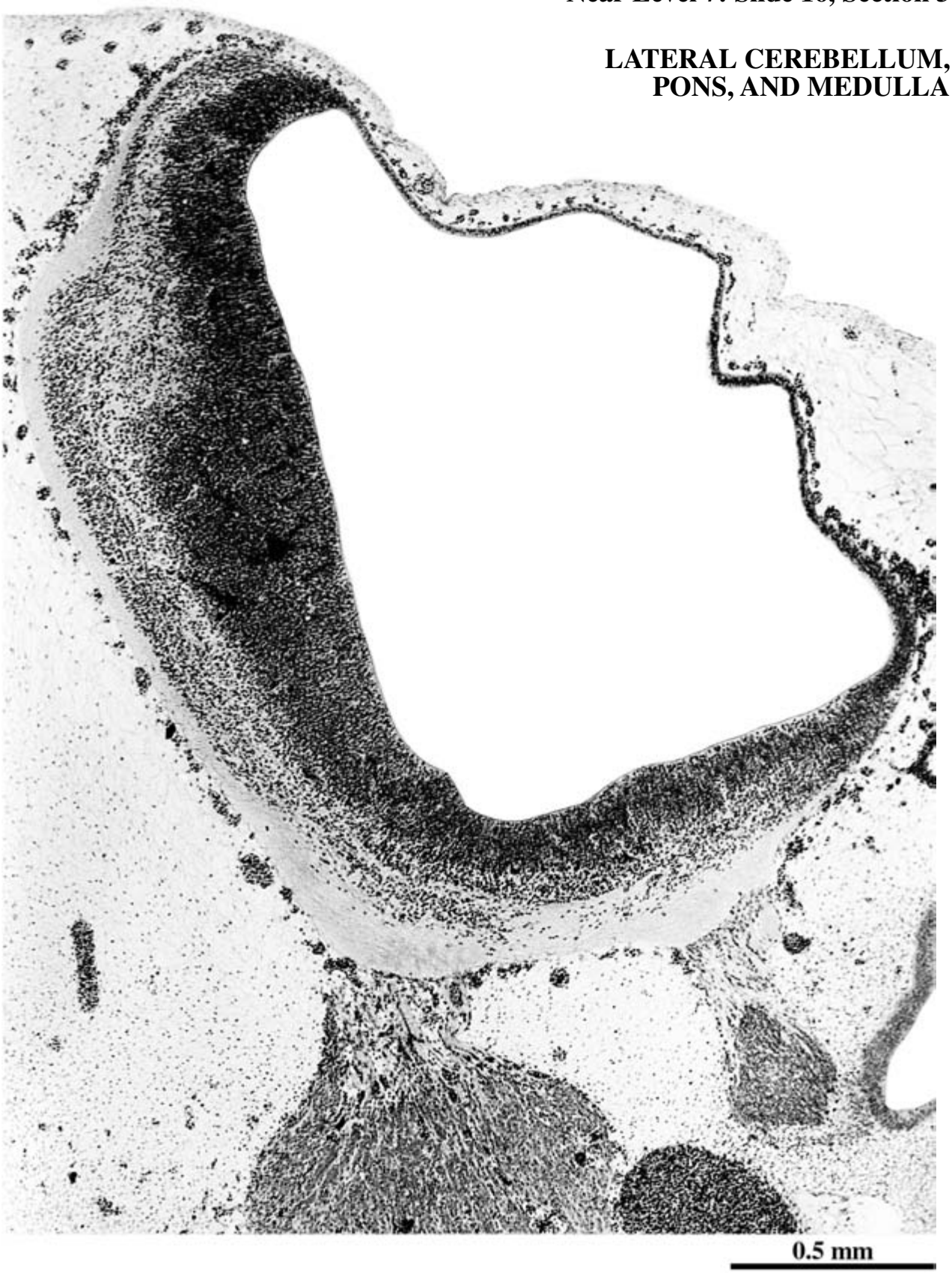
Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 78A

GW6.5 Sagittal, CR 15.0 mm, C9247
Near Level 7: Slide 16, Section 3

LATERAL CEREBELLUM,
PONS, AND MEDULLA



See Level 7 in Plates 70A and B.

PLATE 78B

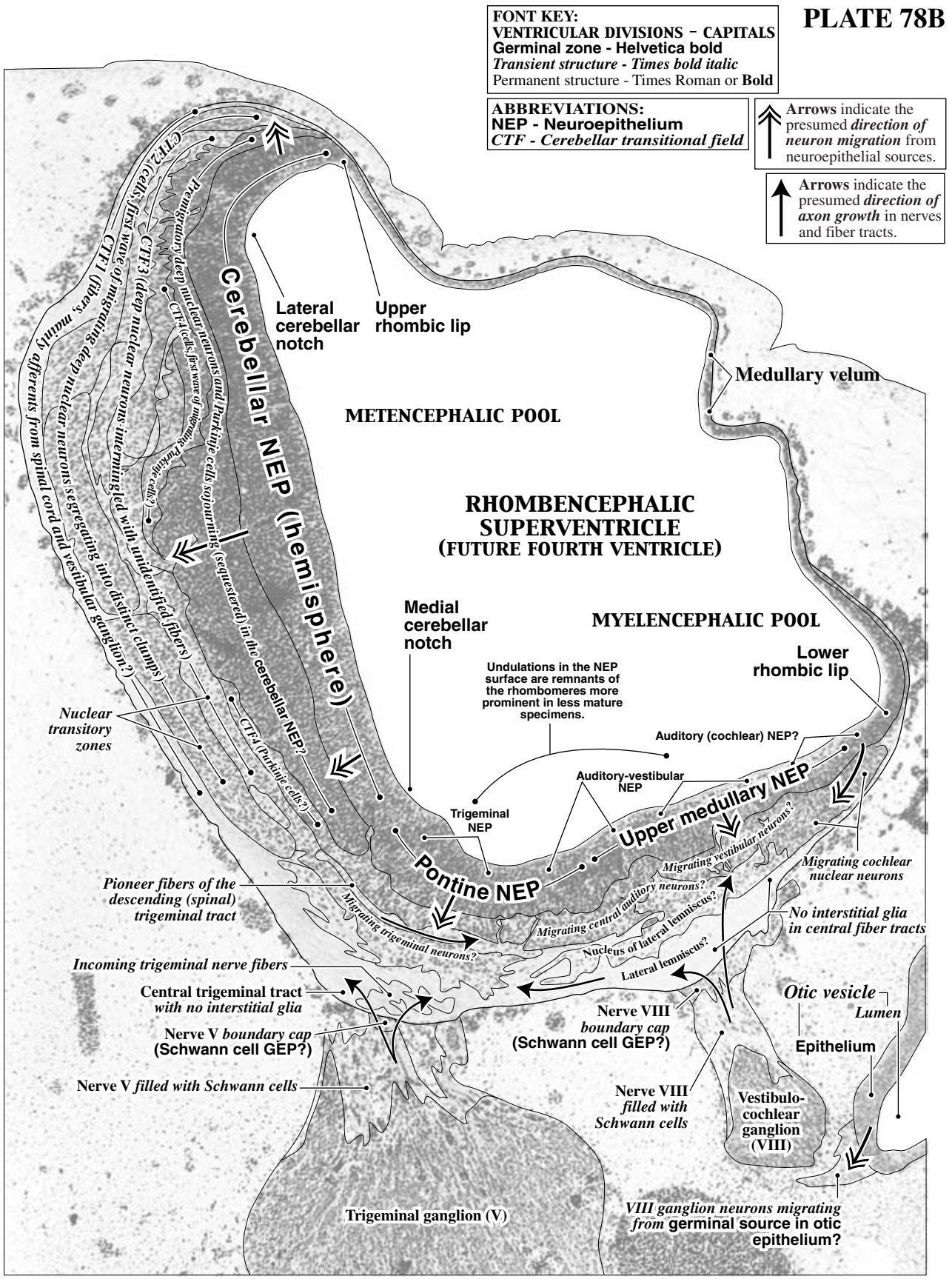
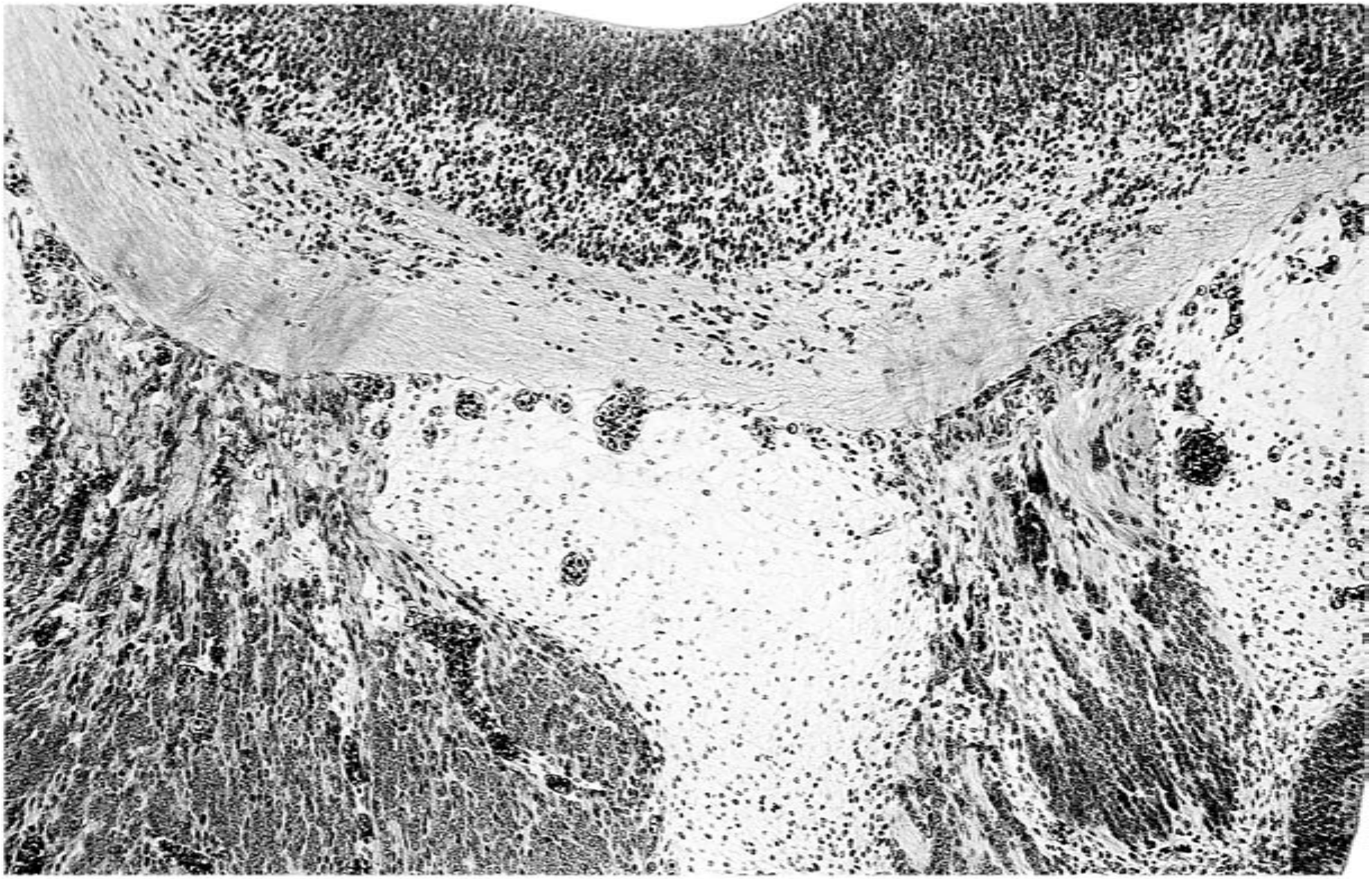

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
NEP - Neuroepithelium
CTF - Cerebellar transitional field
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the presumed direction of axon growth in nerves and fiber tracts.
Cerebellar NEP (hemisphere)
Lateral cerebellar notch
Upper rhombic lip
Medullary velum
METENCEPHALIC POOL
RHOMBENCEPHALIC SUPERVENTRICLE
(FUTURE FOURTH VENTRICLE)
MYELENCEPHALIC POOL
Medial cerebellar notch
Lower rhombic lip
Undulations in the NEP surface are remnants of the rhombomeres more prominent in less mature specimens.
Auditory (cochlear) NEP?
Auditory-vestibular NEP
Upper medullary NEP
Trigeminal NEP
Pontine NEP
Migrating vestibular neurons?
Migrating cochlear nuclear neurons
Migrating central auditory neurons?
Nucleus of lateral lemniscus?
Lateral lemniscus?
No interstitial glia in central fiber tracts
Migrating trigeminal neurons?
Pioneer fibers of the descending (spinal) trigeminal tract
Incoming trigeminal nerve fibers
Central trigeminal tract with no interstitial glia
Nerve V boundary cap (Schwann cell GEP?)
Nerve V filled with Schwann cells
Nerve VIII boundary cap (Schwann cell GEP?)
Nerve VIII filled with Schwann cells
Otic vesicle
Lumen
Epithelium
Vestibulo-cochlear ganglion (VIII)
Trigeminal ganglion (V)
VIII ganglion neurons migrating from germinal source in otic epithelium?
Nuclear transitory zones
CTF1 (fibers, mainly afferents from spinal cord and vestibular ganglion?)
CTF2 (cells, first wave of migrating deep nuclear neurons segregating into distinct clumps)
CTF3 (deep nuclear neurons intermingled with unidentified fibers)
Premigratory deep nuclear neurons and Purkinje cells sojourning (sequestered) in the cerebellar NEP?
CTF4 (cells, first wave of migrating Purkinje cells?)
CTF4 (Purkinje cells?)
Purkinje cells (?)

PLATE 79A GW6.5 Sagittal, CR 15.0 mm, C9247
Near Level 7: Slide 16, Section 13

TRIGEMINAL AND VESTIBULO-COCHLEAR NERVE ENTRY ZONES



See Level 7 in Plates 70A and B.

PLATE 79B

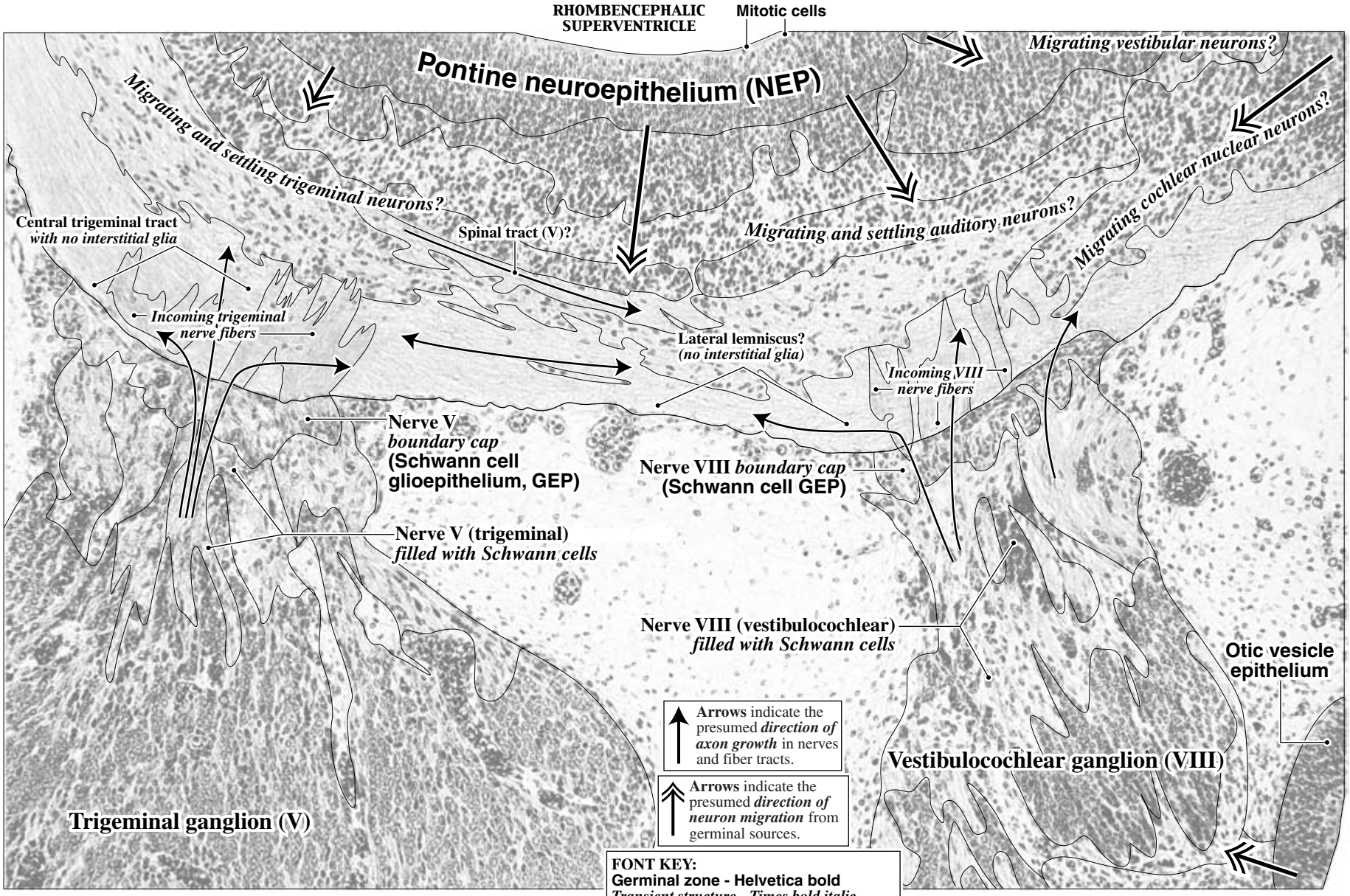
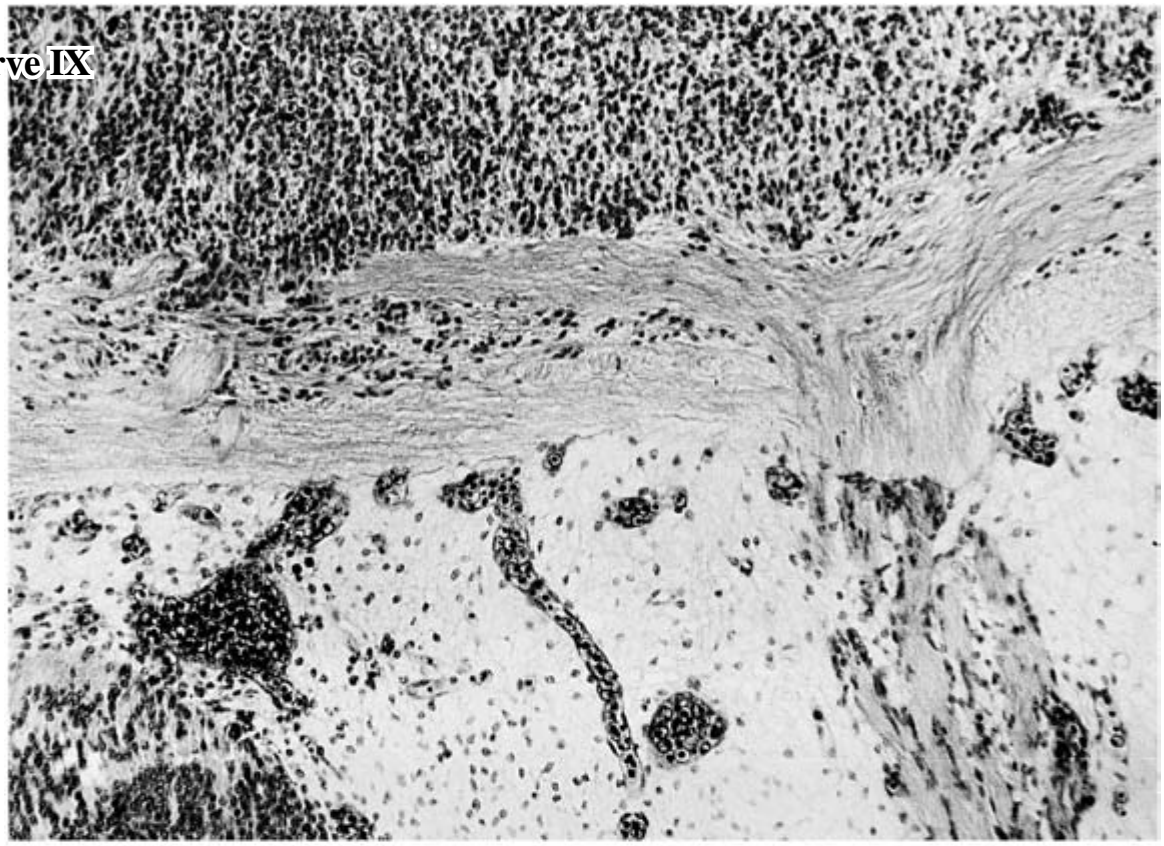
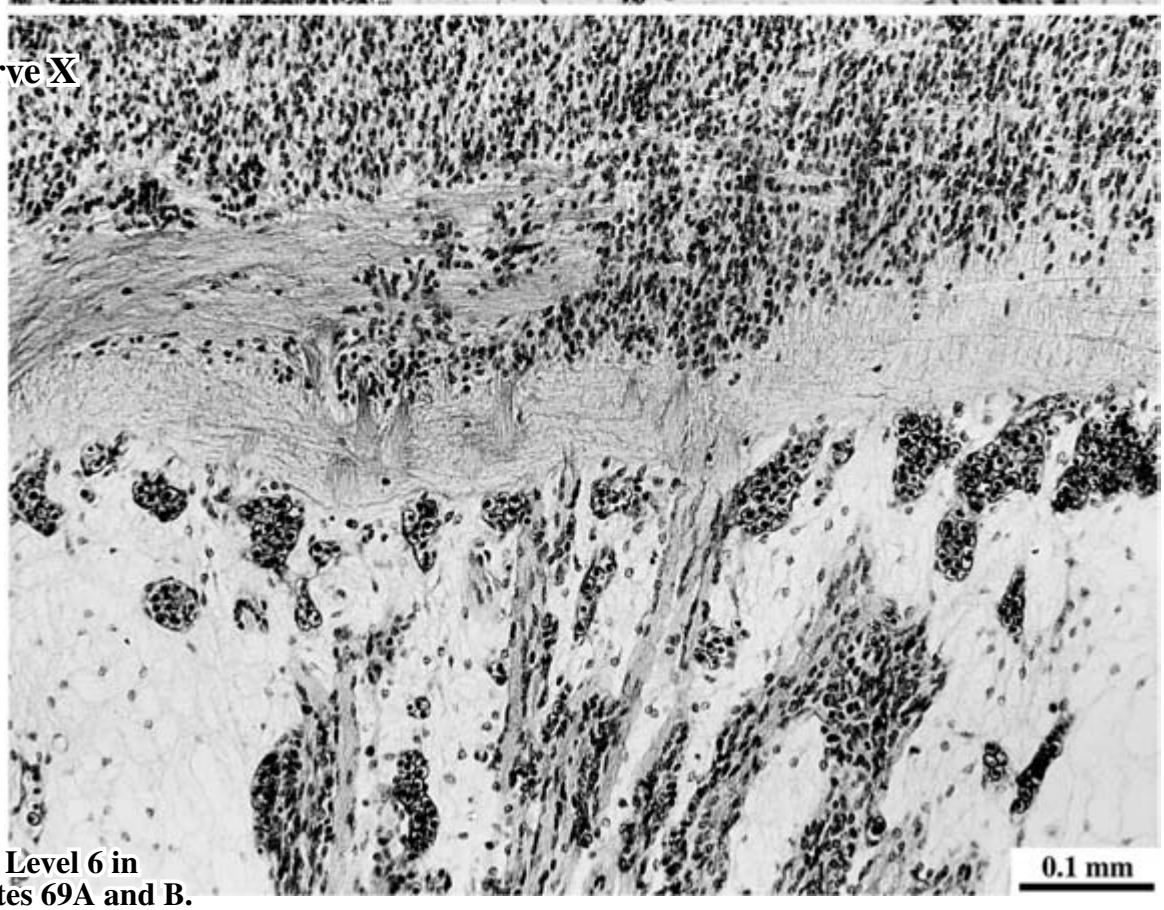

RHOMBENCEPHALIC SUPERVENTRICLE
Mitotic cells
Pontine neuroepithelium (NEP)
Migrating vestibular neurons?
Migrating and settling trigeminal neurons?
Migrating cochlear nuclear neurons?
Central trigeminal tract
with no interstitial glia
Spinal tract (V)?
Migrating and settling auditory neurons?
Incoming trigeminal nerve fibers
Lateral lemniscus?
(no interstitial glia)
Incoming VIII nerve fibers
Nerve V
boundary cap
(Schwann cell glioepithelium, GEP)
Nerve VIII boundary cap
(Schwann cell GEP)
Nerve V (trigeminal)
filled with Schwann cells
Nerve VIII (vestibulocochlear)
filled with Schwann cells
Otic vesicle epithelium
Arrows indicate the presumed direction of axon growth in nerves and fiber tracts.
Arrows indicate the presumed direction of neuron migration from germinal sources.
Vestibulocochlear ganglion (VIII)
Trigeminal ganglion (V)
FONT KEY:
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold

PLATE 80A GW6.5 Sagittal, CR 15.0 mm, C9247
Near Level 6: Slide 18, Section 13

A.
Nerve IX



B.
Nerve X



See Level 6 in Plates 69A and B.

PLATE 80B

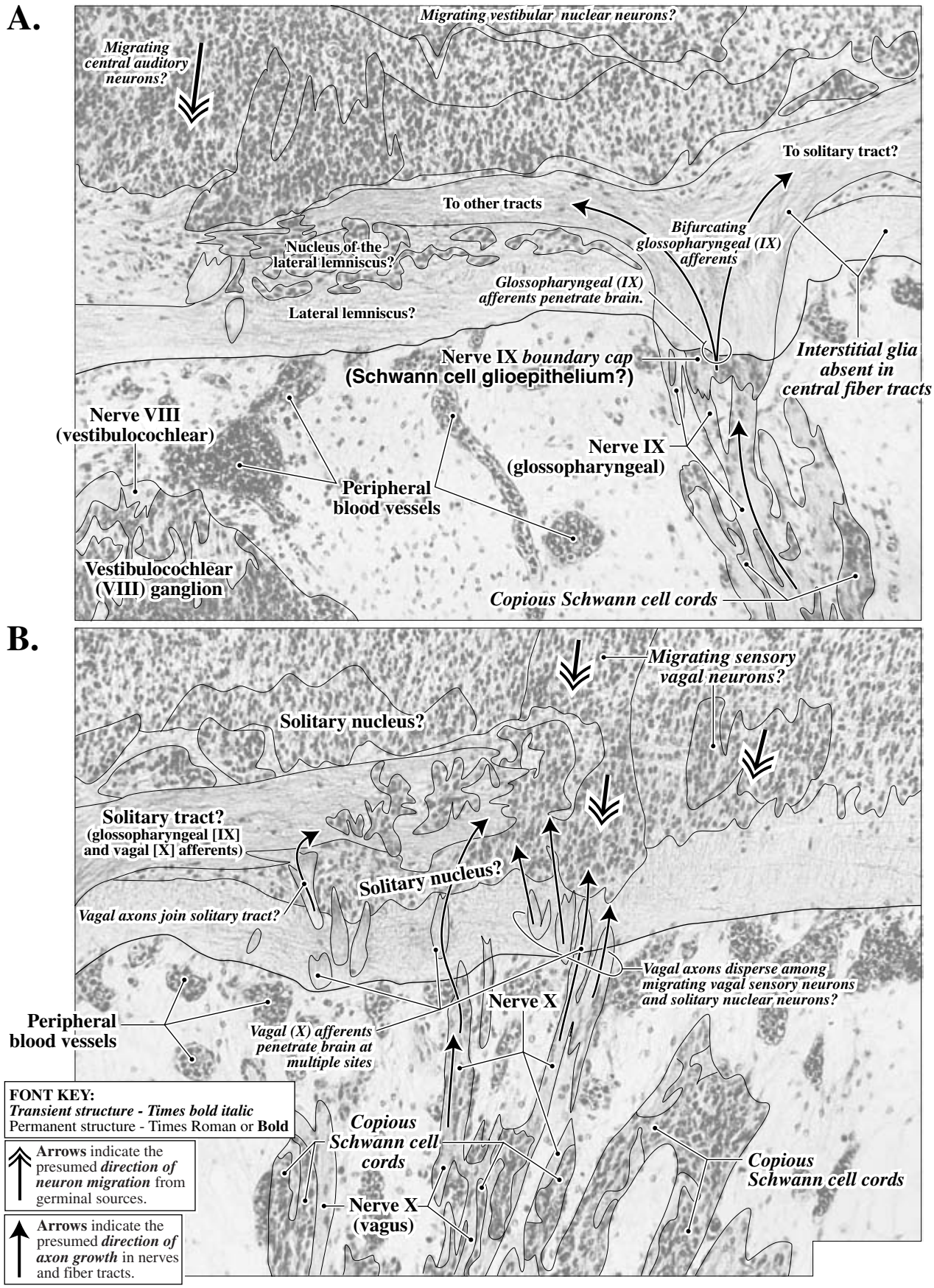

A.
Migrating vestibular nuclear neurons?
Migrating central auditory neurons?
To solitary tract?
To other tracts
Bifurcating glossopharyngeal (IX) afferents
Nucleus of the lateral lemniscus?
Glossopharyngeal (IX) afferents penetrate brain.
Lateral lemniscus?
Nerve IX boundary cap (Schwann cell glioepithelium?)
Interstitial glia absent in central fiber tracts
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Peripheral blood vessels
Vestibulocochlear (VIII) ganglion
Copious Schwann cell cords
B.
Migrating sensory vagal neurons?
Solitary nucleus?
Solitary tract? (glossopharyngeal [IX] and vagal [X] afferents)
Solitary nucleus?
Vagal axons join solitary tract?
Vagal axons disperse among migrating vagal sensory neurons and solitary nuclear neurons?
Nerve X
Peripheral blood vessels
Vagal (X) afferents penetrate brain at multiple sites
FONT KEY:
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
Arrows indicate the presumed direction of neuron migration from germinal sources.
Arrows indicate the presumed direction of axon growth in nerves and fiber tracts.
Copious Schwann cell cords
Nerve X (vagus)
Copious Schwann cell cords

PLATE 81A GW6.5 Sagittal, CR 15.0 mm, C9247
Level 4: Slide 21, Section 8
See Level 4 in Plates 67A and B.

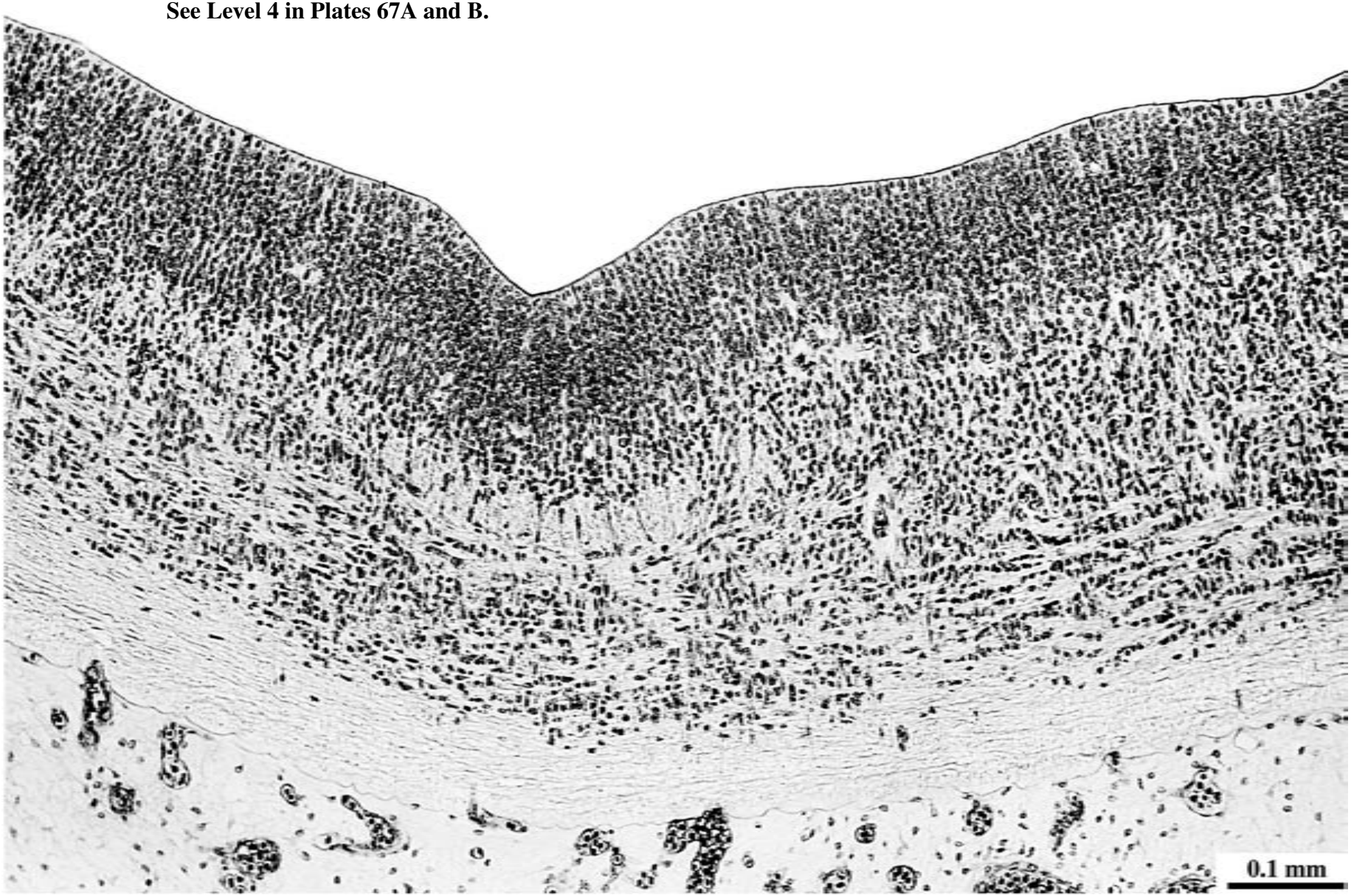


PLATE 81B

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - neuroepithelium

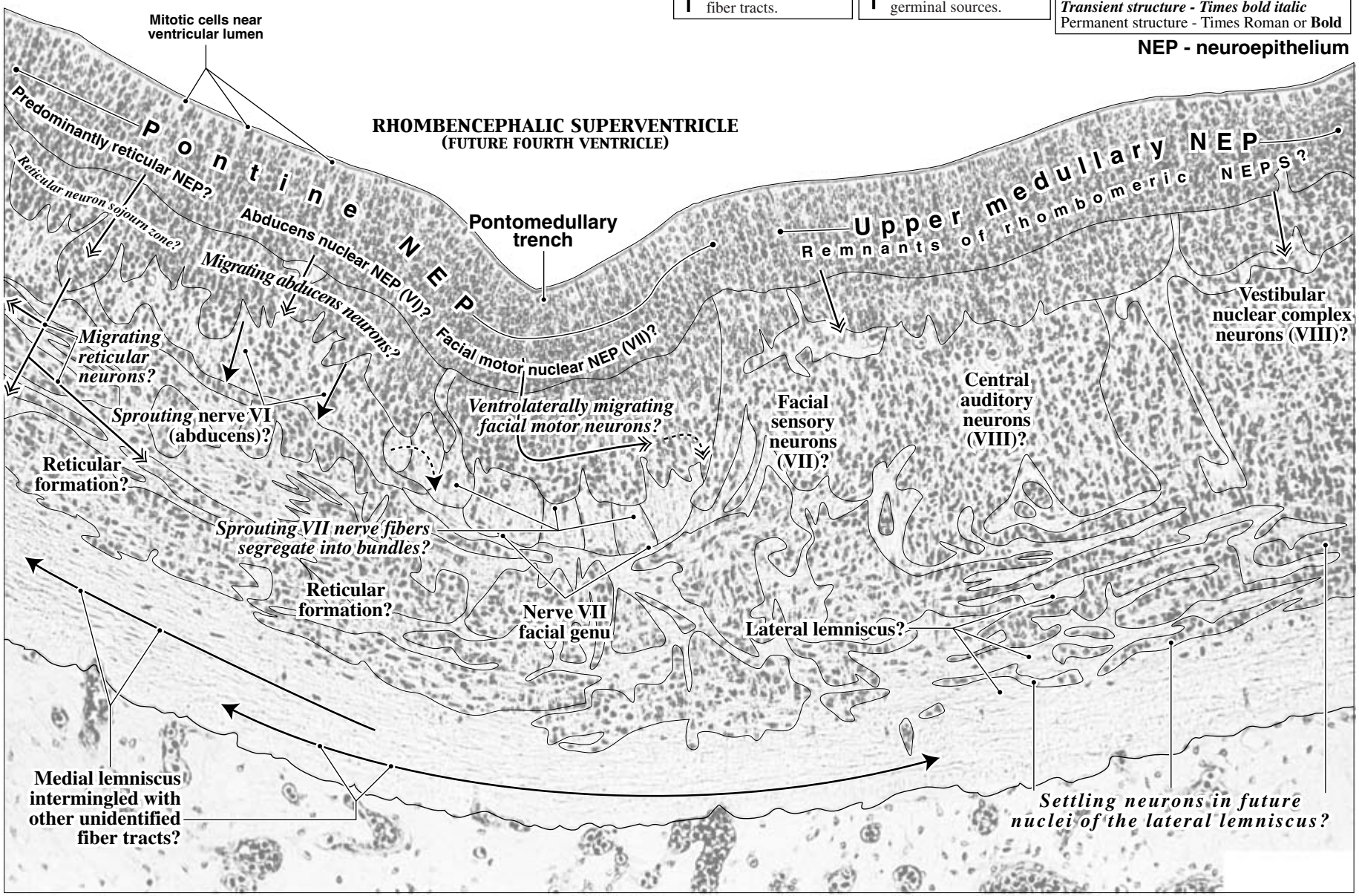


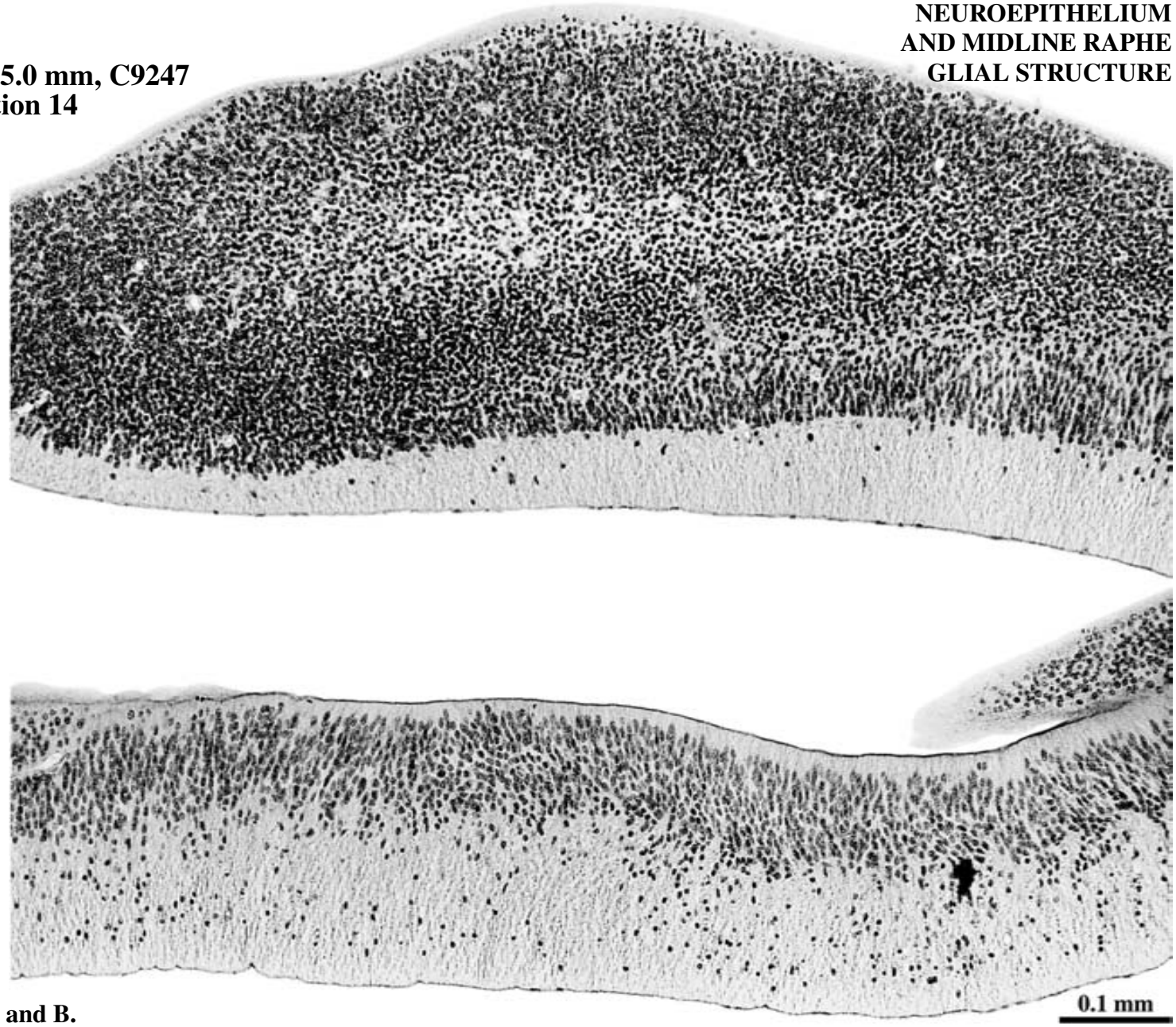
PLATE 82A

NEUROEPITHELIUM AND MIDLINE RAPHE GLIAL STRUCTURE

GW6.5 Sagittal, CR 15.0 mm, C9247
Level 1: Slide 27, Section 14

A. ISTHMUS

B. UPPER PONS



See Level 1 in Plates 64A and B.

PLATE 82B

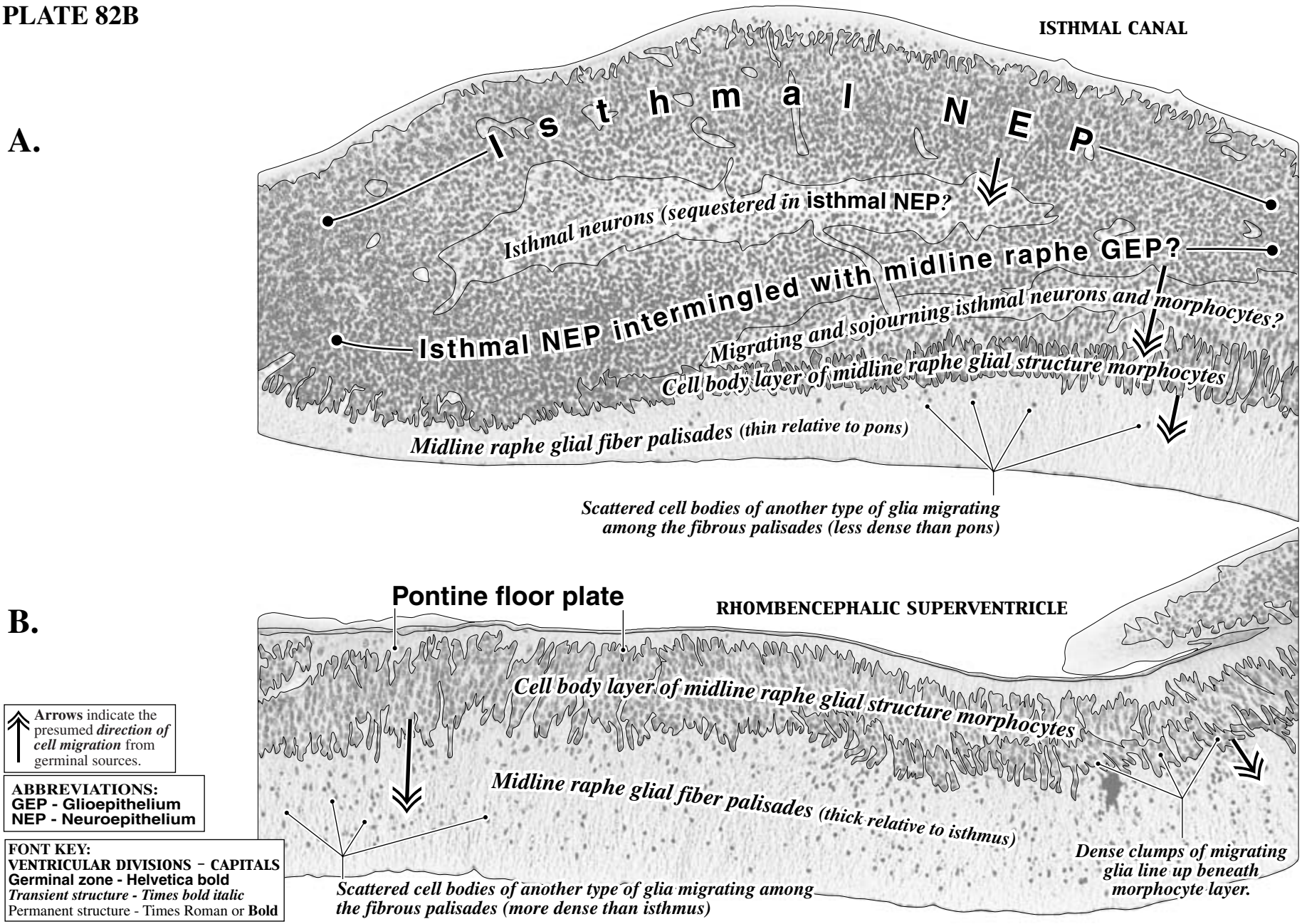
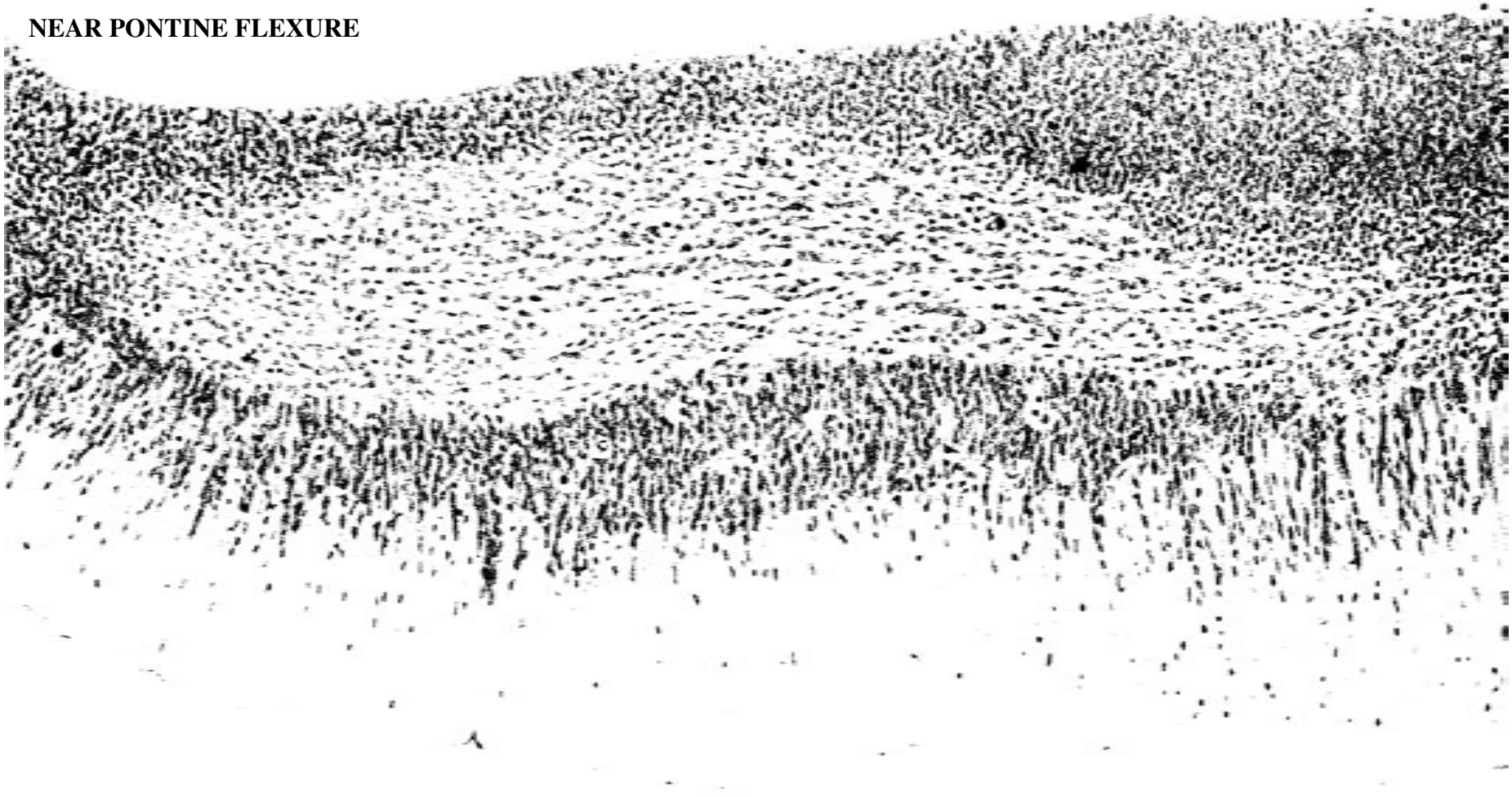

A.
ISTHMAL CANAL
Isthmal NEP
Isthmal neurons (sequestered in isthmal NEP?
Isthmal NEP intermingled with midline raphe GEP?
Migrating and sojourning isthmal neurons and morphocytes?
Cell body layer of midline raphe glial structure morphocytes
Midline raphe glial fiber palisades (thin relative to pons)
Scattered cell bodies of another type of glia migrating among the fibrous palisades (less dense than pons)
B.
Pontine floor plate
RHOMBENCEPHALIC SUPERVENTRICLE
Cell body layer of midline raphe glial structure morphocytes
Midline raphe glial fiber palisades (thick relative to isthmus)
Dense clumps of migrating glia line up beneath morphocyte layer.
Scattered cell bodies of another type of glia migrating among the fibrous palisades (more dense than isthmus)
Arrows indicate the presumed direction of cell migration from germinal sources.
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold

PLATE 83A

GW6.5 Sagittal, CR 15.0 mm, C9247
Level 1: Slide 27, Section 14

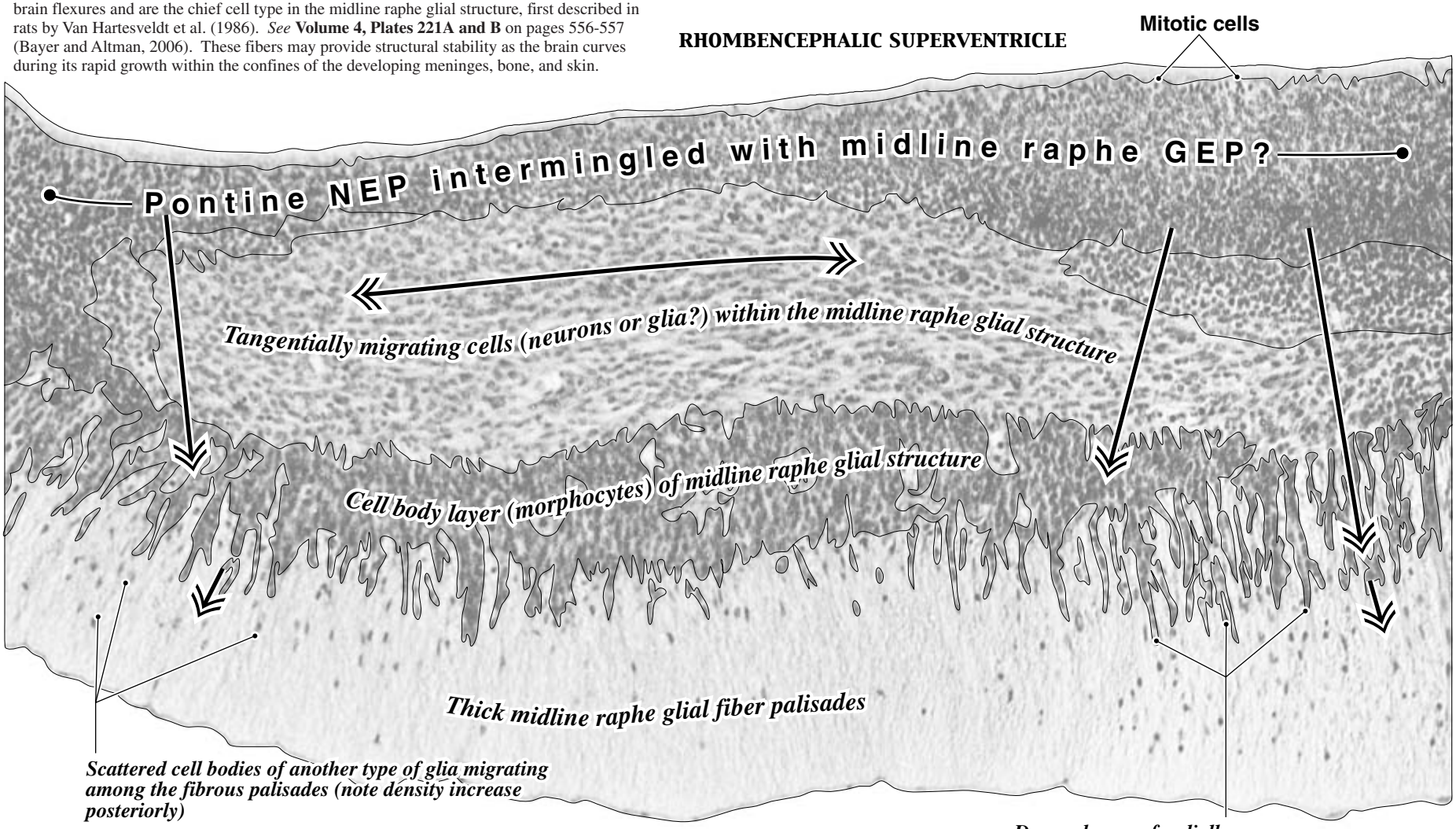
NEAR PONTINE FLEXURE



See Level 1 in Plates 64A and B.

PLATE 83B

MORPHOCYTES are specialized glia that produce fibrous palisades in the region of the brain flexures and are the chief cell type in the midline raphe glial structure, first described in rats by Van Hartesveldt et al. (1986). *See* **Volume 4, Plates 221A and B** on pages 556-557 (Bayer and Altman, 2006). These fibers may provide structural stability as the brain curves during its rapid growth within the confines of the developing meninges, bone, and skin.



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

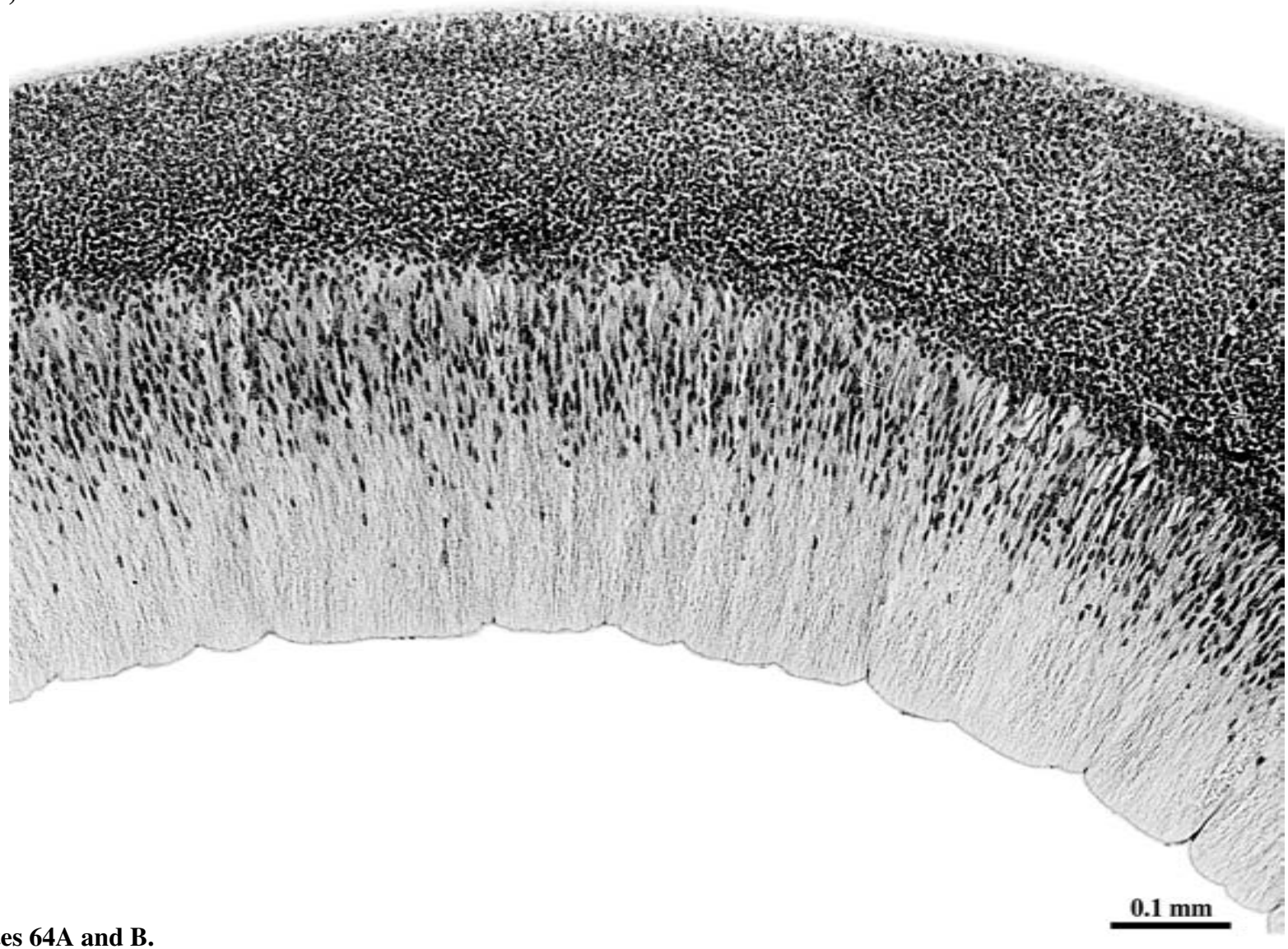
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of cell migration*** from germinal sources.

PLATE 84A

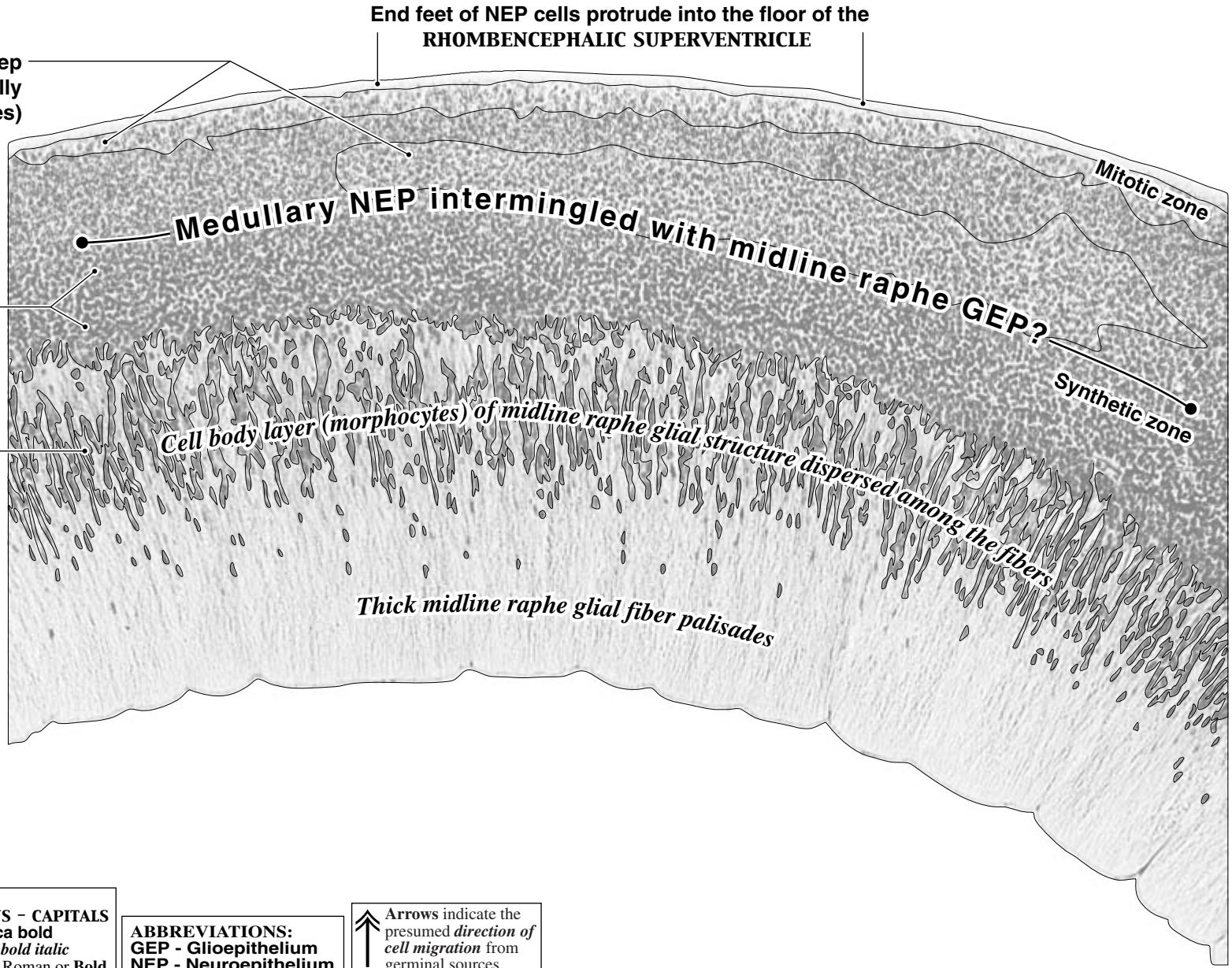
GW6.5 Sagittal, CR 15.0 mm, C9247
Level 1: Slide 27, Section 14

MEDULLA
(slightly anterior to medullary flexure)



See Level 1 in Plates 64A and B.

PLATE 84B



The morphocytes in the lower medulla differ in two ways from others. **First**, they are less densely packed. **Second**, the large cells migrating downward may be morphocytes themselves rather than the smaller cells migrating in the pons and isthmus (*see* **Plates 82 and 83**).

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of cell migration*** from germinal sources.

PART VII: GW5.5 CORONAL

This specimen is embryo #1000 in the Minot Collection, designated here as M1000. The crown-rump length (CR) is 10 mm estimated to be at gestational week (GW) 5.5. Most of M1000's forebrain and midbrain sections are cut (10 μm) in the coronal plane, but the plane shifts to predominantly horizontal in the posterior midbrain, pons, and medulla. We photographed 64 sections at low magnification from the frontal prominence to the posterior tips of the mesencephalon and medulla. Fourteen of these sections are illustrated in **Plates 85AB to 98AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of M1000's brain and eye (**Figure 6**), and to show each illustrated section *in situ* (*insets,* **Plates 85A to 98A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 99AB** show high-magnification views of the telencephalic neuroepithelium.

All parts of the telencephalic neuroepithelium are rapidly increasing their pool of neuronal and glial stem cells as they expand the shorelines of the enlarging telencephalic superventricle. However, the entire telencephalon is much smaller than in the GW6.5 specimens (**Parts V** and **VI**). The primordial plexiform layer adjacent to the cerebral cortical neuroepithelium is nearly devoid of cells except in far ventrolateral areas. The basal ganglionic and basal telencephalic neuroepithelia have only a thin layer of adjacent migrating neurons, many fewer than in the GW6.5 specimens. The posterior olfactory epithelium has only partially invaginated into a developing nasal cavity, while the anterior epithelium is a placode in the anterolateral head. Still, cellular densities outside the placode and invaginated epithelium may be supporting cells surrounding the first olfactory nerve fibers.

The diencephalic neuroepithelium surrounds a superventricle that will narrow (shrinking shorelines) by GW6.5 in the preoptic, hypothalamic, and subthalamic areas. It is postulated that the superficial parts of the anterior hypothalamic and subthalamic neuroepithelia contain premigratory, postmitotic neurons that are sequestered there. More posteriorly, these neuroepithelia are surrounded by sequential waves of migrating neurons. In contrast, the thalamic neuroepithelium is in the "stockbuilding" stage, increasing its population of neuronal and glial stem cells as the thalamic pool of the diencephalic superventricle expands. The eye is clearly connected to the ventral diencephalon by a thick, short stalk that is the glioepithelium of the future optic nerve. As in the more mature specimens, the retinal neuroepithelium is clearly differentiated from the pigment epithelium.

The mesencephalon contains a stockbuilding neuroepithelium in the pretectum and tectum (virtually no adjacent migrating neurons). The tegmental and isthmal neuroepithelia are thick, but their population of stem cells begins to decrease as massive waves of migrating neurons leave. The subpial fiber band is considerably thinner than in the GW6.5 specimens.

Both the pons and medulla have neuroepithelia that are thicker than at GW6.5, but are nevertheless shrinking as they unloaded their neuronal and glial progeny into an expanding parenchyma. In lateral areas, the neuroepithelium forms crescent-shaped evaginagions, the rhombomeres. The rhombomeres are associated with the entry zones of sensory cranial nerves V, VII, VIII, IX, and X; they will be the most distinctive features of the thombencephalon for the remainder of brain development. Cells are migrating and settling in longitudinal arrays at the pontine flexure. Most regions of the pons and medulla are characterized by large bands of migrating neurons with few nuclear divisions. A few cells are settling in the barely recognizable superior olivary complex and many are settling in the reticular formation throughout the pons and medulla. Some facial motor neurons are migrating from medial to lateral, leaving behind their axons in a small, but definite genu of the facial motor nerve. Migrating inferior olive neurons are in the posterior intramural migratory stream outside the precerebellar neuroepithelium in the posterior lower rhombic lip, but no neurons have settled in the inferior olivary complex. The solitary nucleus and tract cannot be identified, although solitary nuclear neurons are undoubtedly migrating outside the rhombomere 6 medullary neuroepithelium. The subpial fiber band is thick in the pons and medulla, especially at the entry points of the sensory nerves. The cerebellar neuroepithelium is much smaller than at GW6.5. Some early-generated deep nuclear neurons are migrating in the cellular layers of the cerebellar transitional field, but these and the fibrous layers are thinner and less definite than at GW6.5.

M1000 Computer-aided 3-D Brain Reconstructions

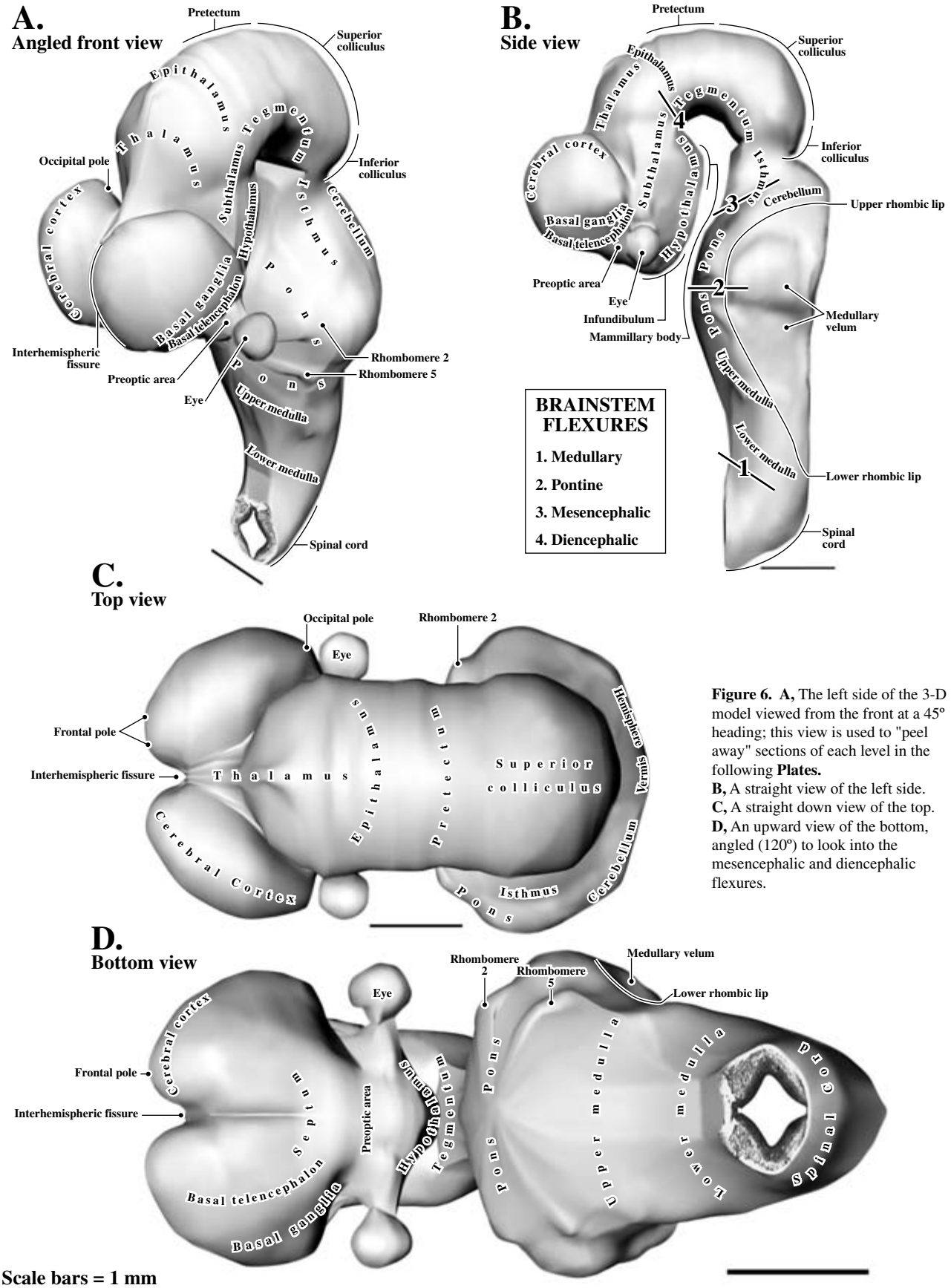


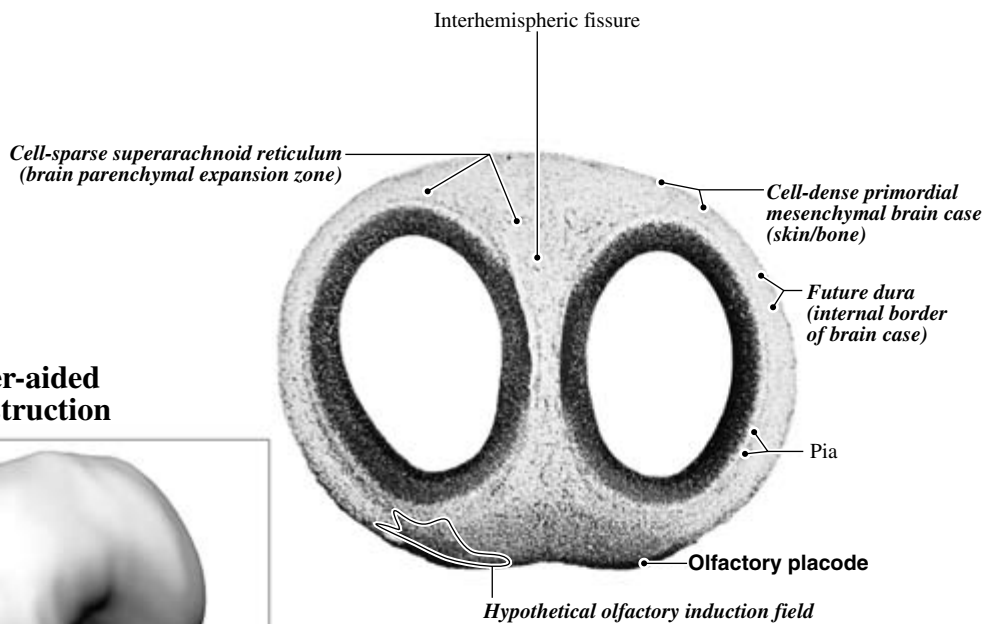
Figure 6. A, The left side of the 3-D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.**
B, A straight view of the left side.
C, A straight down view of the top.
D, An upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures.

Scale bars = 1 mm

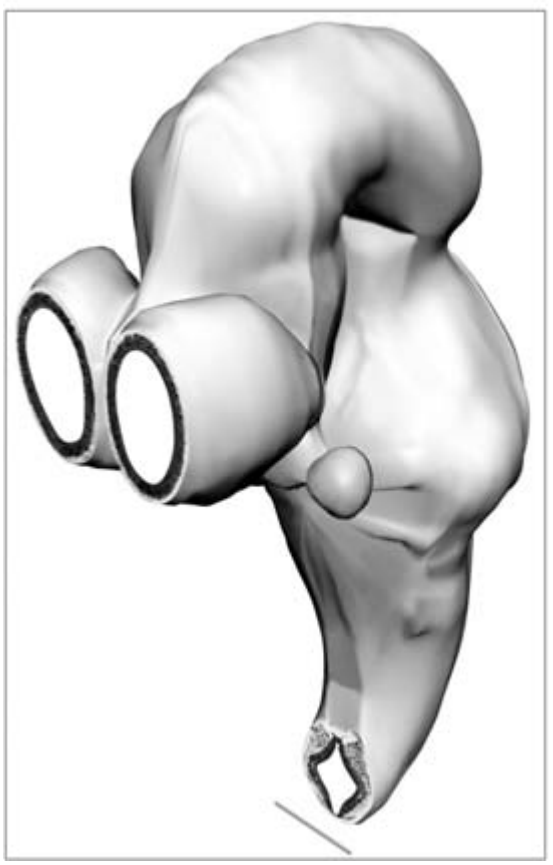
PLATE 85A

GW5.5 Coronal
CR 10 mm
M1000
Level 1: Section 29

Non-neural structures labeled



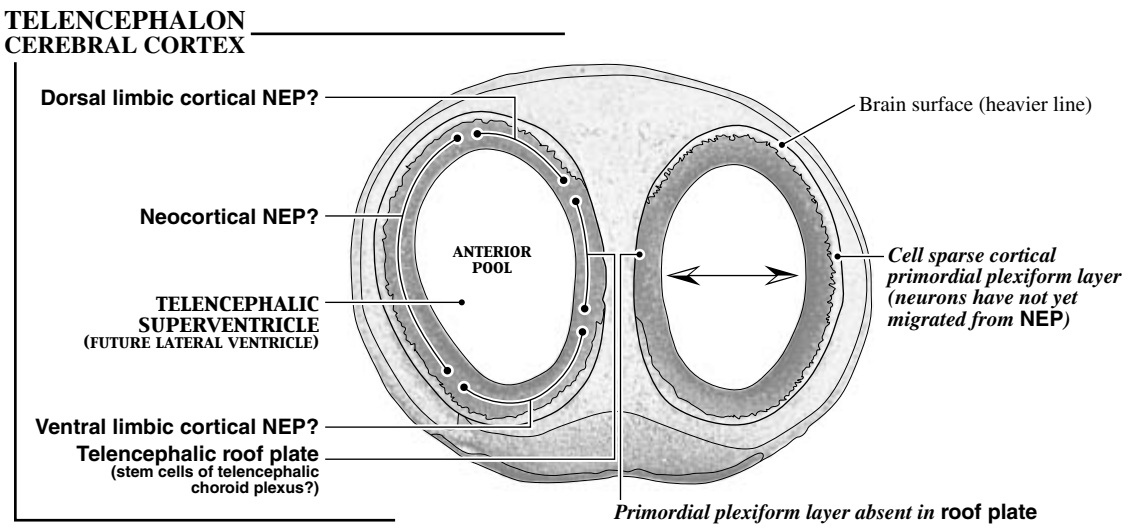
Level 1: Computer-aided 3-D Brain Reconstruction



1 mm

PLATE 85B

Neural structures labeled



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

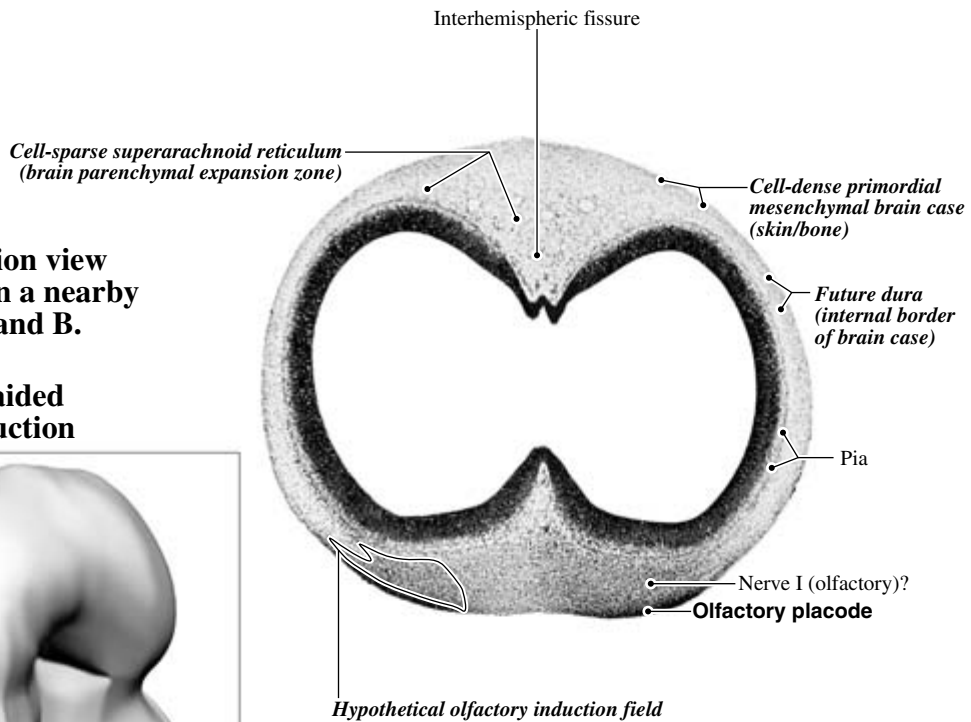
NEP - Neuroepithelium

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 86A

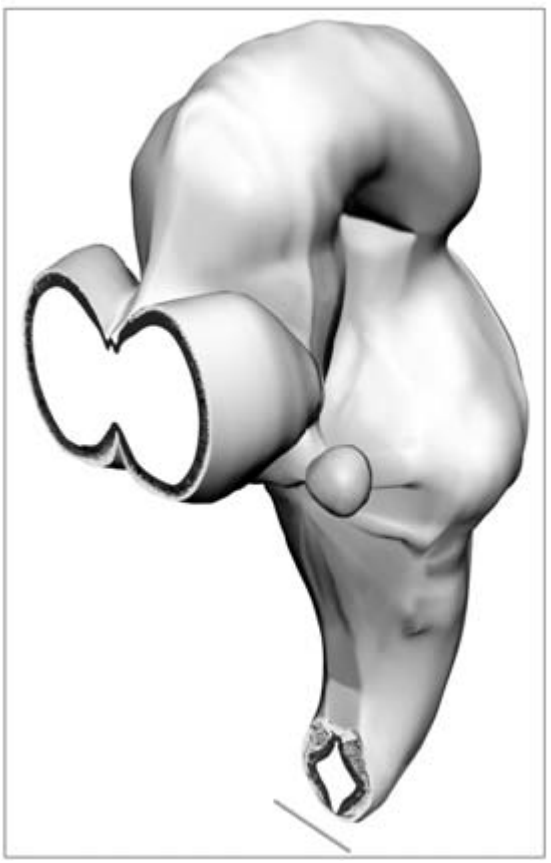
GW5.5 Coronal
CR 10 mm
M1000
Level 2: Section 42

Peripheral neural and non-neural structures labeled



See a high magnification view of the telencephalon in a nearby section in Plates 99A and B.

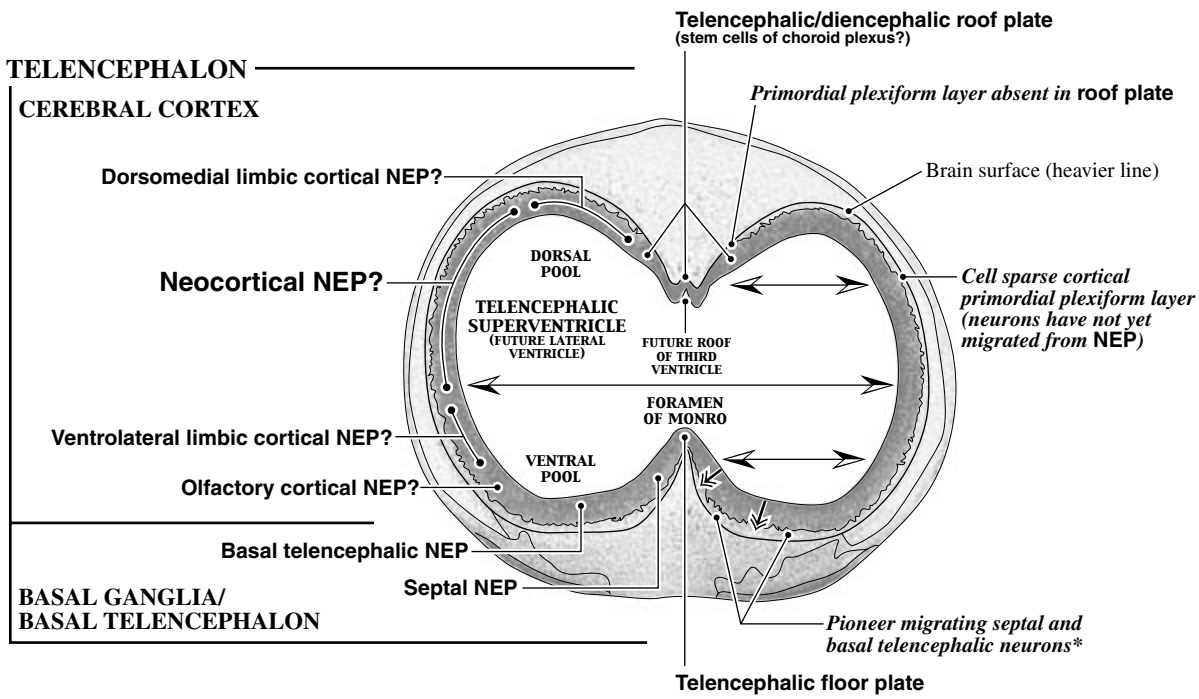
Level 2: Computer-aided 3-D Brain Reconstruction



1 mm

PLATE 86B

Central neural structures labeled



Note that the group of basal telencephalic migrating neurons may contain mitral cells heading for the future olfactory evagination.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - Neuroepithelium

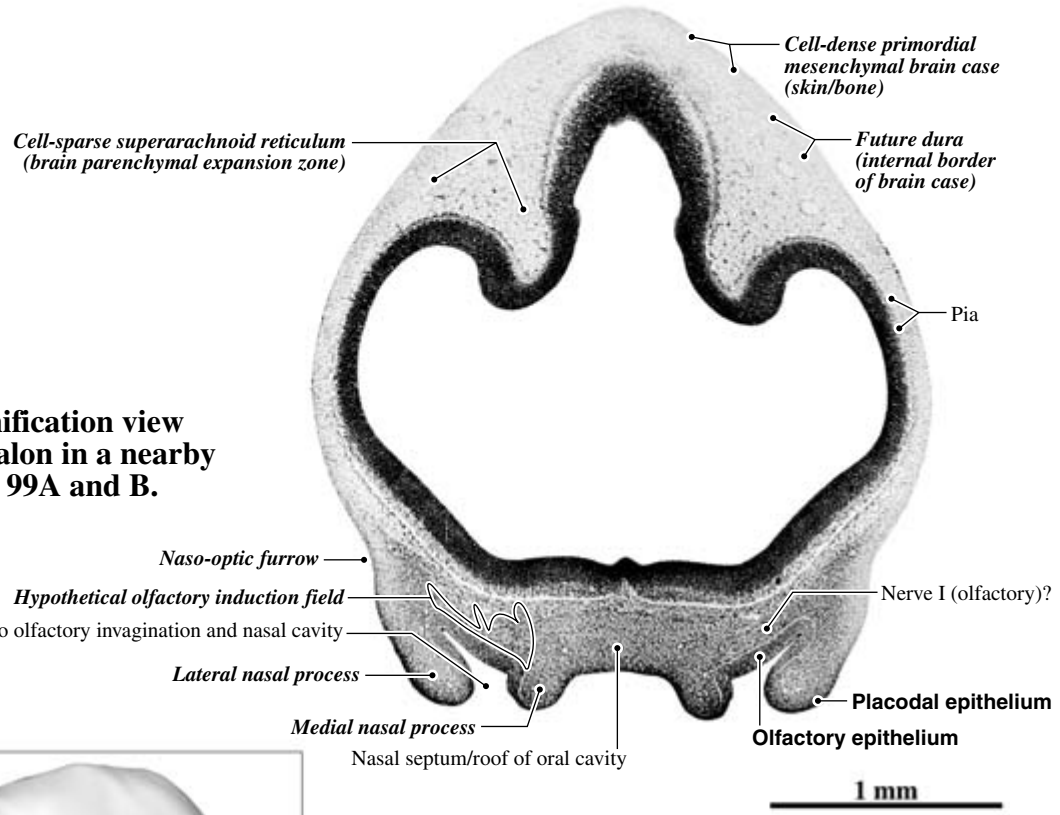
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

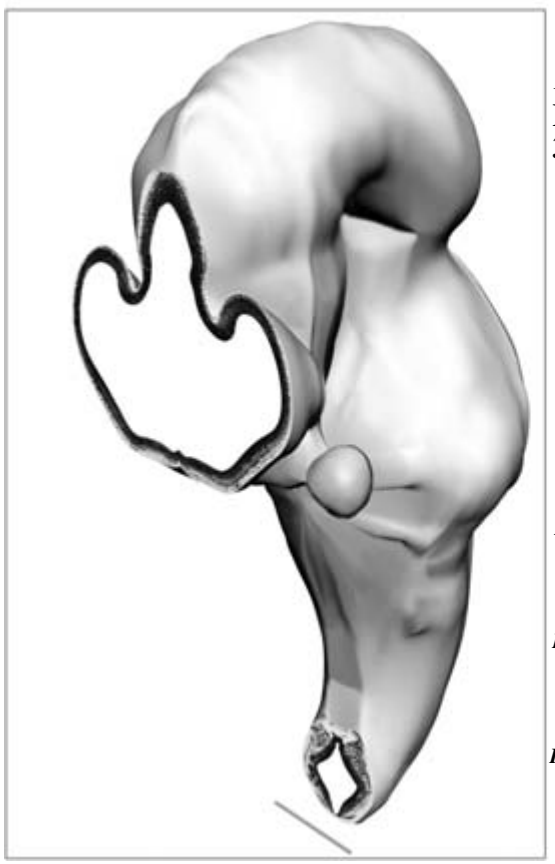
PLATE 87A

GW5.5 Coronal
CR 10 mm
M1000
Level 3: Section 100

Peripheral neural and non-neural structures labeled



See a high magnification view of the telencephalon in a nearby section in Plates 99A and B.



Level 3: Computer-aided 3-D Brain Reconstruction

The GW5.5 Face and Neck
Figure 247C modified (Patten, 1953, p. 429.)

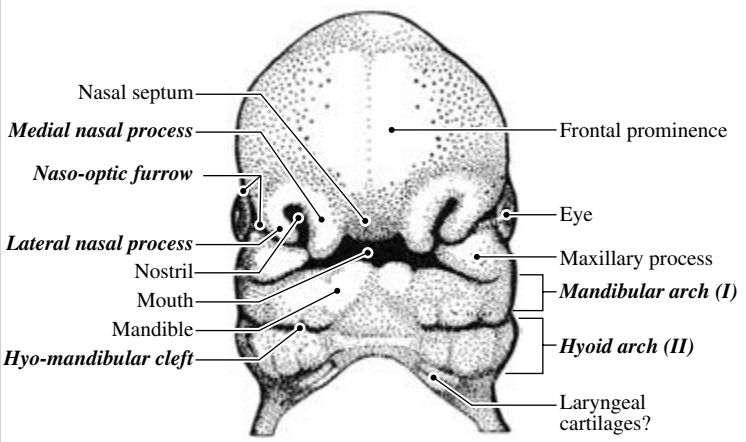
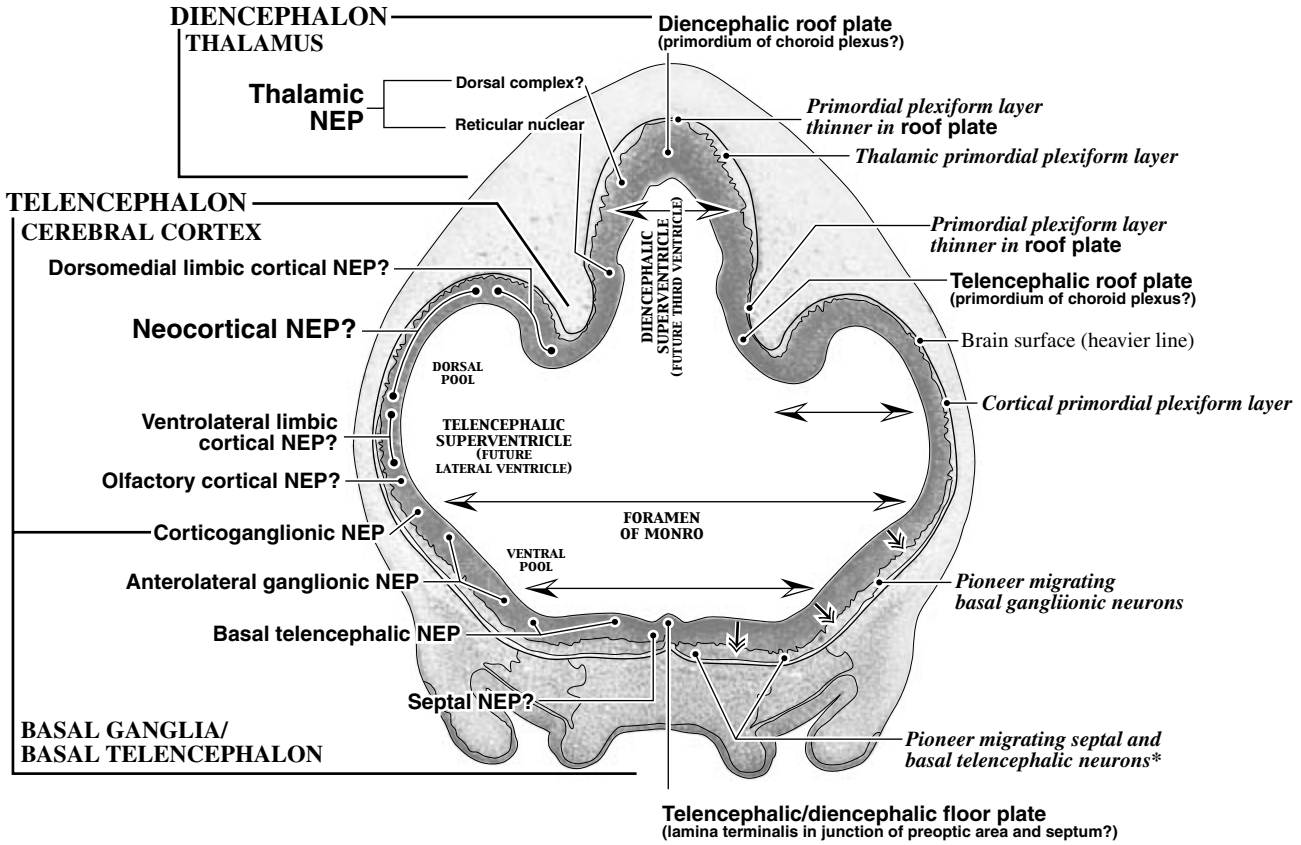


PLATE 87B

Central neural structures labeled



Note that the group of basal telencephalic migrating neurons may contain mitral cells heading for the future olfactory evagination.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - Neuroepithelium

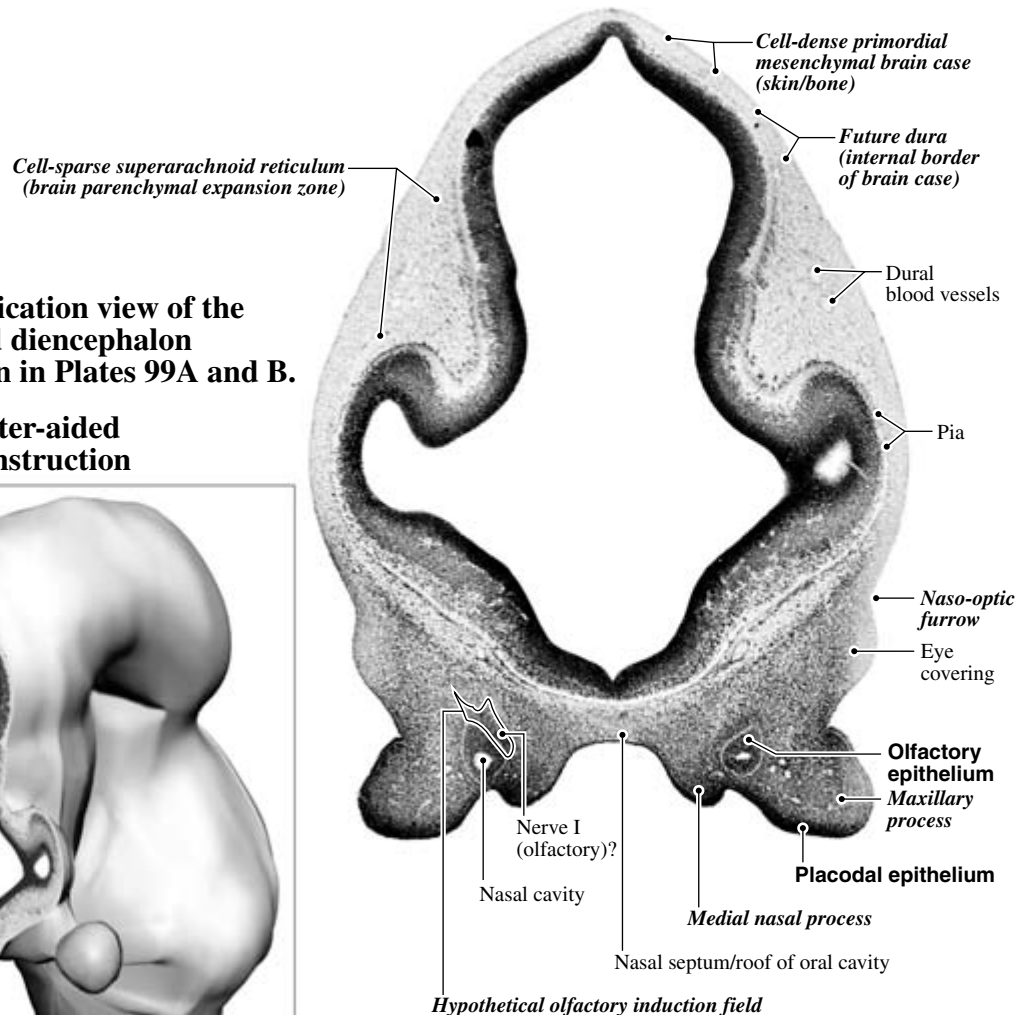
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 88A

GW5.5 Coronal
CR 10 mm
M1000
Level 4: Section 128

Peripheral neural and non-neural structures labeled



See a high magnification view of the telencephalon and diencephalon in a nearby section in Plates 99A and B.

Level 4: Computer-aided 3-D Brain Reconstruction

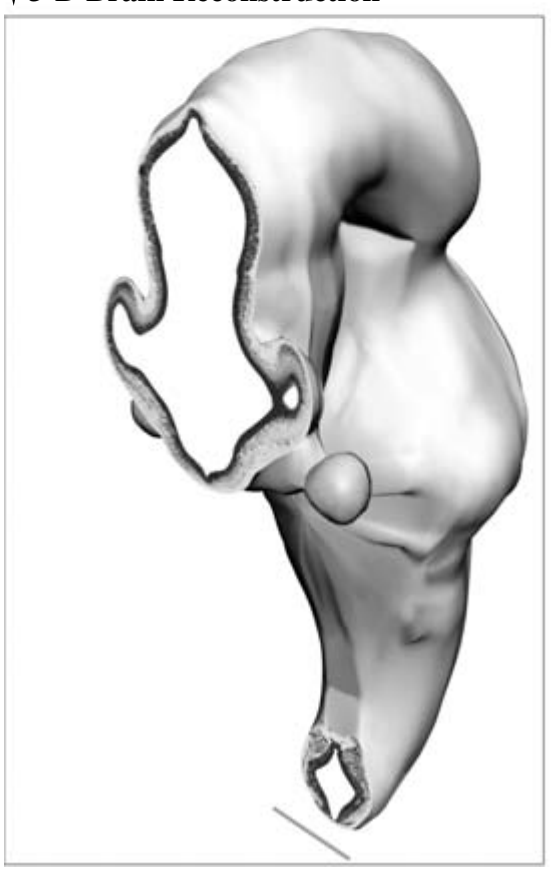
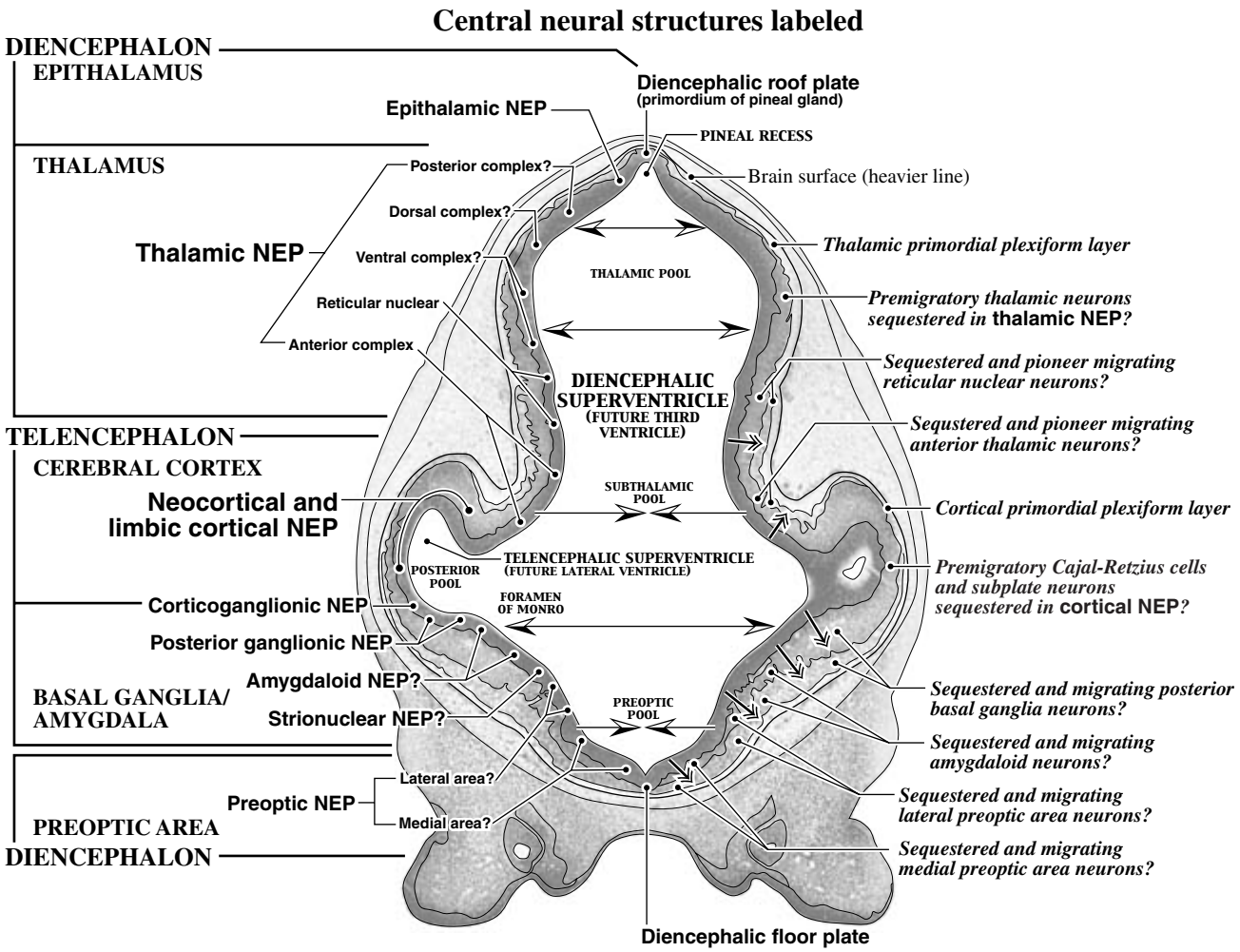


PLATE 88B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

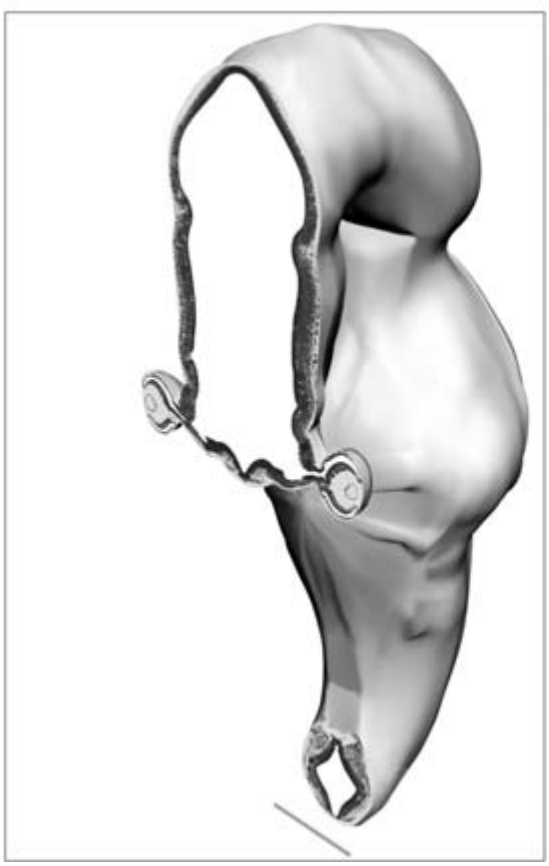
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

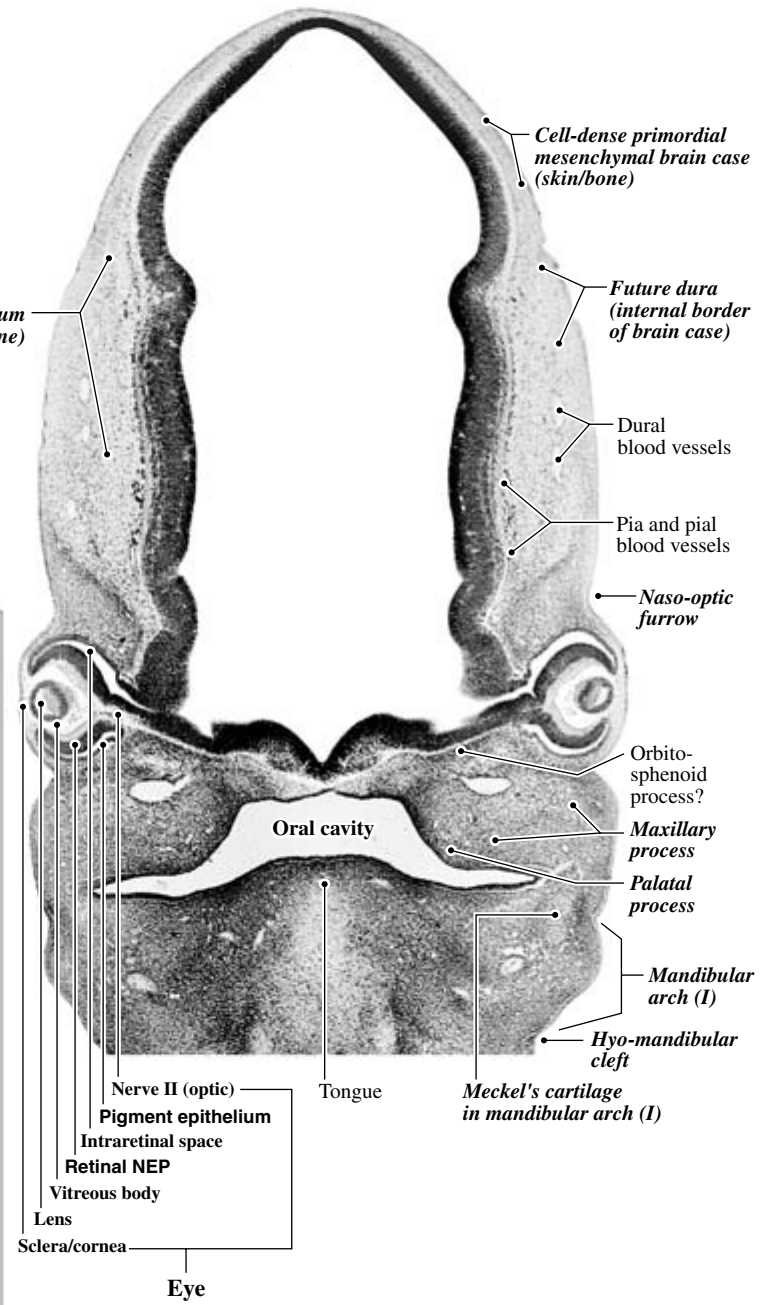
NEP - Neuroepithelium

PLATE 89A

GW5.5 Coronal
CR 10 mm
M1000
Level 5: Section 169

Peripheral neural and non-neural structures labeled



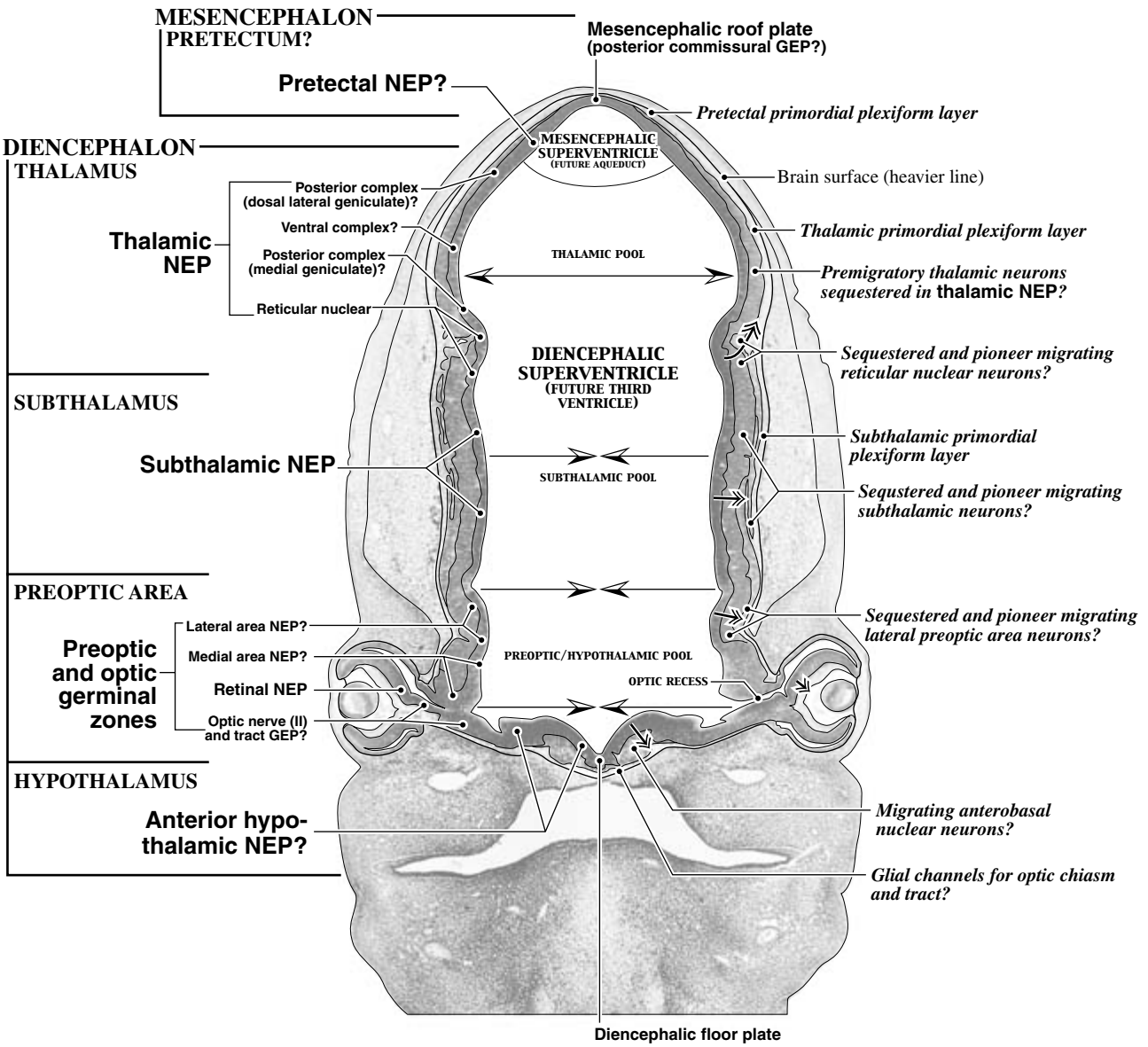


Level 5: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 89B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

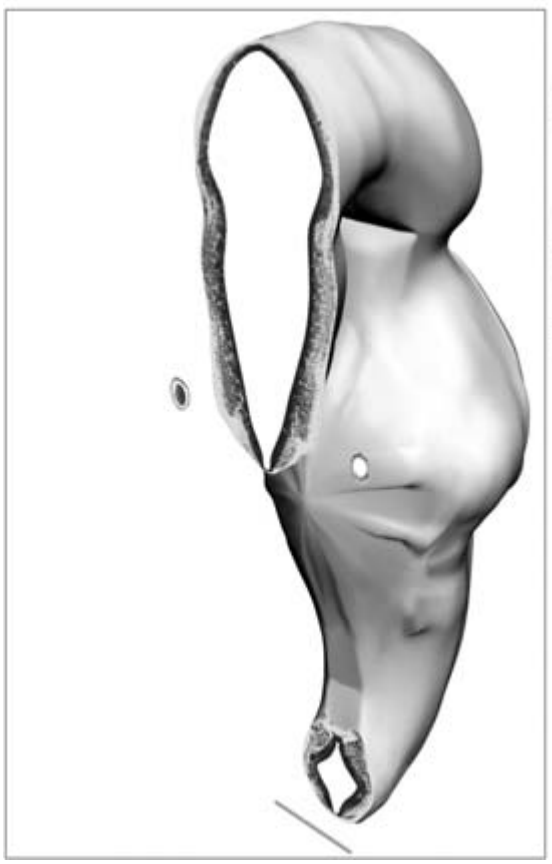
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 90A

GW5.5 Coronal
CR 10 mm
M1000
Level 6: Section 192

Peripheral neural and non-neural structures labeled

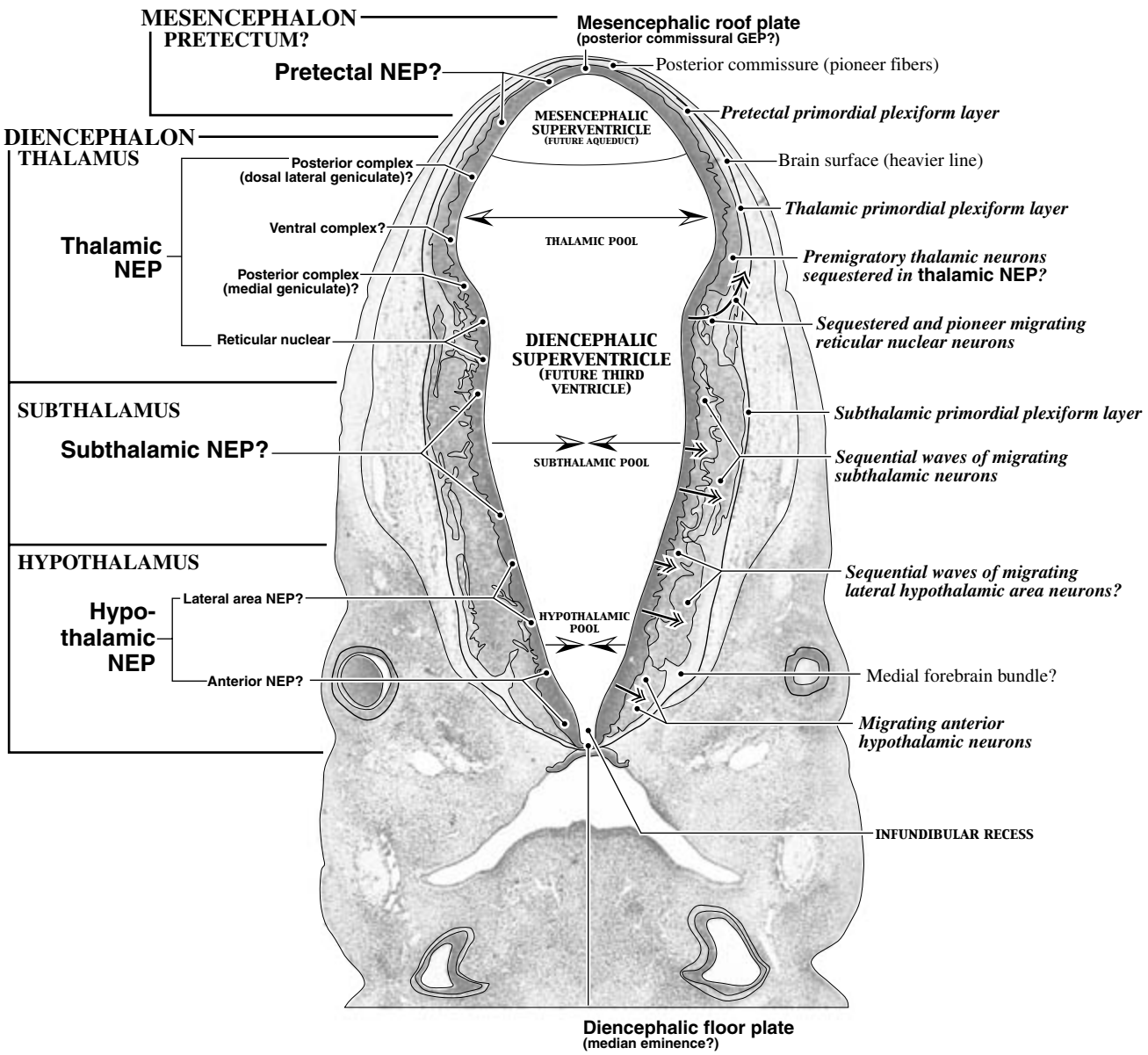


Level 6: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 90B

Central neural structures labeled



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

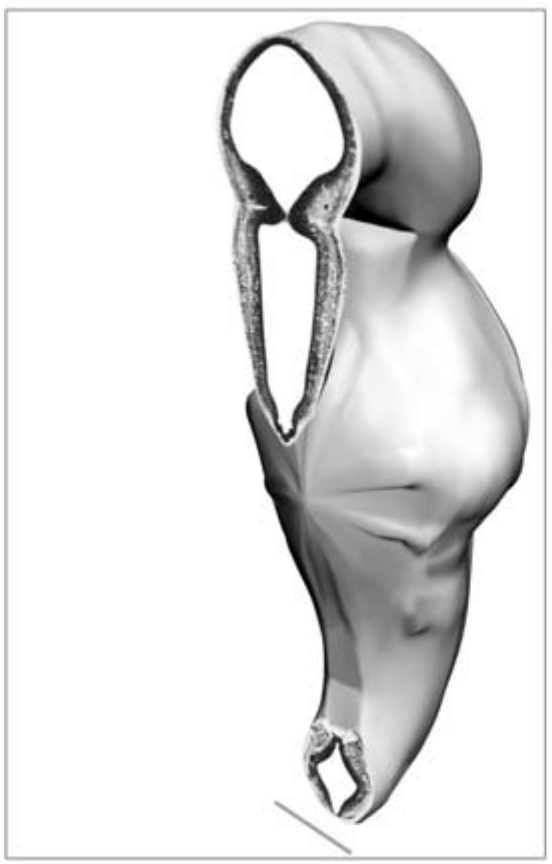
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 91A

GW5.5 Coronal
CR 10 mm
M1000
Level 7: Section 215

Peripheral neural and non-neural structures labeled

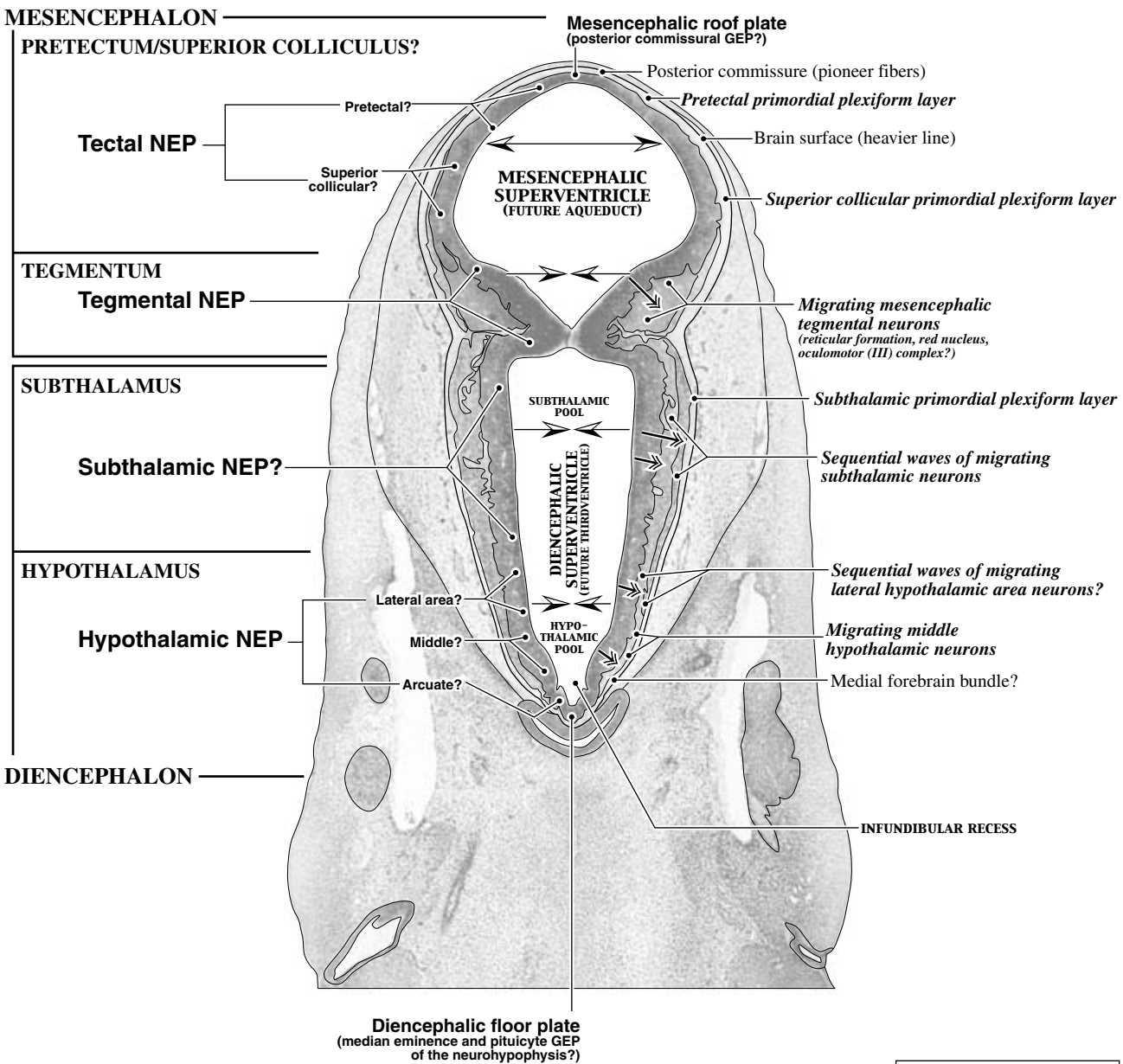


Level 7: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 91B

Central neural structures labeled



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 92A

GW5.5 Coronal
CR 10 mm
M1000
Level 8: Section 237

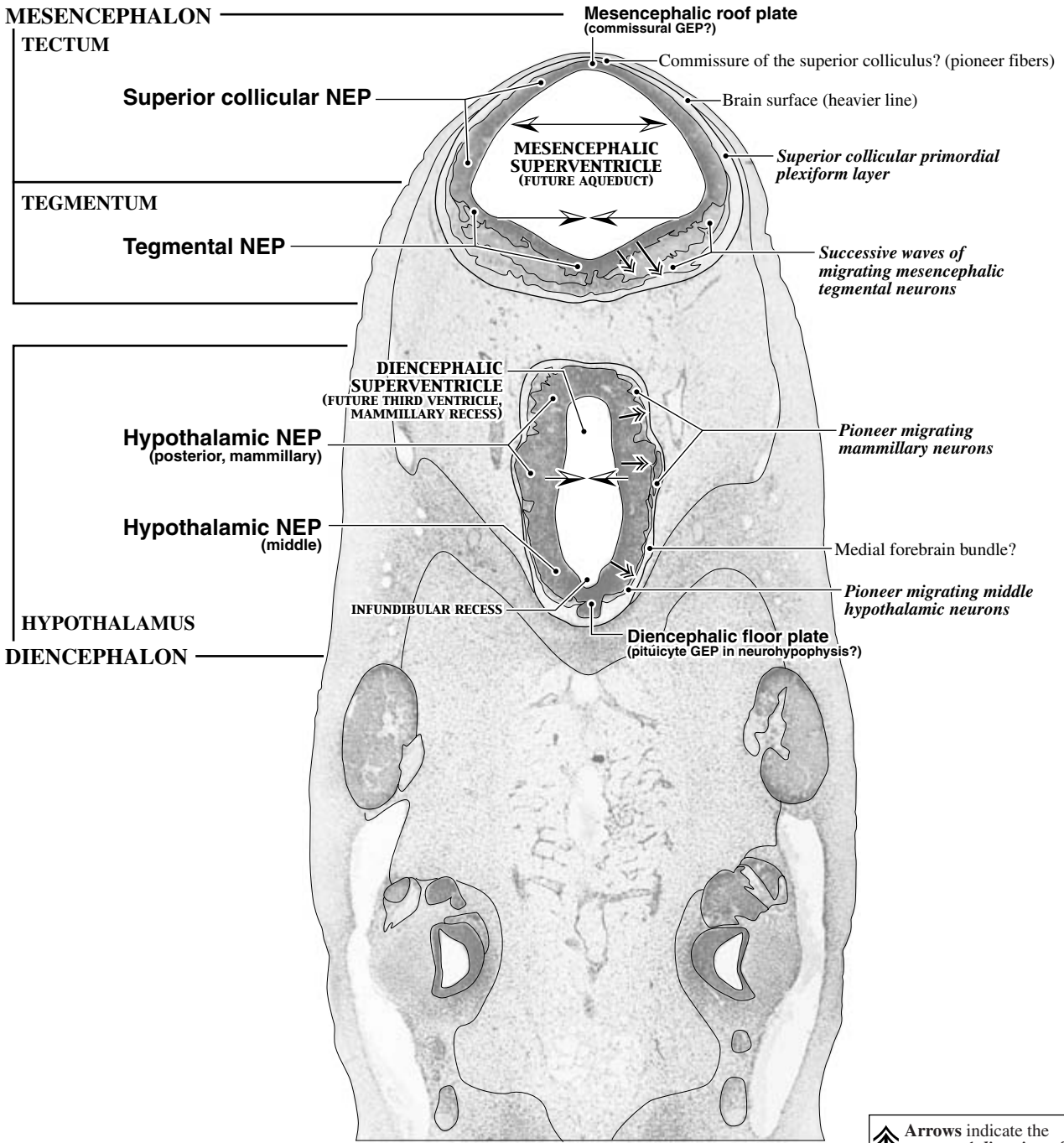
Peripheral neural and non-neural structures labeled

Level 8: Computer-aided 3-D Brain Reconstruction

1 mm

PLATE 92B

Central neural structures labeled



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 93A

GW5.5 Coronal
CR 10 mm
M1000
Level 9: Section 255

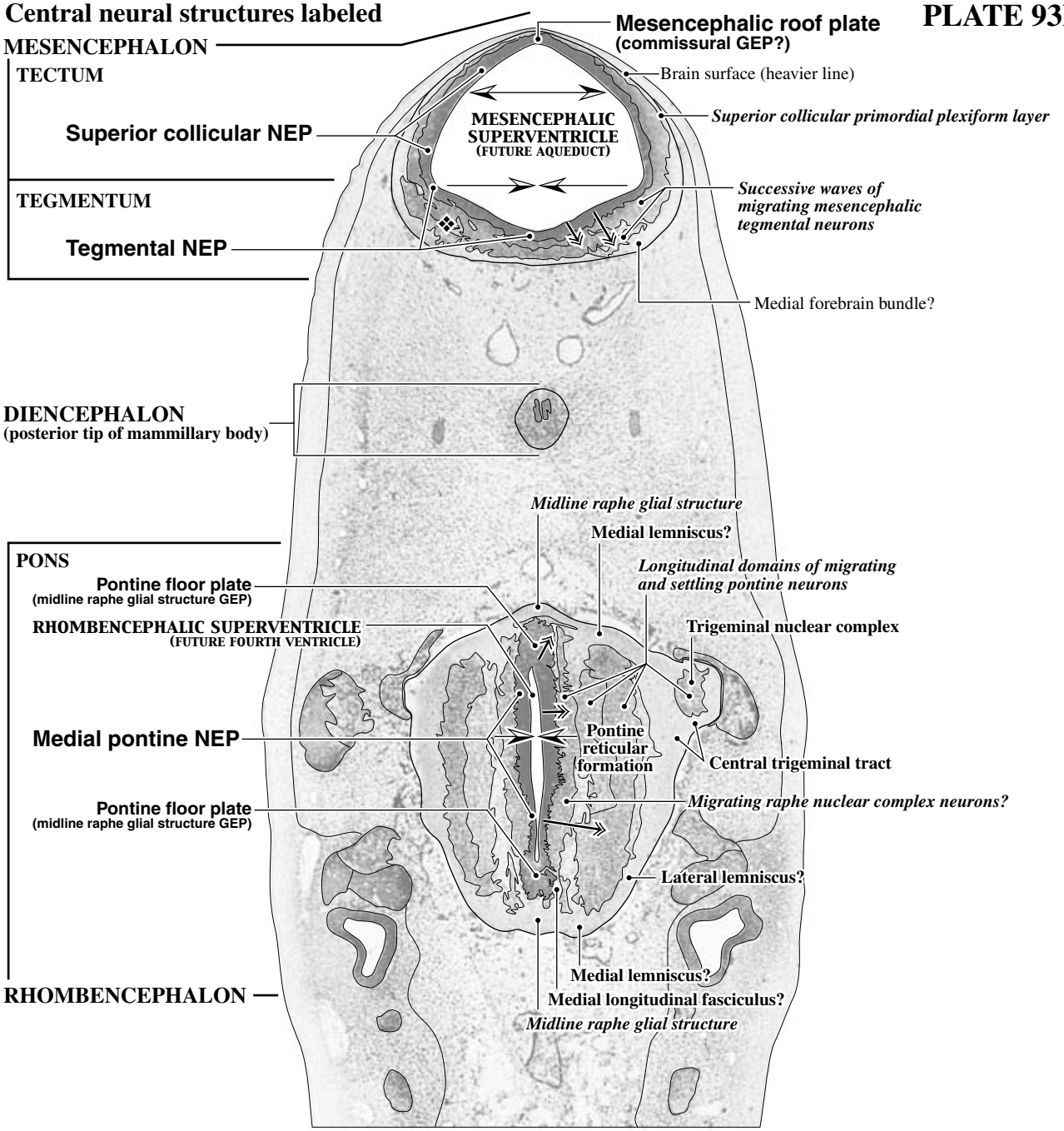
Peripheral neural and non-neural structures labeled

Level 9: Computer-aided 3-D Brain Reconstruction

1 mm

Central neural structures labeled

PLATE 93B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

PLATE 94A

Peripheral neural and non-neural structures labeled

GW5.5 Coronal
CR 10 mm
M1000
Level 10: Section 269

Pia and pial blood vessels

Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

Cell-dense primordial mesenchymal brain case (skin/bone)

Future dura (internal border of brain case) and blood vessels

Basilar artery

Nerve V *boundary cap*

Schwann cell GEP *in boundary caps?*

Nerve VIII *boundary cap*

Nerve VIII (vestibulocochlear)

Vestibular ganglion (VIII)

Superior glossopharyngeal ganglion (IX)?

Petrous temporal bone

Superior vagal ganglion (X)?

Vertebral artery

Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

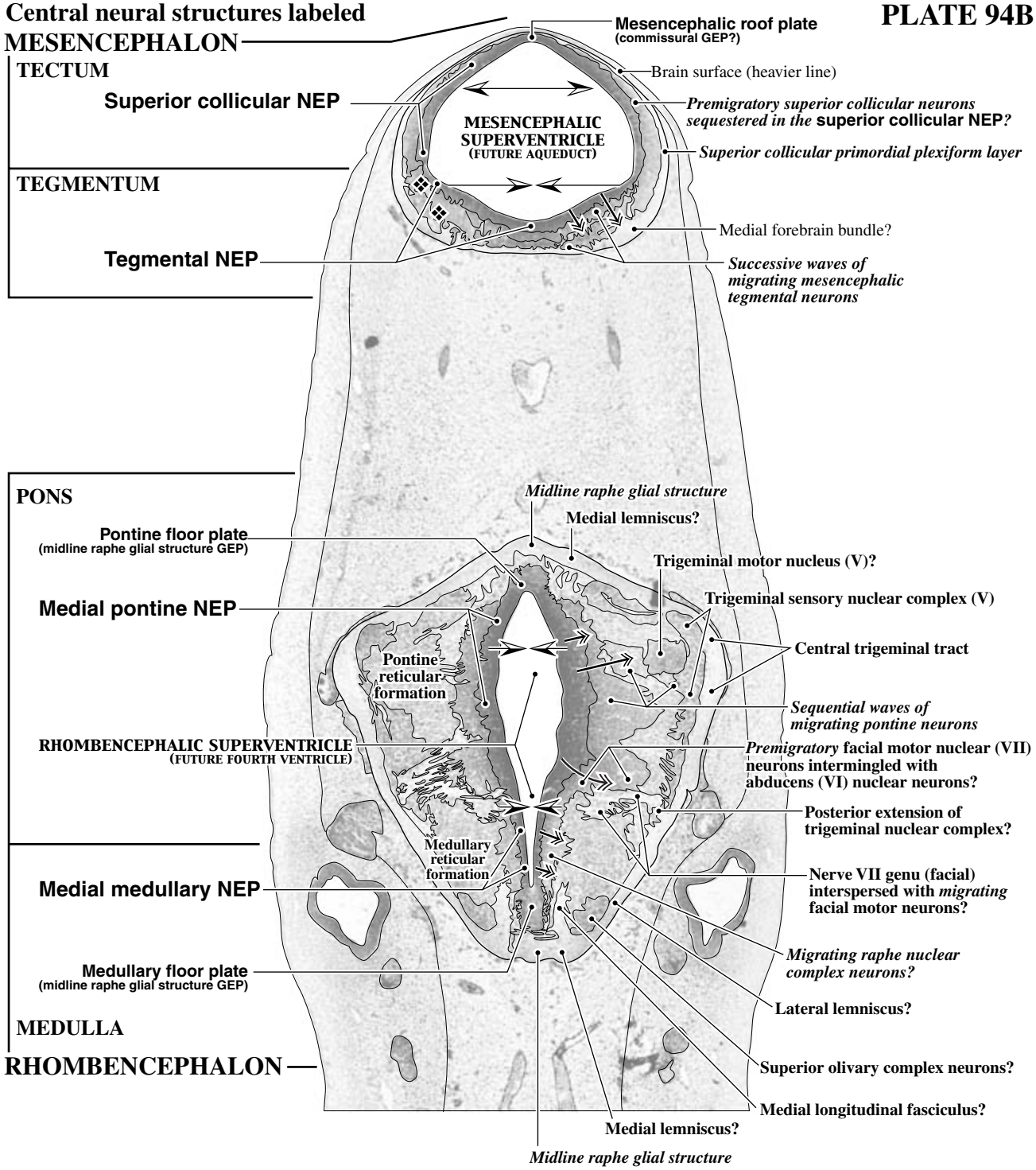
Otic vesicle and **epithelium** *(future cochlea, semicircular canals, utricle, and saccule)*

Level 10: Computer-aided 3-D Brain Reconstruction

1 mm

Central neural structures labeled

PLATE 94B



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

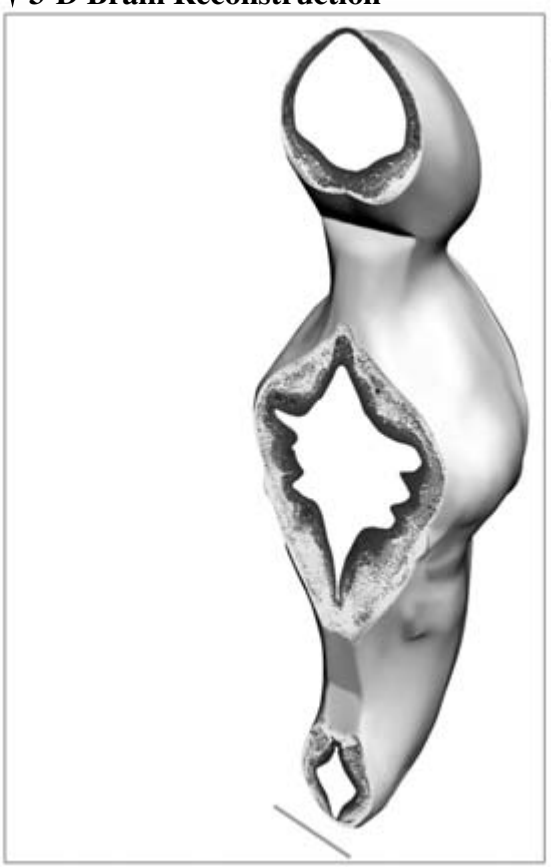
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

PLATE 95A

GW5.5 Coronal
CR 10 mm
M1000
Level 11: Section 285

Peripheral neural and non-neural structures labeled



Level 11: Computer-aided 3-D Brain Reconstruction

Pia and pial blood vessels

Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

Cell-dense primordial mesenchymal brain case (skin/bone)

Future dura (internal border of brain case) and blood vessels

Nerve III sheath (oculomotor)

Nerve VIII *boundary cap* **(Schwann cell GEP?)**

Spiral ganglion (VIII) *budding from* **otic epithelium***?*

Petrous temporal bone

Superior glossopharyngeal ganglion (IX)?

Superior vagal ganglion (X)?

Dorsal root ganglion

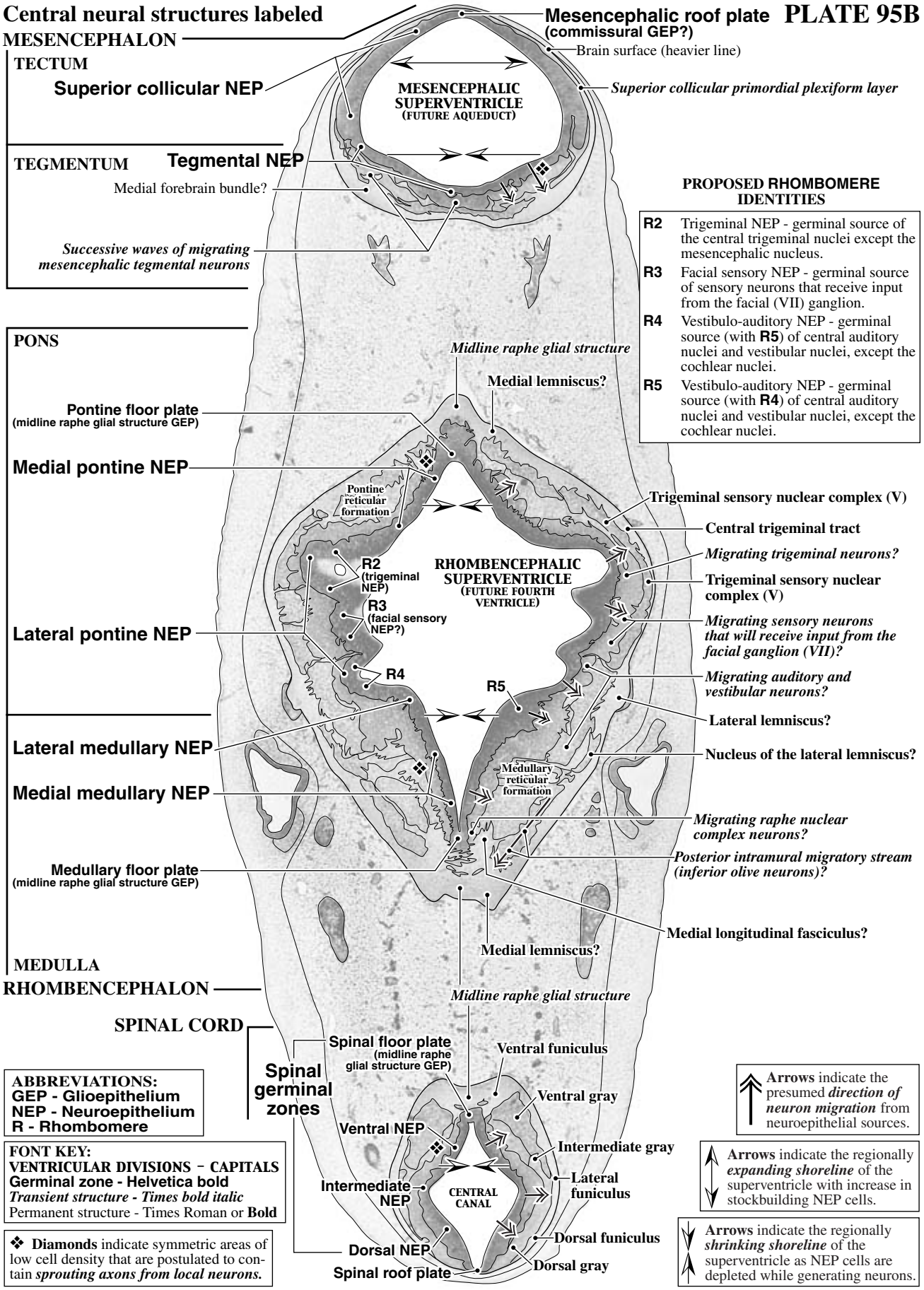
Cell-sparse superarachnoid reticulum (brain parenchymal expansion zone)

Otic vesicle and* epithelium *(future cochlea, semicircular canals, utricle, and saccule)

1 mm

Central neural structures labeled

PLATE 95B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 96A

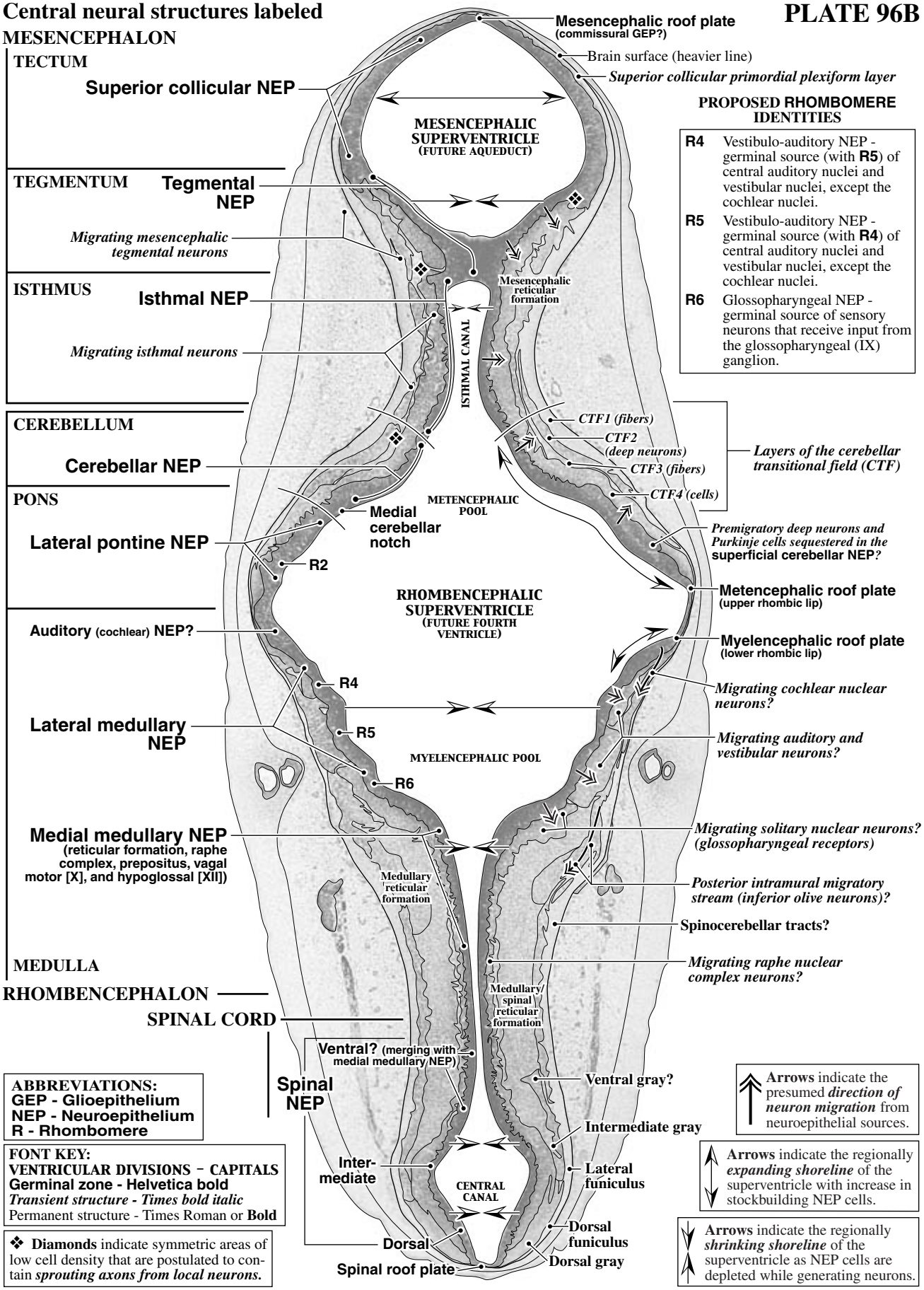
GW5.5 Coronal
CR 10 mm
M1000
Level 12: Section 308

Peripheral neural and non-neural structures labeled

Level 12: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 96B



PROPOSED RHOMBOMERE IDENTITIES

R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

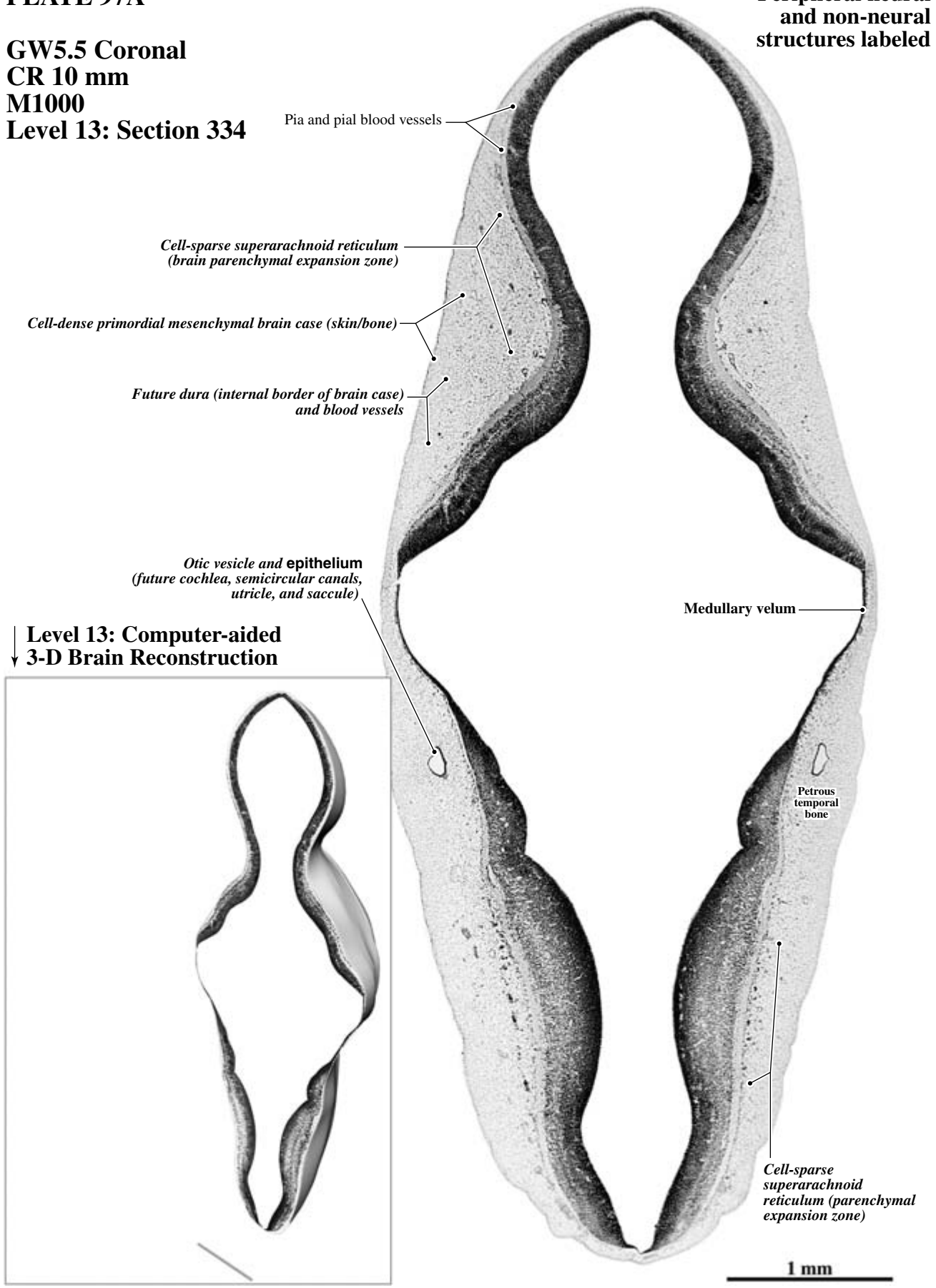
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 97A

Peripheral neural and non-neural structures labeled

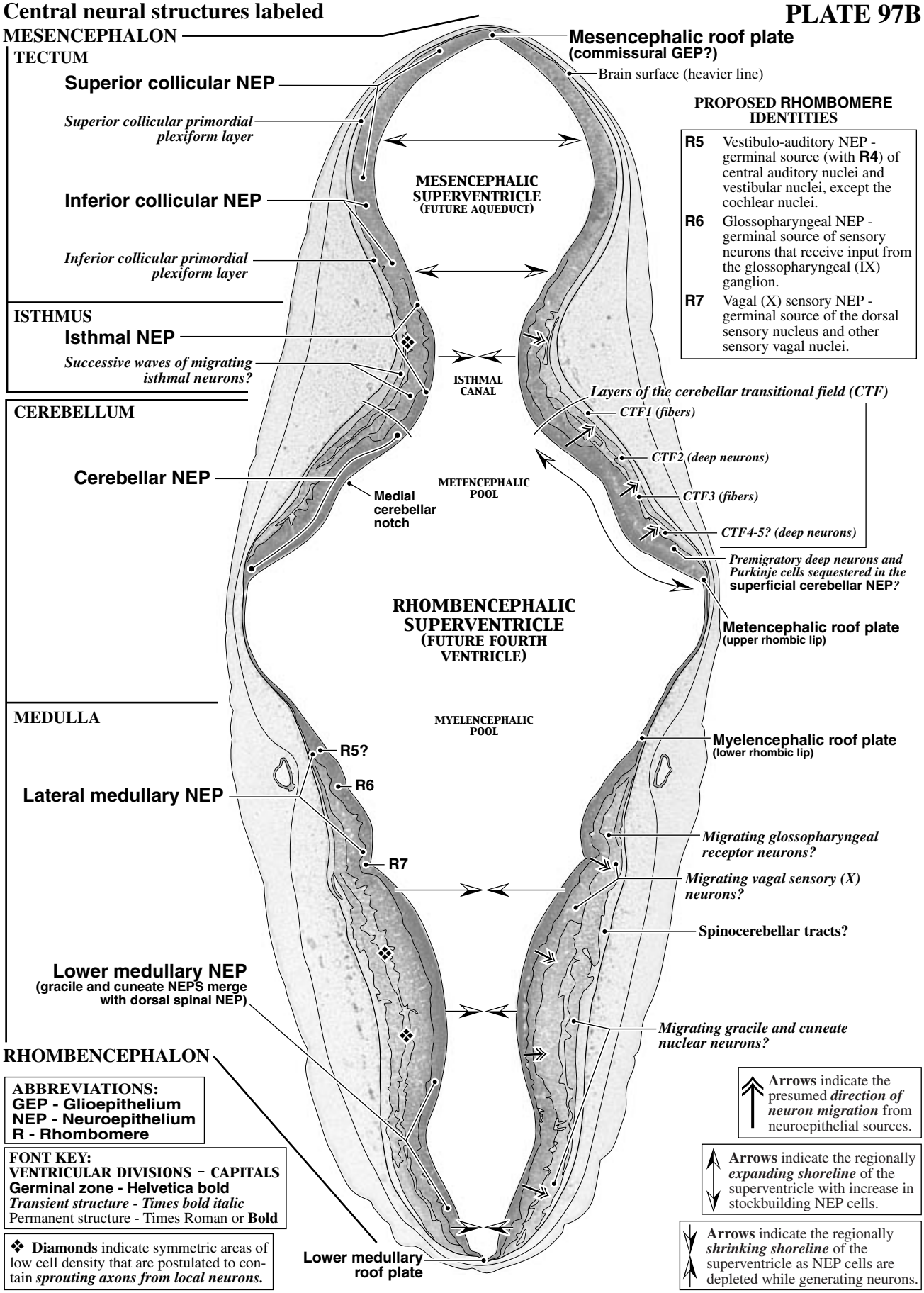
GW5.5 Coronal
CR 10 mm
M1000
Level 13: Section 334



Level 13: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 97B



PROPOSED RHOMBOMERE IDENTITIES

R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

❖ **Diamonds** indicate symmetric areas of low cell density that are postulated to contain ***sprouting axons from local neurons.***

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

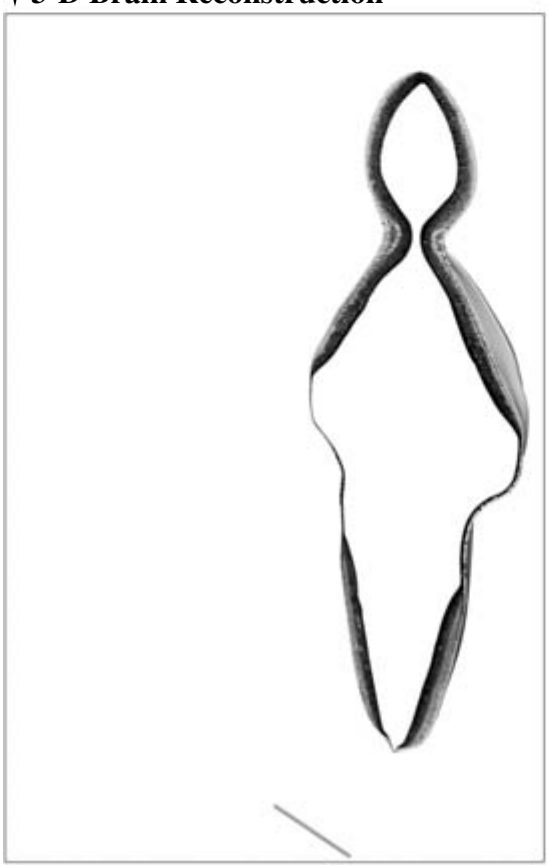
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

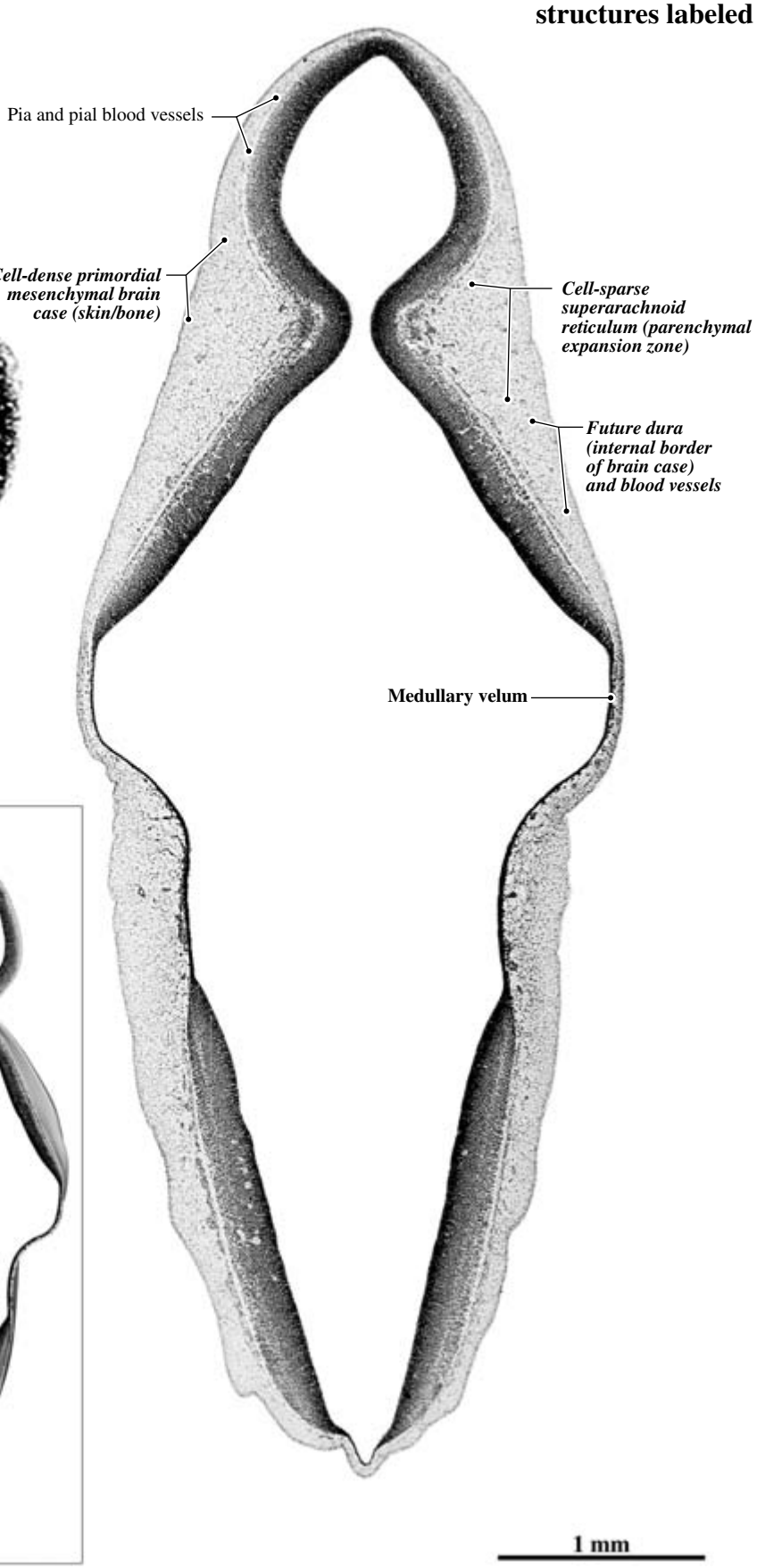
PLATE 98A

GW5.5 Coronal
CR 10 mm
M1000
Level 14: Section 376

Level 14: Computer-aided 3-D Brain Reconstruction



Peripheral neural and non-neural structures labeled



Central neural structures labeled

PLATE 98B

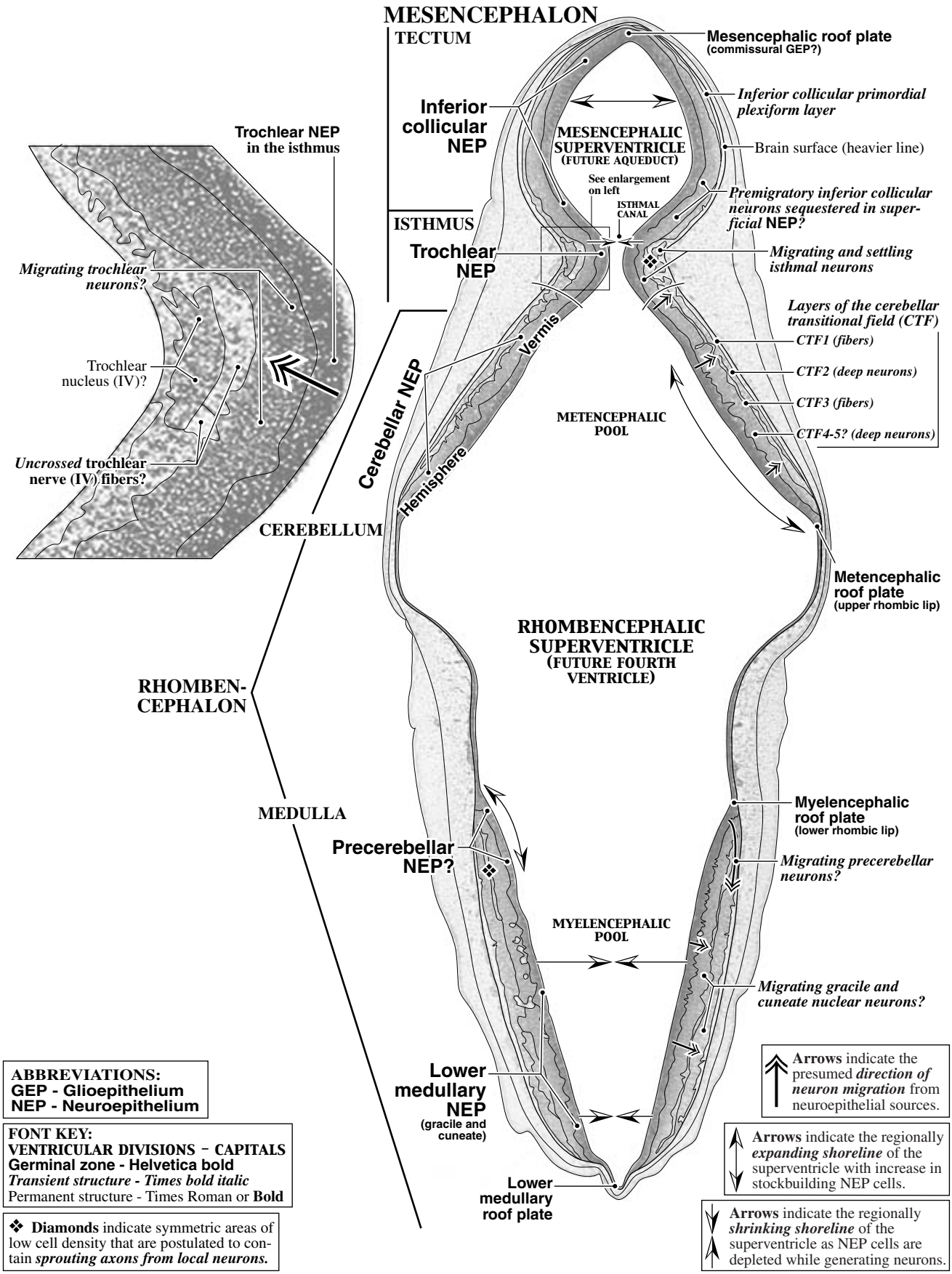
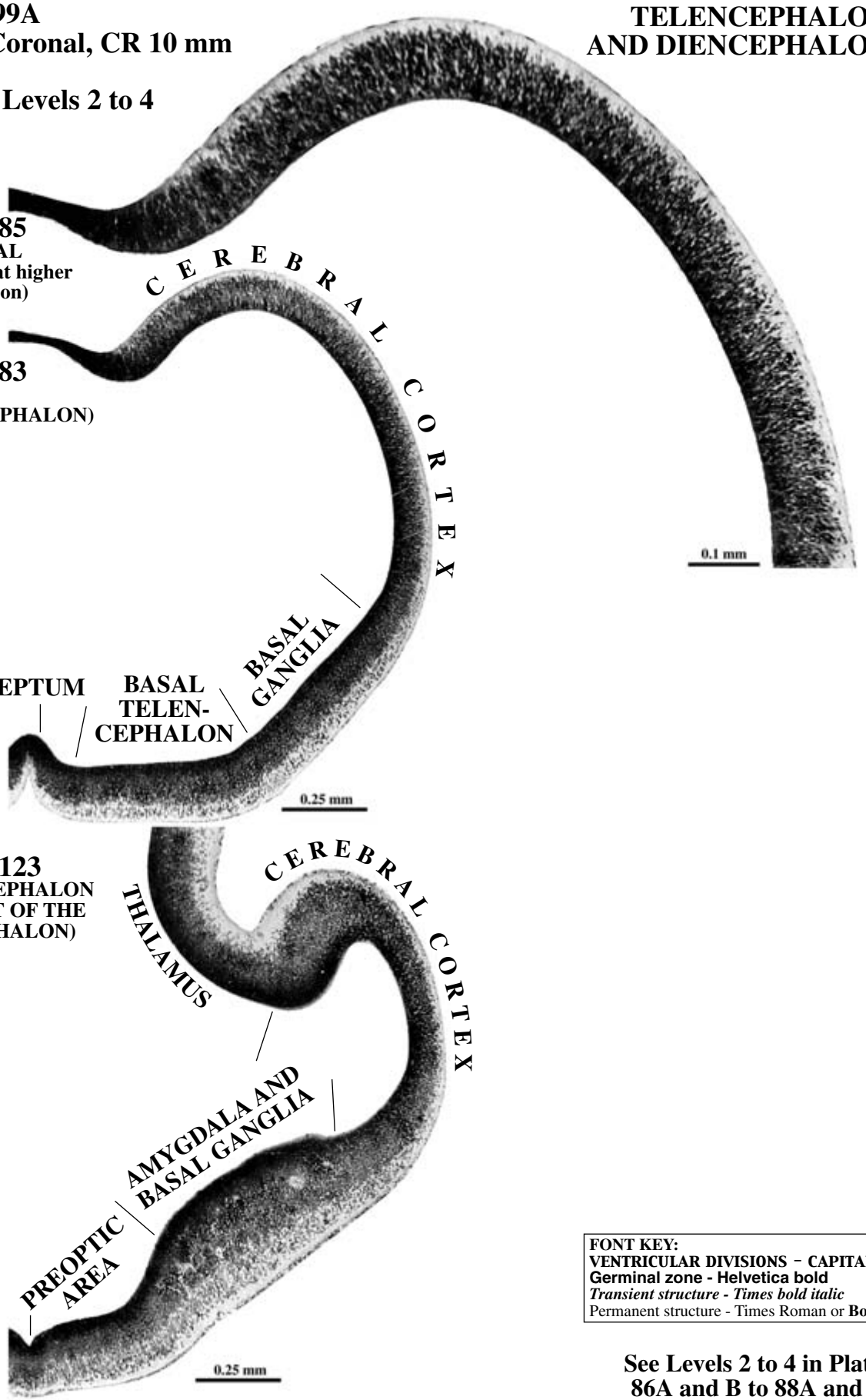


PLATE 99A
GW5.5 Coronal, CR 10 mm
M1000
Between Levels 2 to 4

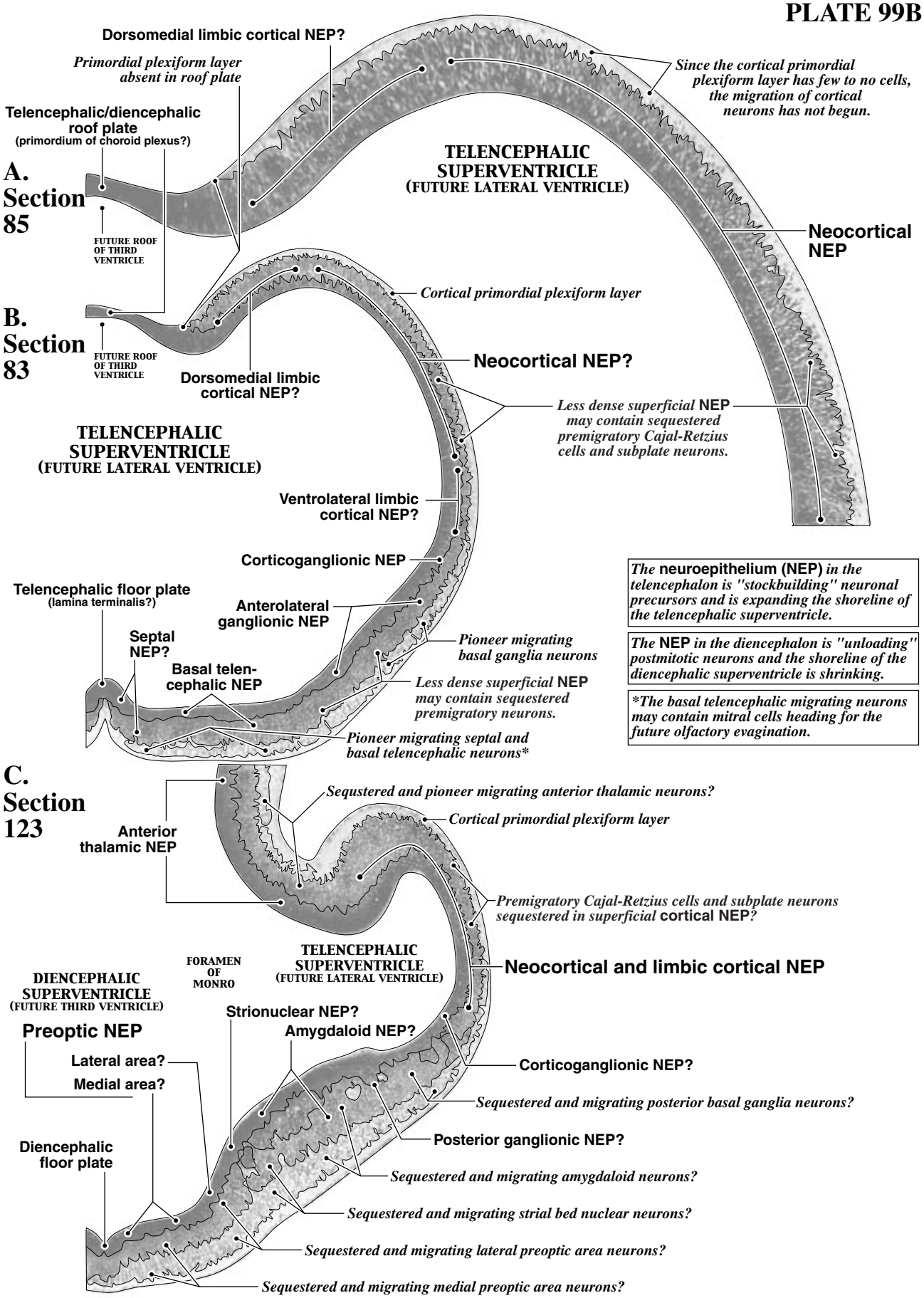
TELENCEPHALON AND DIENCEPHALON



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

See Levels 2 to 4 in Plates 86A and B to 88A and B.

PLATE 99B


Dorsomedial limbic cortical NEP?
Primordial plexiform layer absent in roof plate
Telencephalic/diencephalic roof plate
(primordium of choroid plexus?)
A. Section 85
FUTURE ROOF OF THIRD VENTRICLE
Since the cortical primordial plexiform layer has few to no cells, the migration of cortical neurons has not begun.
TELENCEPHALIC SUPERVENTRICLE
(FUTURE LATERAL VENTRICLE)
Neocortical NEP
B. Section 83
FUTURE ROOF OF THIRD VENTRICLE
Cortical primordial plexiform layer
Neocortical NEP?
Dorsomedial limbic cortical NEP?
Less dense superficial NEP may contain sequestered premigratory Cajal-Retzius cells and subplate neurons.
TELENCEPHALIC SUPERVENTRICLE
(FUTURE LATERAL VENTRICLE)
Ventrolateral limbic cortical NEP?
Corticoganglionic NEP
Telencephalic floor plate
(lamina terminalis?)
Anterolateral ganglionic NEP
Septal NEP?
Basal telencephalic NEP
Pioneer migrating basal ganglia neurons
Less dense superficial NEP may contain sequestered premigratory neurons.
Pioneer migrating septal and basal telencephalic neurons*
The neuroepithelium (NEP) in the telencephalon is "stockbuilding" neuronal precursors and is expanding the shoreline of the telencephalic superventricle.
The NEP in the diencephalon is "unloading" postmitotic neurons and the shoreline of the diencephalic superventricle is shrinking.
*The basal telencephalic migrating neurons may contain mitral cells heading for the future olfactory evagination.
C. Section 123
Sequestered and pioneer migrating anterior thalamic neurons?
Cortical primordial plexiform layer
Anterior thalamic NEP
Premigratory Cajal-Retzius cells and subplate neurons sequestered in superficial cortical NEP?
FORAMEN OF MONRO
TELENCEPHALIC SUPERVENTRICLE
(FUTURE LATERAL VENTRICLE)
Neocortical and limbic cortical NEP
DIENCEPHALIC SUPERVENTRICLE
(FUTURE THIRD VENTRICLE)
Strionuclear NEP?
Amygdaloid NEP?
Preoptic NEP
Lateral area?
Medial area?
Corticoganglionic NEP?
Sequestered and migrating posterior basal ganglia neurons?
Posterior ganglionic NEP?
Diencephalic floor plate
Sequestered and migrating amygdaloid neurons?
Sequestered and migrating strial bed nuclear neurons?
Sequestered and migrating lateral preoptic area neurons?
Sequestered and migrating medial preoptic area neurons?

PART VIII: GW5.5 SAGITTAL

Carnegie Collection specimen #6516 (designated here as C6516) with a 10.5 mm crown-rump length (CR) is estimated to be at gestational week (GW) 5.5. C6516 was fixed in corrosive acetic acid, embedded in a celloidin/paraffin mix, and was cut in 8-µm sagittal sections that were stained with aluminum cochineal. Various orientations of the computer-aided 3-D reconstruction of M1000's brain are used to show the gross external features of a GW5.5 brain (**Figure 7**). Like most sagittally cut specimens, C6516's sections are not parallel to the midline; **Figure 7** shows the approximate rotations in front (**B**) and back views (**C**). We photographed 65 sections at low magnification from the left to right sides of the brain. Five of the sections, mainly from the left side of the brain, are illustrated in **Plates 100AB to 104AB**. Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify the approximate midline, non-neural structures, peripheral neural structures, and brain ventricular divisions; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 105AB to 114AB** show high-magnification views of many parts of the developing brain.

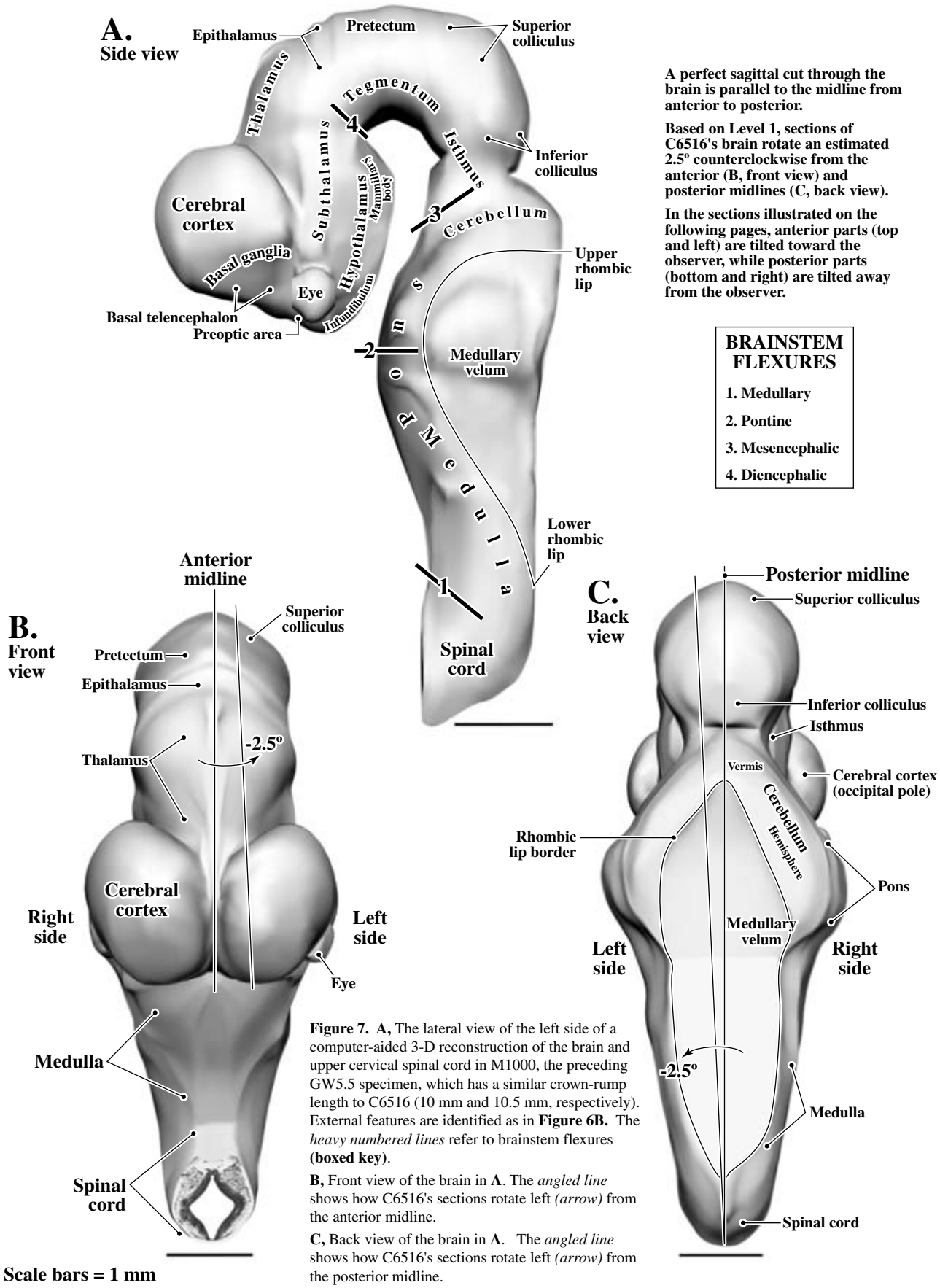
The telencephalon is the smallest major brain structure, composed mainly of a "stockbuilding" neuroepithelium surrounding an expanding telencephalic superventricle. The primordial plexiform layer consists of discontinuous cell-sparse areas. The cortical neuroepithelium nearly reaches the pial surface with some of its outermost feathered edges. It is postulated that the superficial cortical neuroepithelium has postmitotic Cajal-Retzius cells sequestered there prior to migration. Few migrating neurons are adjacent to the very thick basal ganglionic and basal telencephalic neuroepithelia; nevertheless, these neuroepithelia are beginning to form mounds in the floor of the telencephalon. The olfactory epithelium is well established in the nasal cavity and olfactory nerve fibers are growing toward the brain.

The diencephalon is the larger forebrain structure. The "stockbuilding" neuroepithelium surrounds a dorsally expanding superventricle in the future thalamic area. The thick neuroepithelium in the hypothalamic and subthalamic areas is depleting its population of stem cells and postmitotic, premigratory neurons are postulated to be sequestered in its superficial parts. Some migrating and settling young neurons are outside the neuroepithelium in the ventral diencephalic parenchyma adjacent to a thin subpial fibrous band.

The mesencephalon, a prominent arch between the mesencephalic and diencephalic flexures, is relatively smaller than at GW6.5. The roof (tectum and pretectum) of the mesencephalon contains a stockbuilding neuroepithelium adjacent to a thin cell-sparse layer. In contract to the GW6.5 specimens, fibers in the posterior commissure are absent. The tegmental and isthmal neuroepithelia are rapidly unloading their neuronal progeny in dense bands in the adjacent parenchyma. The outermost clumps of young neurons appear to interact with axons in the subpial fiber band.

The rhombencephalon is the largest brain structure. Both the pons and medulla have neuroepithelia that form crescent-shaped rhombomeres in lateral areas. In the sagittal plane, it is easy to see that rhombomeres are unloading their neuronal and glial progeny into parenchymal expansions at the entry zones of sensory cranial nerves V, VII, VIII, IX, and X. Neurons migrating in these areas are tentatively identified as receptors of the incoming sensory axons. For example, trigeminal nuclear neurons (mainly those in the principal sensory nucleus) are generated in rhombomere 2 and migrate outward to mingle with incoming afferents from the trigeminal ganglion. Medially, the pons and medulla contain longitudinal bands of migrating cells, but nuclear subdivisions are generally absent in the parenchyma. The genu of the facial motor nerve forms fascicles adjacent to a neuroepithelium medial to rhombomere 3, the presumptive source of neurons that will be receptive to axons of the facial ganglion. The subpial fiber band is definitely thicker in lateral areas where the axons from sensory ganglia enter the brain. As in the GW6.5 specimens, peripheral nerves have dense glia (Schwann cells), while central fiber tracts are clear. The cerebellum stands out as the most immature rhombencephalic structure. All parts of the cerebellar neuroepithelium are stockbuilding neuronal and glial stem cells. Relatively indistinct layers are in the cerebellar transitional field.

EXTERNAL FEATURES OF THE GW5.5 BRAIN



A perfect sagittal cut through the brain is parallel to the midline from anterior to posterior.

Based on Level 1, sections of C6516's brain rotate an estimated 2.5° counterclockwise from the anterior (B, front view) and posterior midlines (C, back view).

In the sections illustrated on the following pages, anterior parts (top and left) are tilted toward the observer, while posterior parts (bottom and right) are tilted away from the observer.

BRAINSTEM FLEXURES

1. Medullary
2. Pontine
3. Mesencephalic
4. Diencephalic

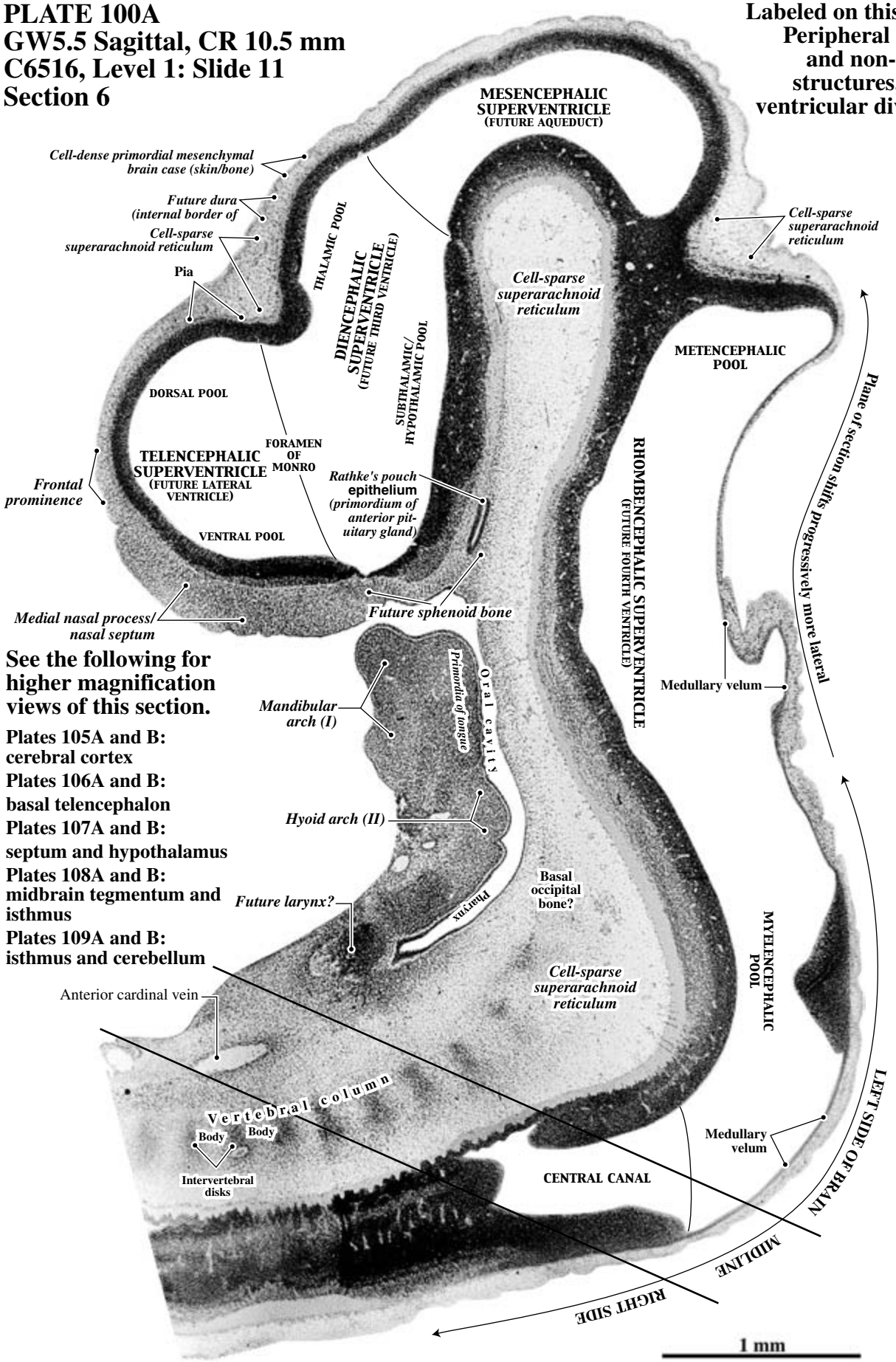
Figure 7. A, The lateral view of the left side of a computer-aided 3-D reconstruction of the brain and upper cervical spinal cord in M1000, the preceding GW5.5 specimen, which has a similar crown-rump length to C6516 (10 mm and 10.5 mm, respectively). External features are identified as in **Figure 6B.** The *heavy numbered lines* refer to brainstem flexures (**boxed key**).

B, Front view of the brain in **A**. The *angled line* shows how C6516's sections rotate left *(arrow)* from the anterior midline.

C, Back view of the brain in **A**. The *angled line* shows how C6516's sections rotate left *(arrow)* from the posterior midline.

PLATE 100A
GW5.5 Sagittal, CR 10.5 mm
C6516, Level 1: Slide 11
Section 6

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



See the following for higher magnification views of this section.

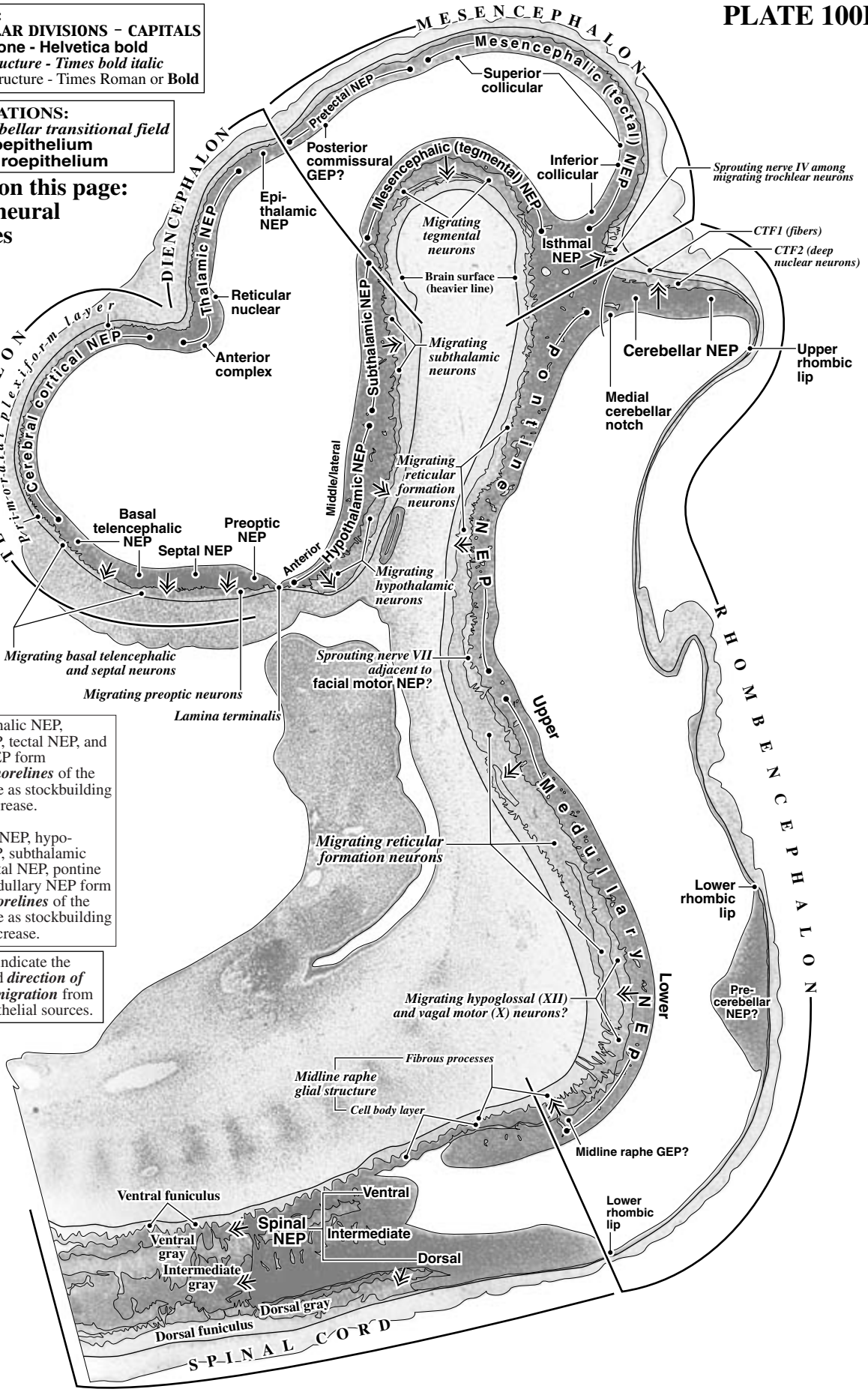
Plates 105A and B: cerebral cortex
Plates 106A and B: basal telencephalon
Plates 107A and B: septum and hypothalamus
Plates 108A and B: midbrain tegmentum and isthmus
Plates 109A and B: isthmus and cerebellum

PLATE 100B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium

Labeled on this page: Central neural structures



The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The preoptic NEP, hypothalamic NEP, subthalamic NEP, tegmental NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 101A
GW5.5 Sagittal, CR 10.5 mm, C6516
Level 2: Slide 9, Section 14

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

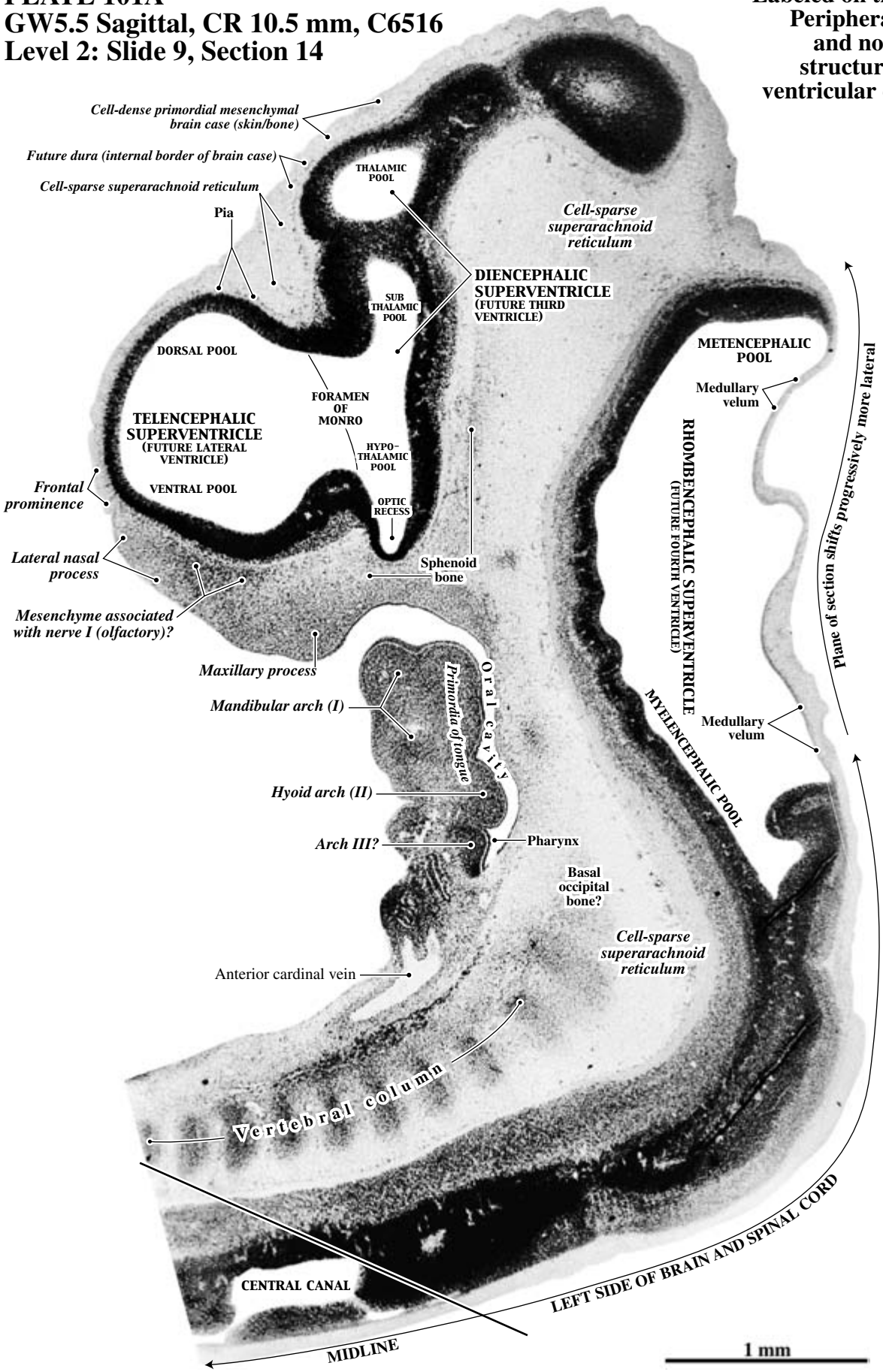


PLATE 101B

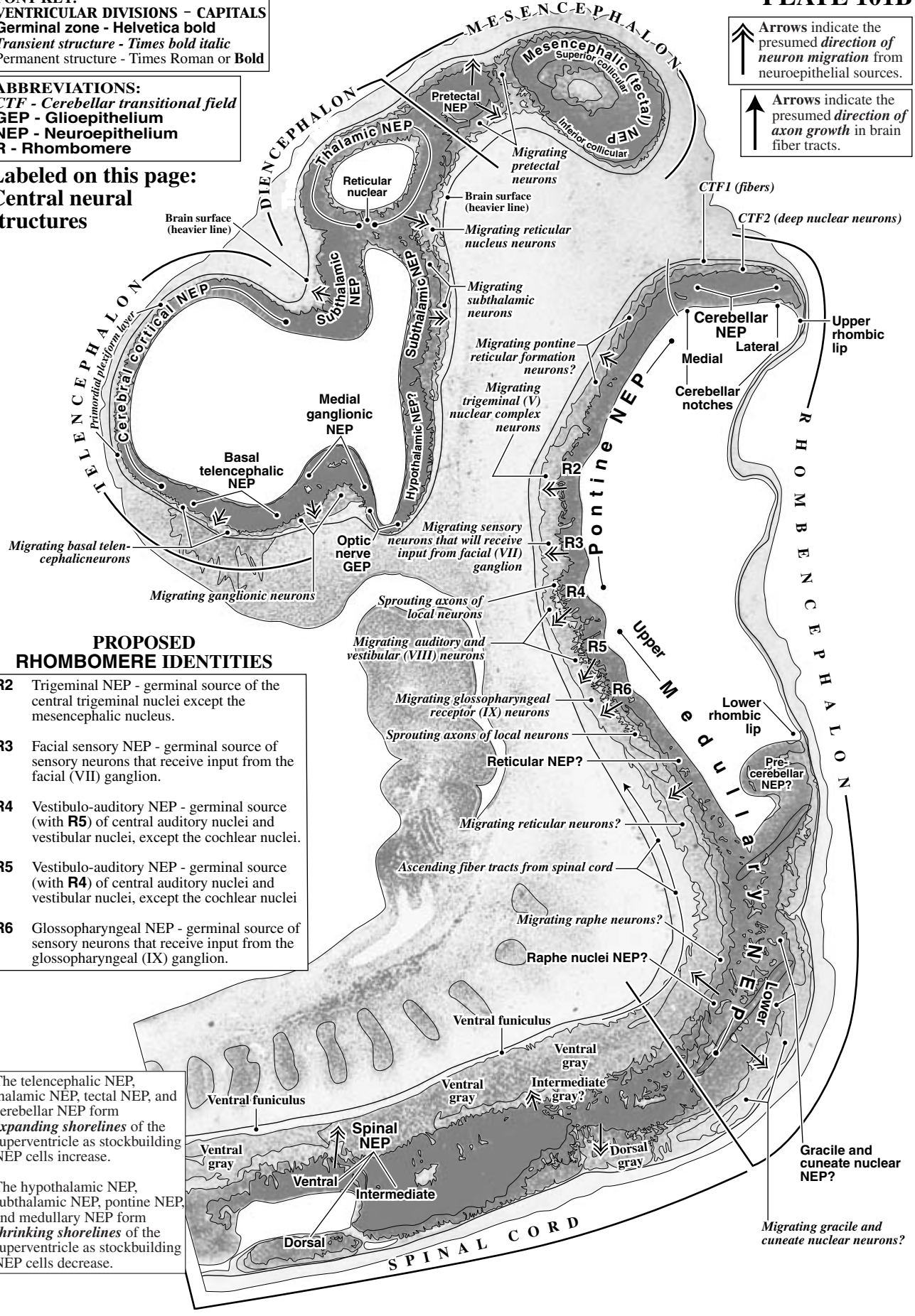
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Labeled on this page: Central neural structures



PROPOSED RHOMBOMERE IDENTITIES

R2 Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.

R3 Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.

R4 Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

R5 Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei

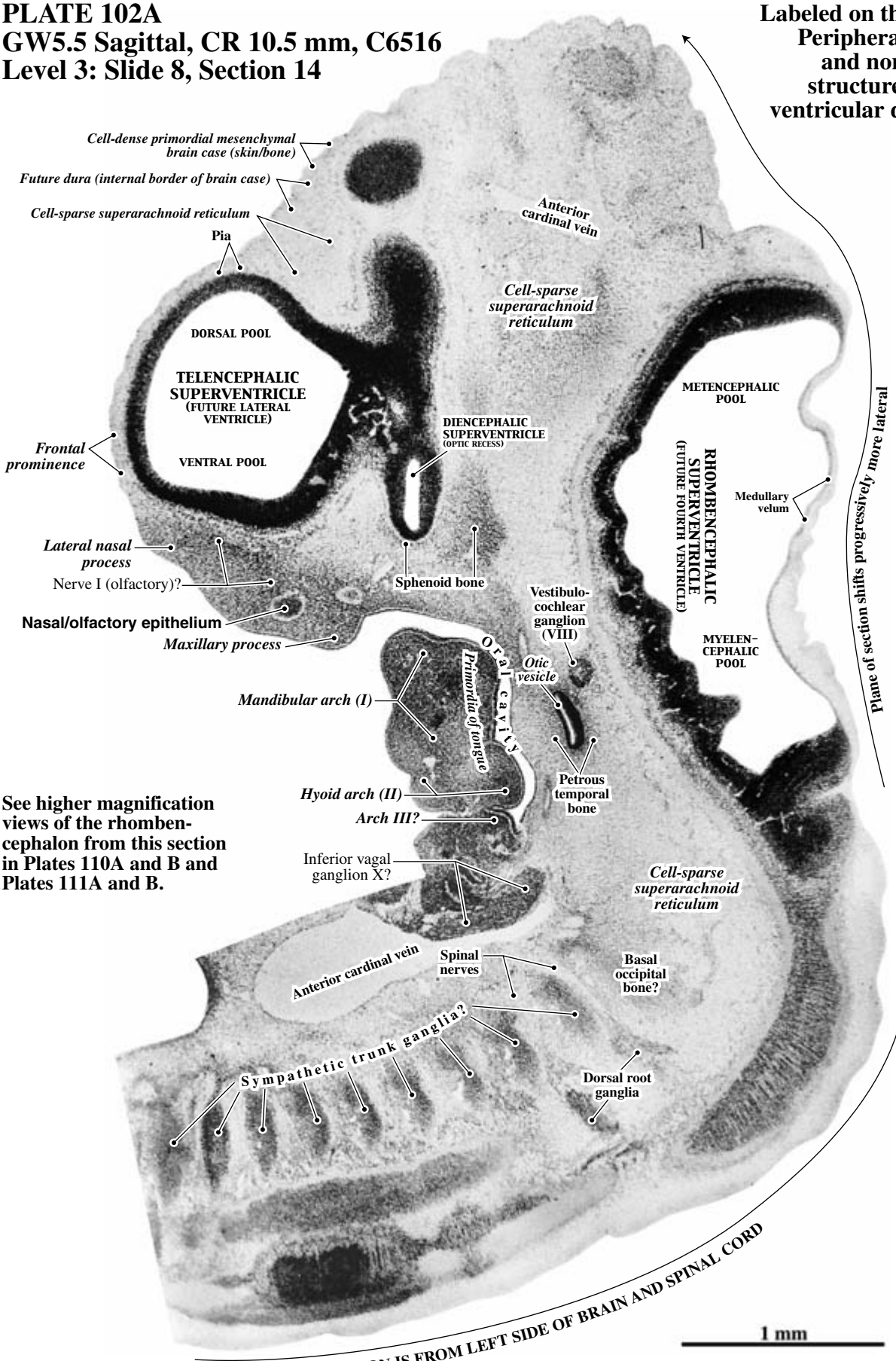
R6 Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

The telencephalic NEP, thalamic NEP, tectal NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricle as stockbuilding NEP cells increase.

The hypothalamic NEP, subthalamic NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

PLATE 102A
GW5.5 Sagittal, CR 10.5 mm, C6516
Level 3: Slide 8, Section 14

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



See higher magnification views of the rhombencephalon from this section in Plates 110A and B and Plates 111A and B.

PLATE 102B

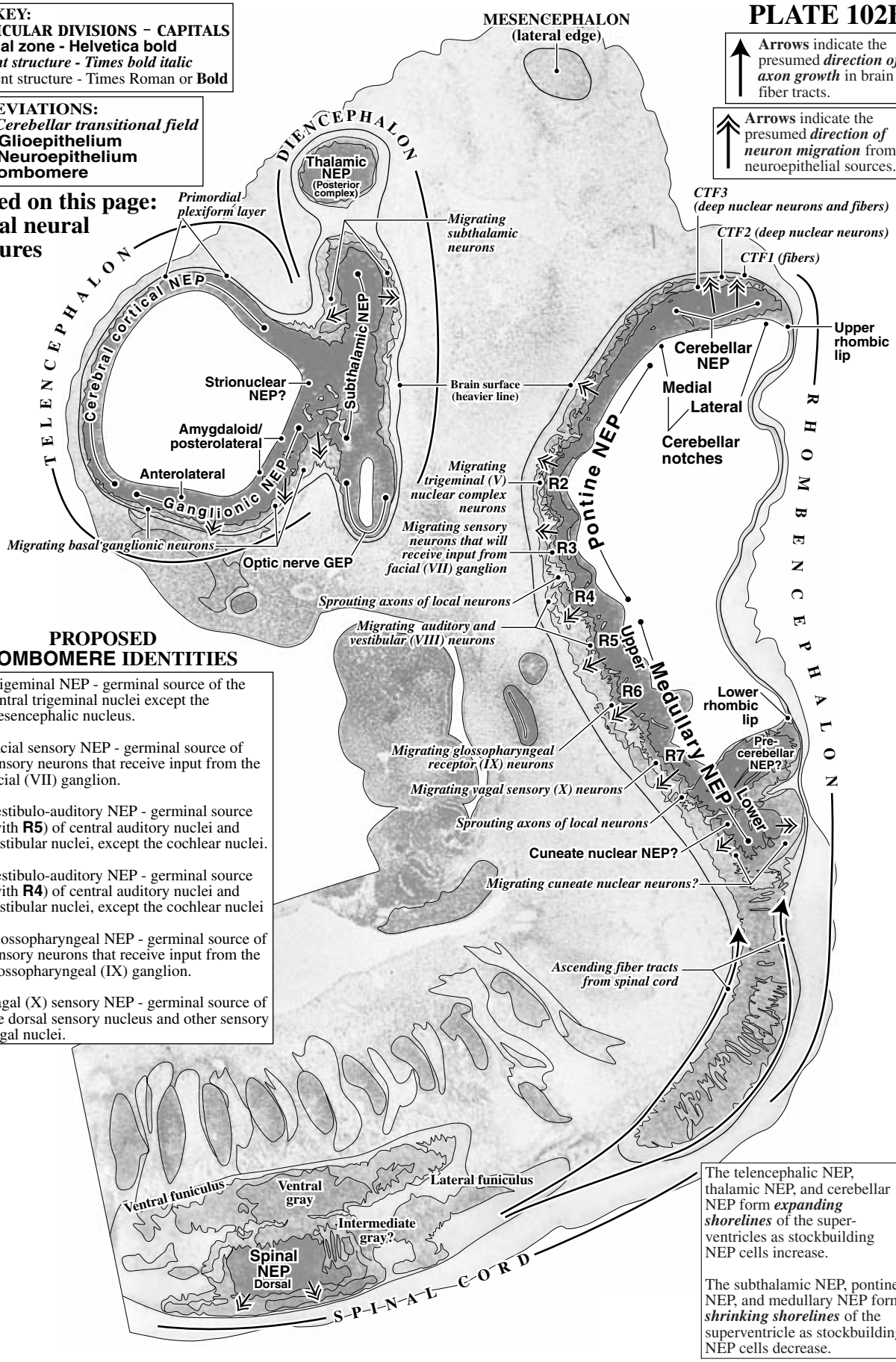
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Labeled on this page: Central neural structures



PROPOSED RHOMBOMERE IDENTITIES

R2 Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.

R3 Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.

R4 Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

R5 Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei

R6 Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

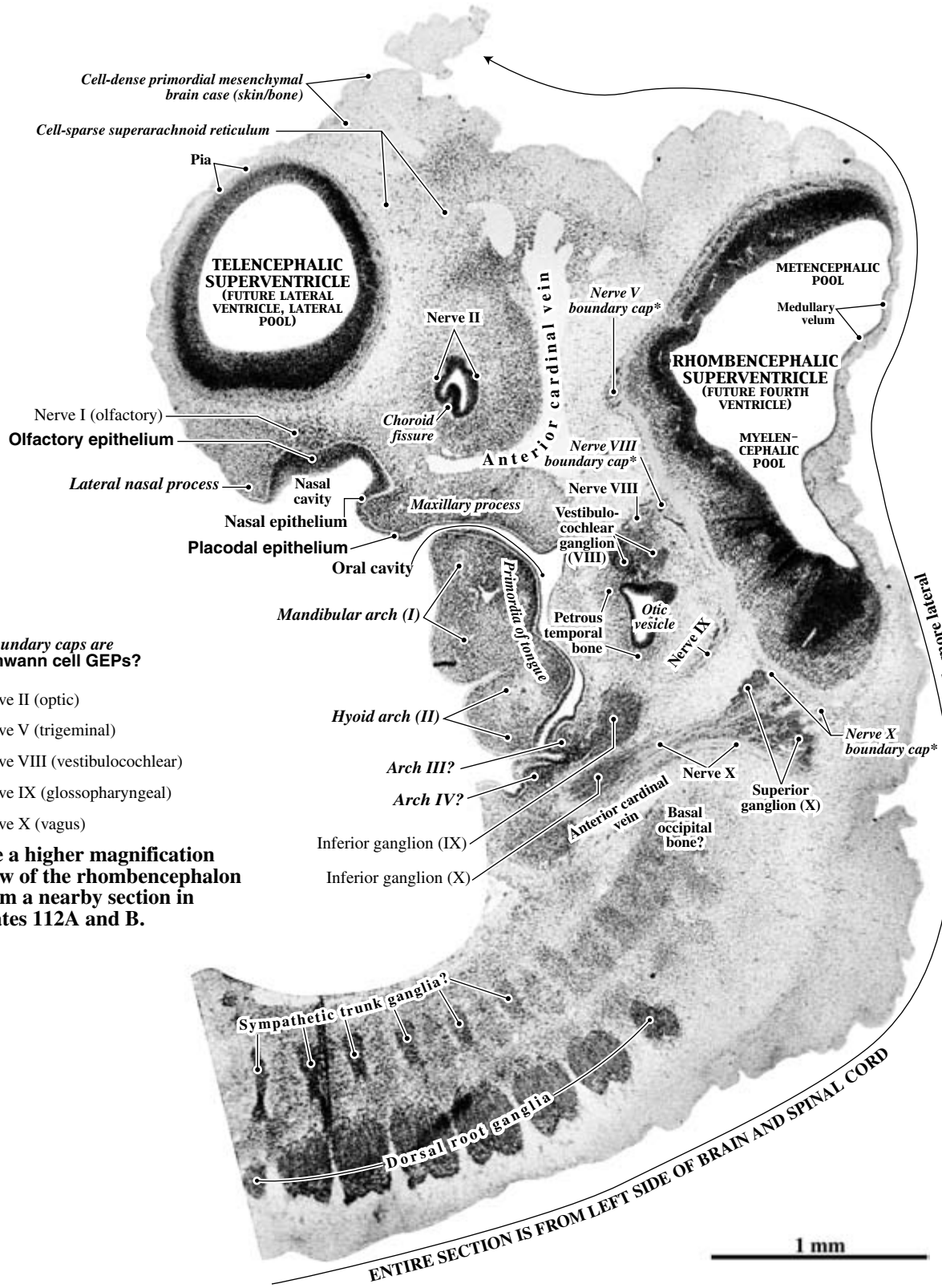
R7 Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

The telencephalic NEP, thalamic NEP, and cerebellar NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

The subthalamic NEP, pontine NEP, and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

PLATE 103A
GW5.5 Sagittal, CR 10.5 mm, C6516
Level 4: Slide 7, Section 10

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



*Boundary caps are Schwann cell GEPs?

Nerve II (optic)

Nerve V (trigeminal)

Nerve VIII (vestibulocochlear)

Nerve IX (glossopharyngeal)

Nerve X (vagus)

See a higher magnification view of the rhombencephalon from a nearby section in Plates 112A and B.

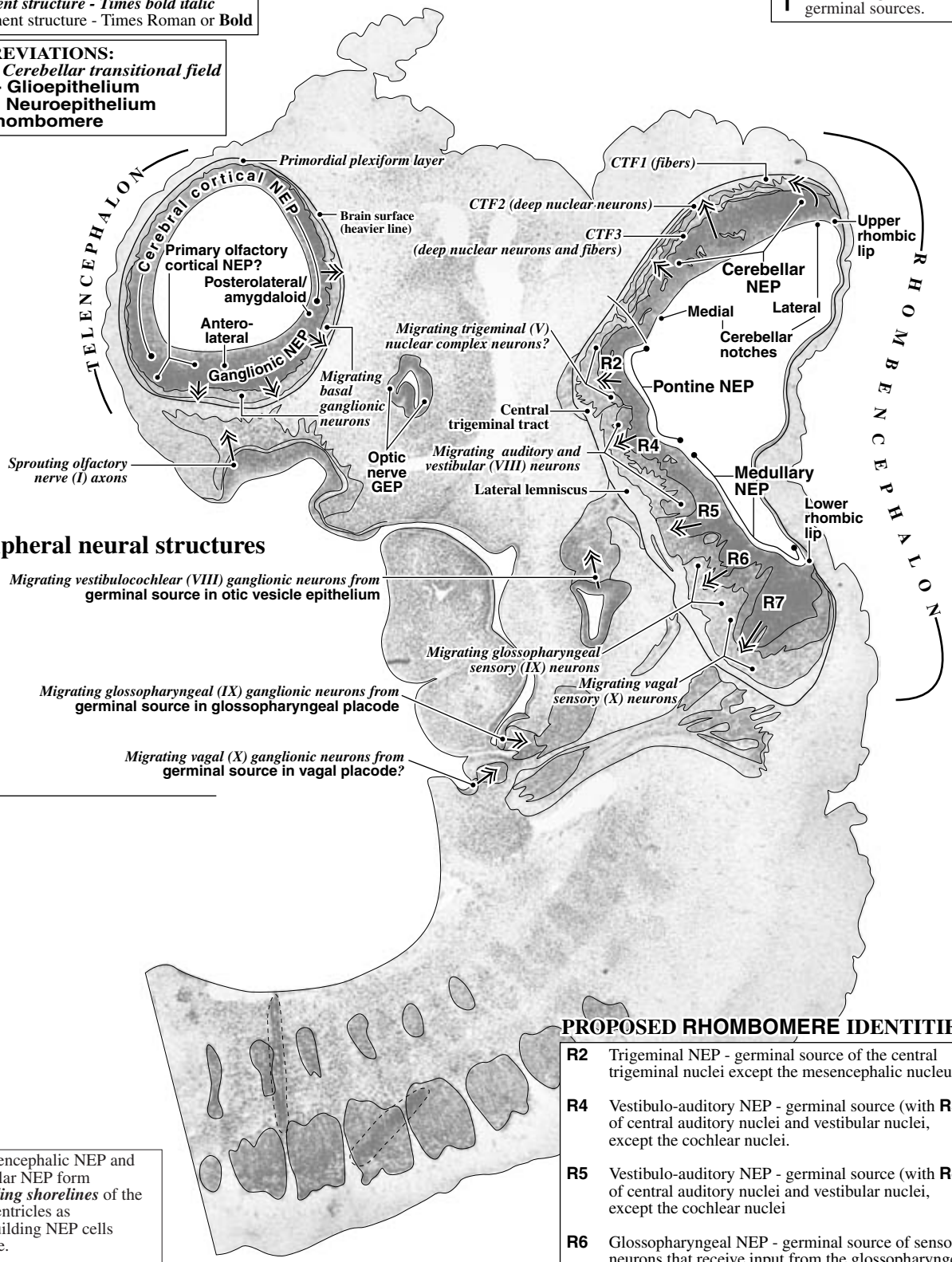
Labeled on this page: Central neural structures

PLATE 103B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.



Peripheral neural structures

The telencephalic NEP and cerebellar NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

The pontine NEP and medullary NEP form ***shrinking shorelines*** of the superventricle as stockbuilding NEP cells decrease.

PROPOSED RHOMBOMERE IDENTITIES

R2 Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.

R4 Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

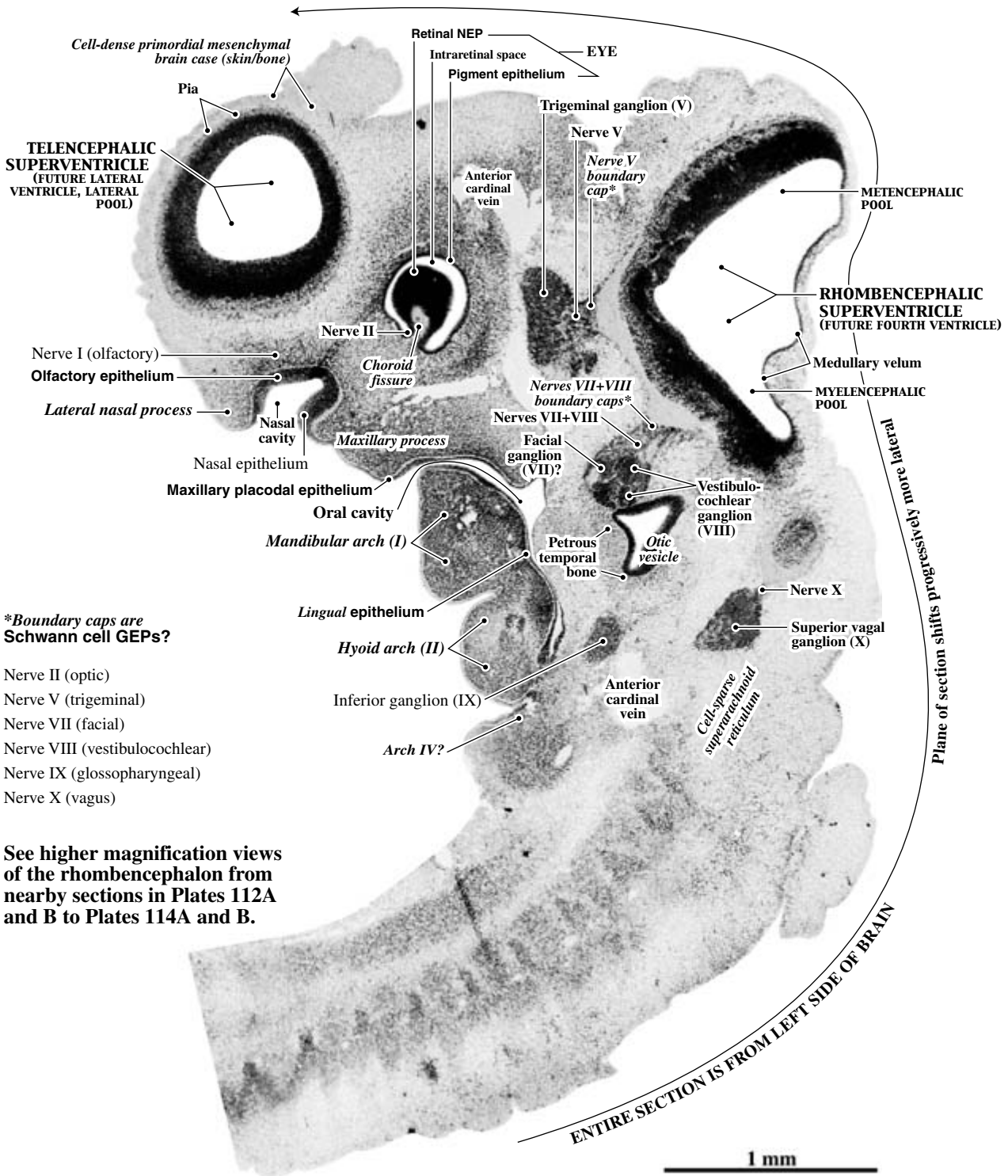
R5 Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei

R6 Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

R7 Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

PLATE 104A
GW5.5 Sagittal, CR 10.5 mm, C6516
Level 5: Slide 6, Section 15

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



*Boundary caps are Schwann cell GEPs?

Nerve II (optic)
Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Nerve X (vagus)

See higher magnification views of the rhombencephalon from nearby sections in Plates 112A and B to Plates 114A and B.

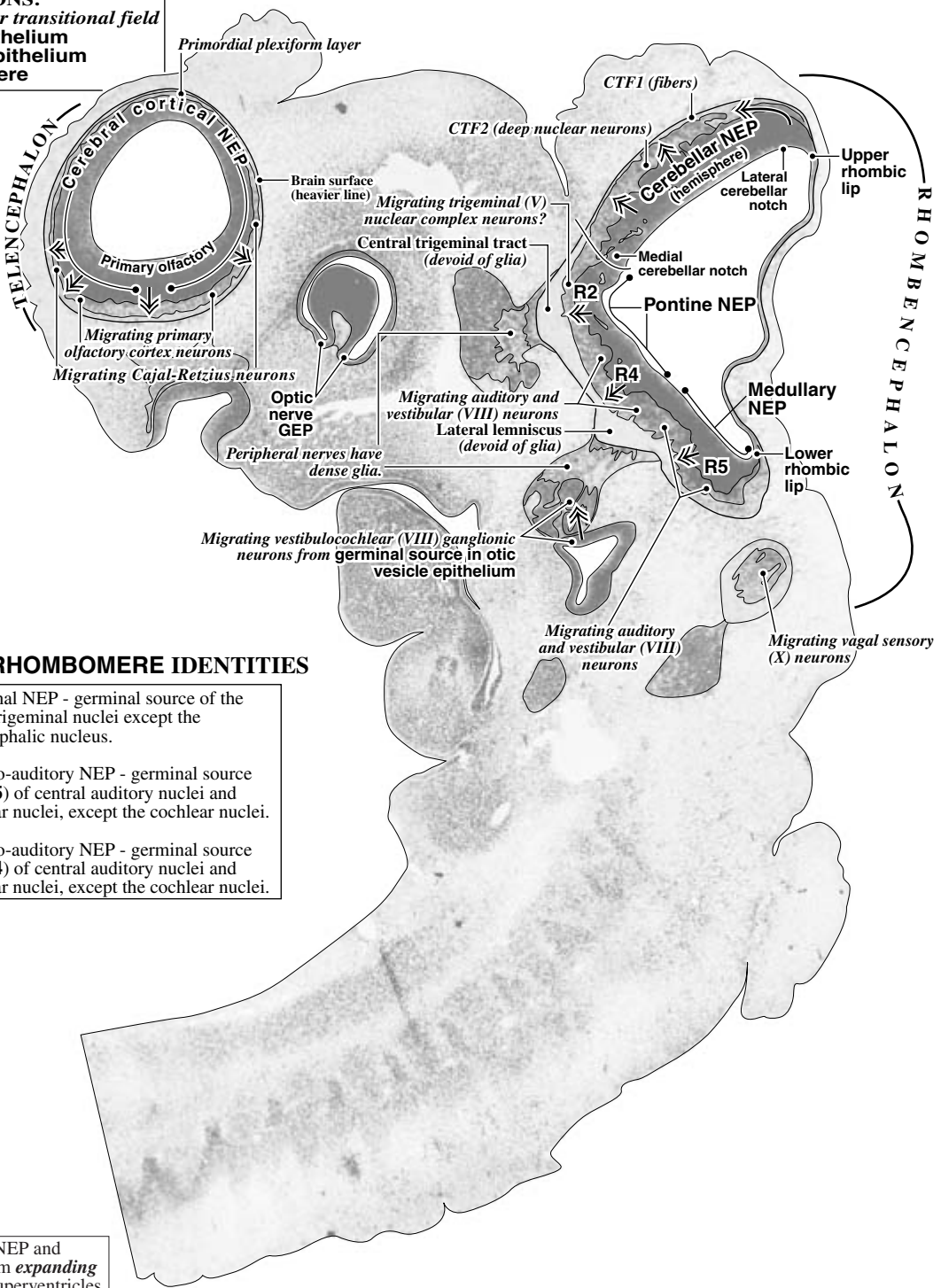
Labeled on this page: Central neural structures

PLATE 104B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere



PROPOSED RHOMBOMERE IDENTITIES

R2 Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.

R4 Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

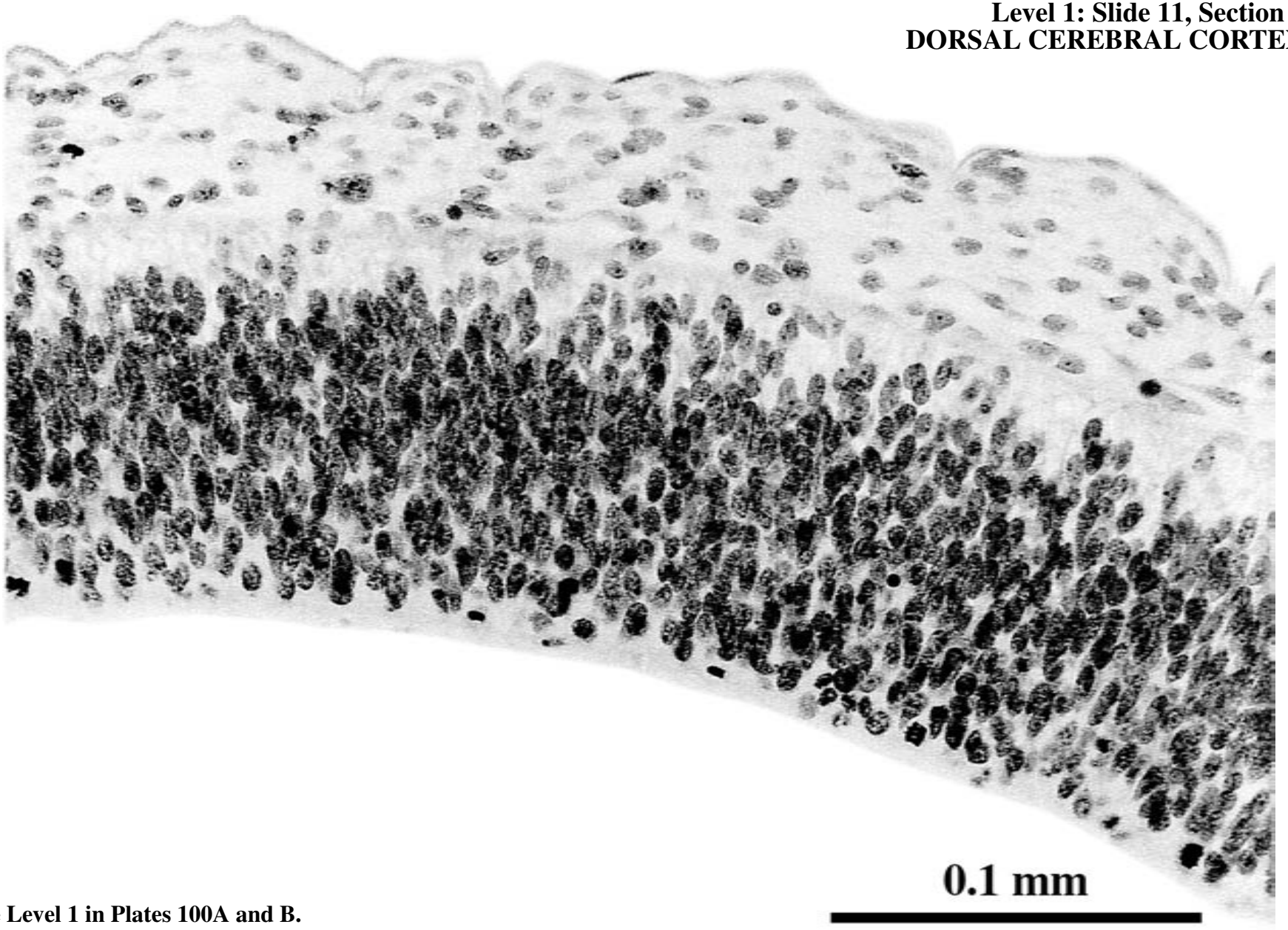
R5 Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

The telencephalic NEP and cerebellar NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

The pontine NEP and medullary NEP form ***shrinking shorelines*** of the superven-tricle as stockbuilding NEP cells decrease.

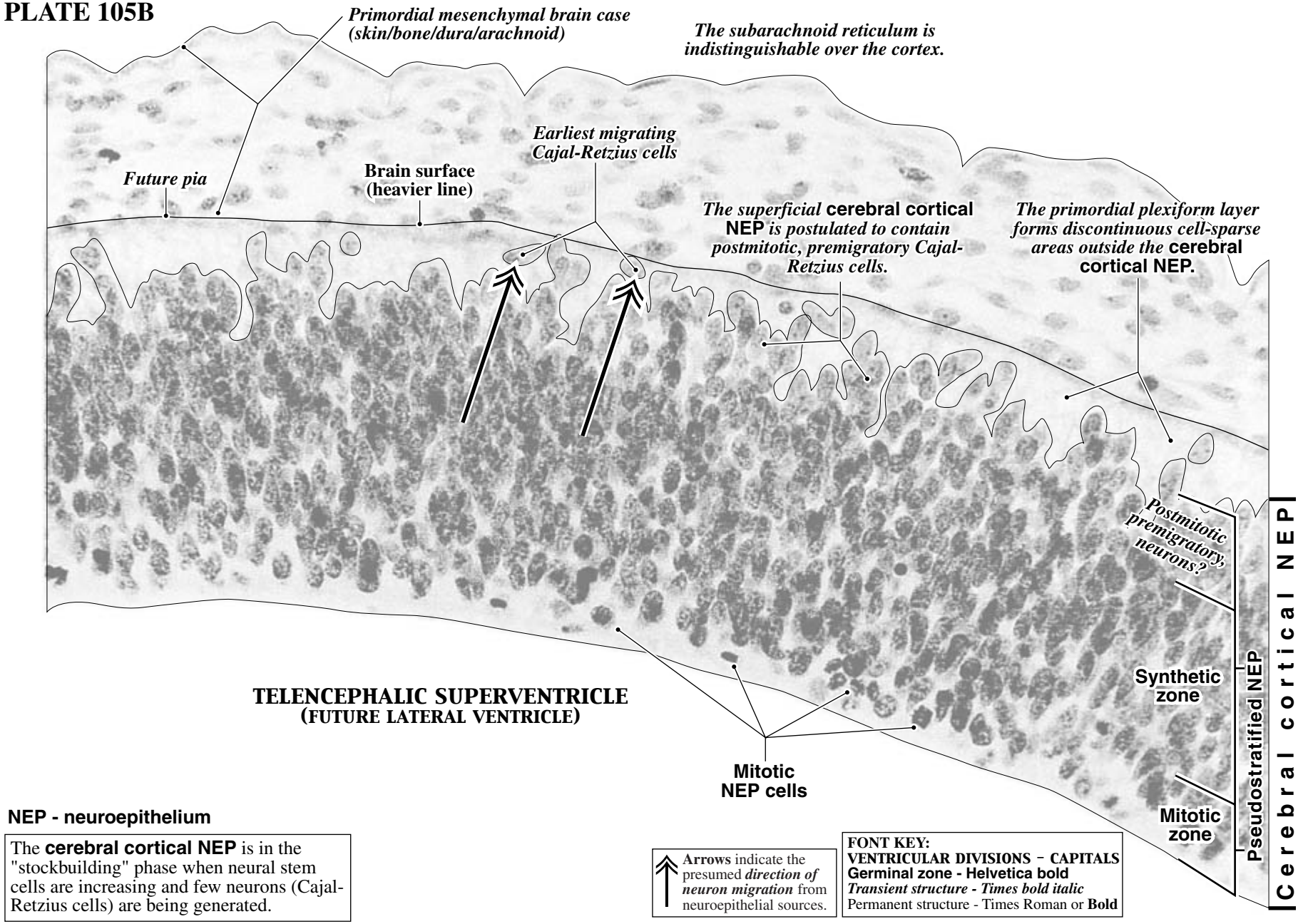
PLATE 105A

GW5.5 Sagittal, CR 10.5 mm, C6516
Level 1: Slide 11, Section 6
DORSAL CEREBRAL CORTEX



See Level 1 in Plates 100A and B.

PLATE 105B



NEP - neuroepithelium

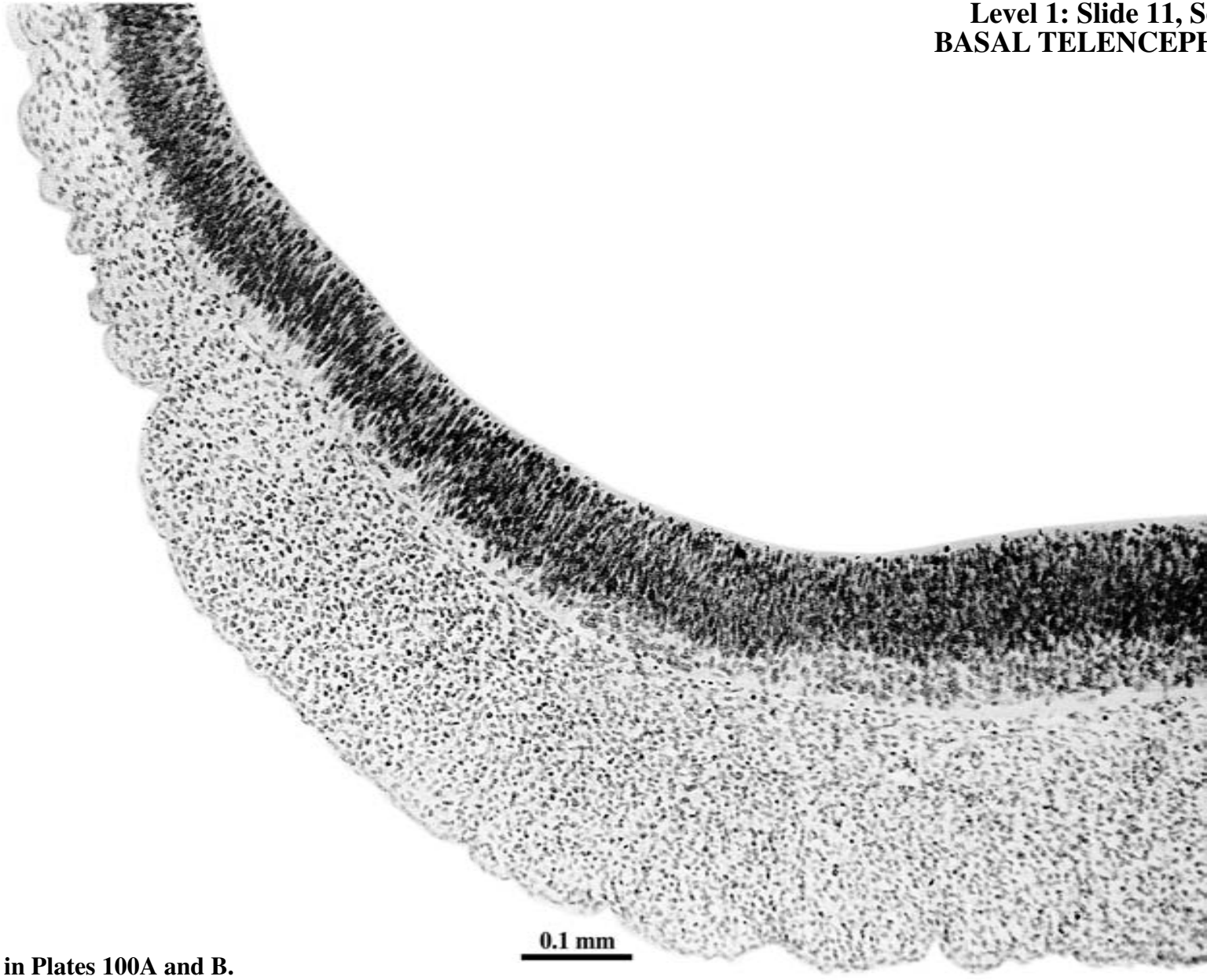
The **cerebral cortical NEP** is in the "stockbuilding" phase when neural stem cells are increasing and few neurons (Cajal-Retzius cells) are being generated.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

FONT KEY:
VENTRICULAR DIVISIONS - CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

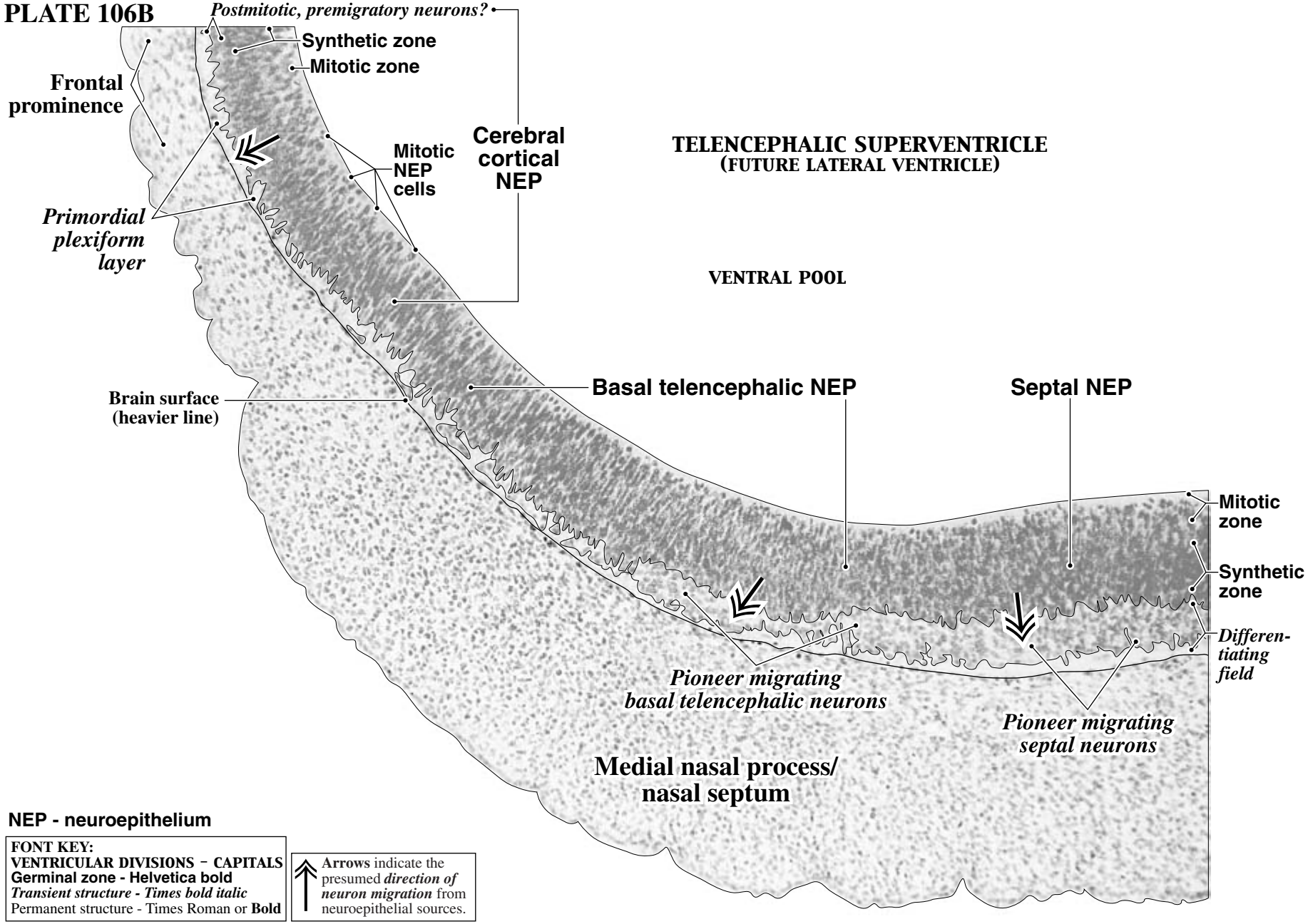
PLATE 106A

GW5.5 Sagittal, CR 10.5 mm, C6516
Level 1: Slide 11, Section 6
BASAL TELENCEPHALON



See Level 1 in Plates 100A and B.

PLATE 106B



NEP - neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 107A

GW5.5 Sagittal, CR 10.5 mm, C6516
Level 1: Slide 11, Section 6
SEPTUM/DIENCEPHALON

See Level 1 in Plates 100A and B.

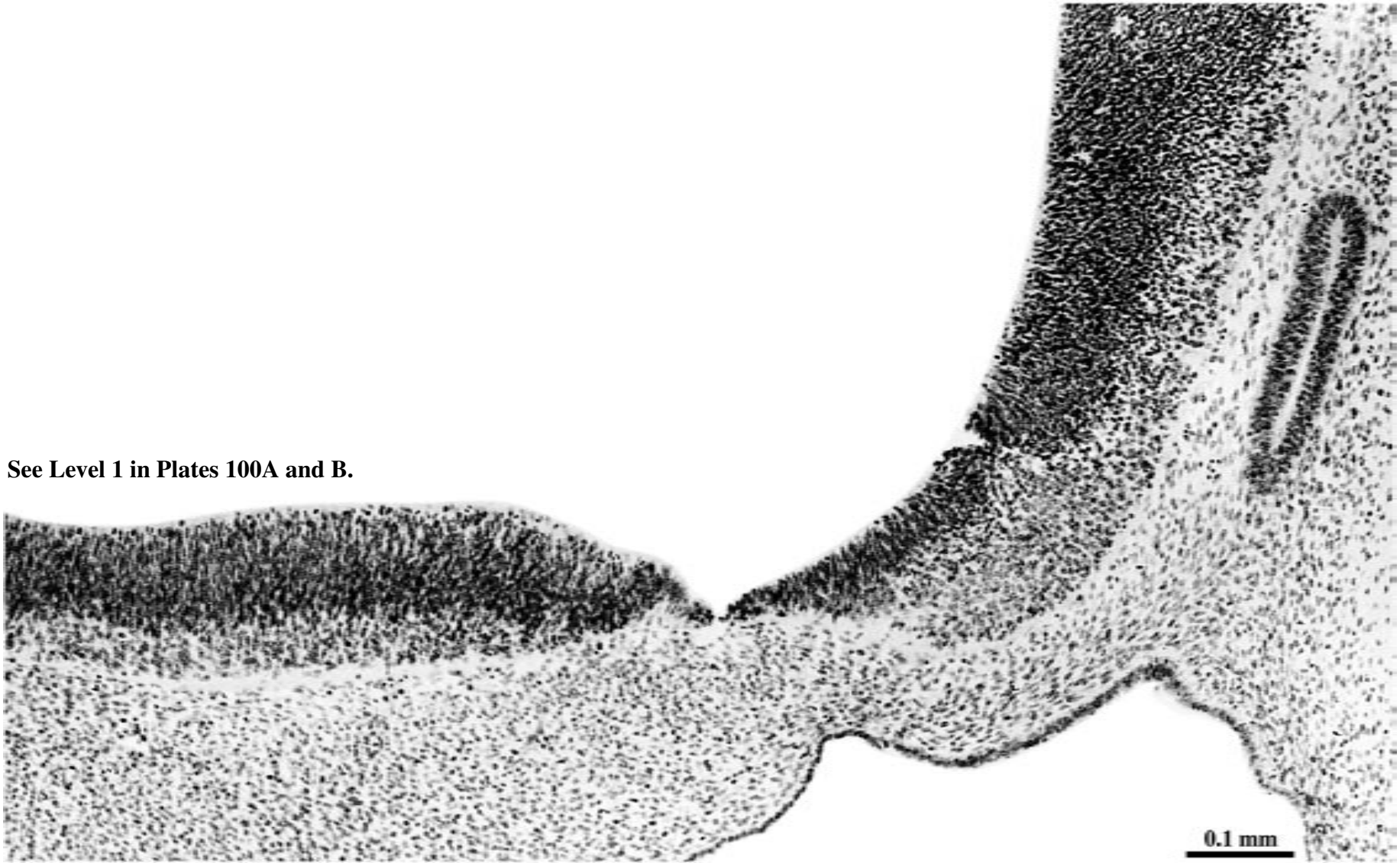


PLATE 107B

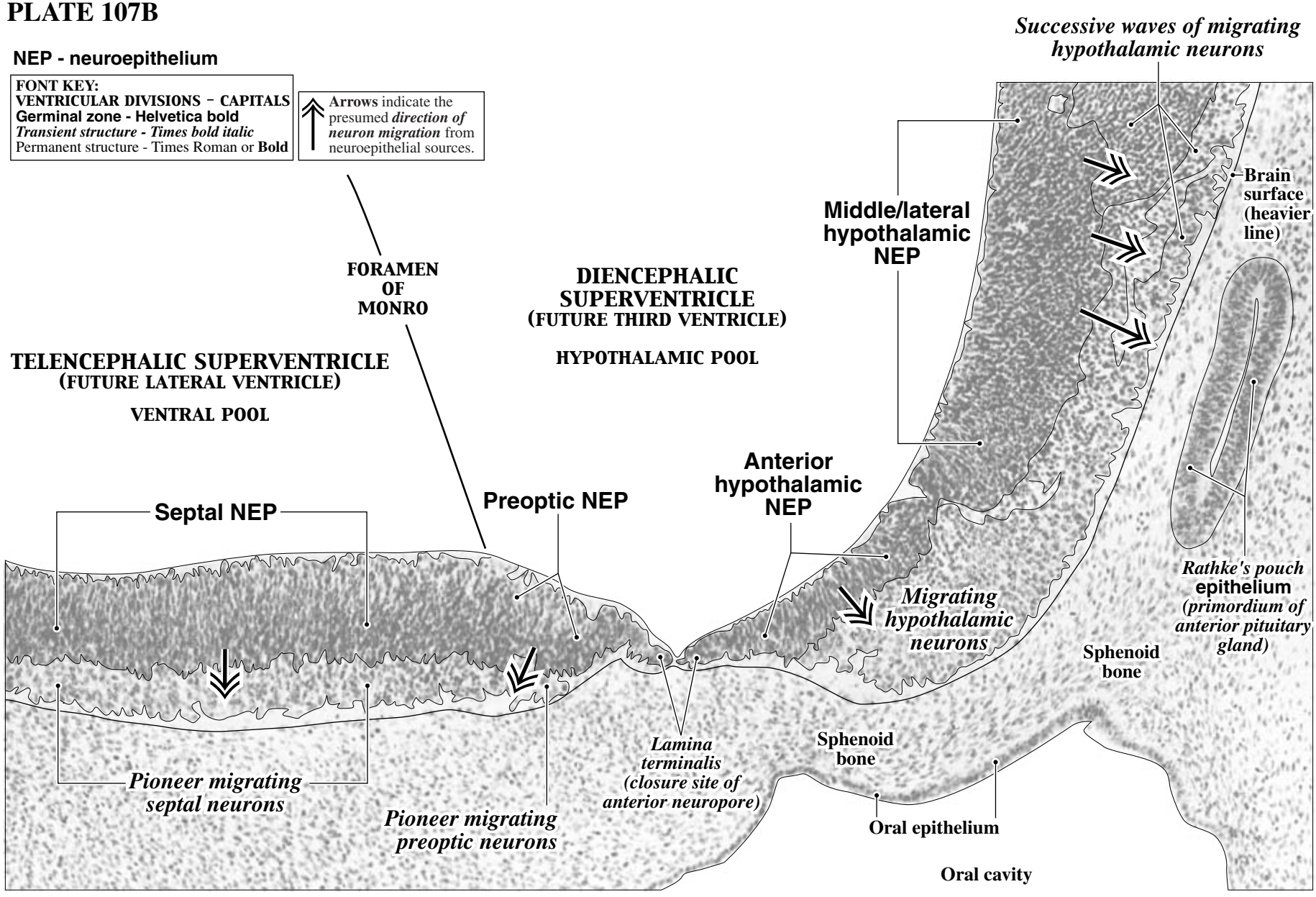

NEP - neuroepithelium
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Successive waves of migrating hypothalamic neurons
Middle/lateral hypothalamic NEP
Brain surface (heavier line)
FORAMEN OF MONRO
DIENCEPHALIC SUPERVENTRICLE (FUTURE THIRD VENTRICLE)
HYPOTHALAMIC POOL
TELENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL VENTRICLE)
VENTRAL POOL
Septal NEP
Preoptic NEP
Anterior hypothalamic NEP
Migrating hypothalamic neurons
Rathke's pouch epithelium (primordium of anterior pituitary gland)
Sphenoid bone
Lamina terminalis (closure site of anterior neuropore)
Sphenoid bone
Pioneer migrating septal neurons
Pioneer migrating preoptic neurons
Oral epithelium
Oral cavity

PLATE 108A

GW5.5 Sagittal, CR 10.5 mm, C6516
Level 1: Slide 11, Section 6
MIDBRAIN TEGMENTUM

See Level 1 in Plates 100A and B.

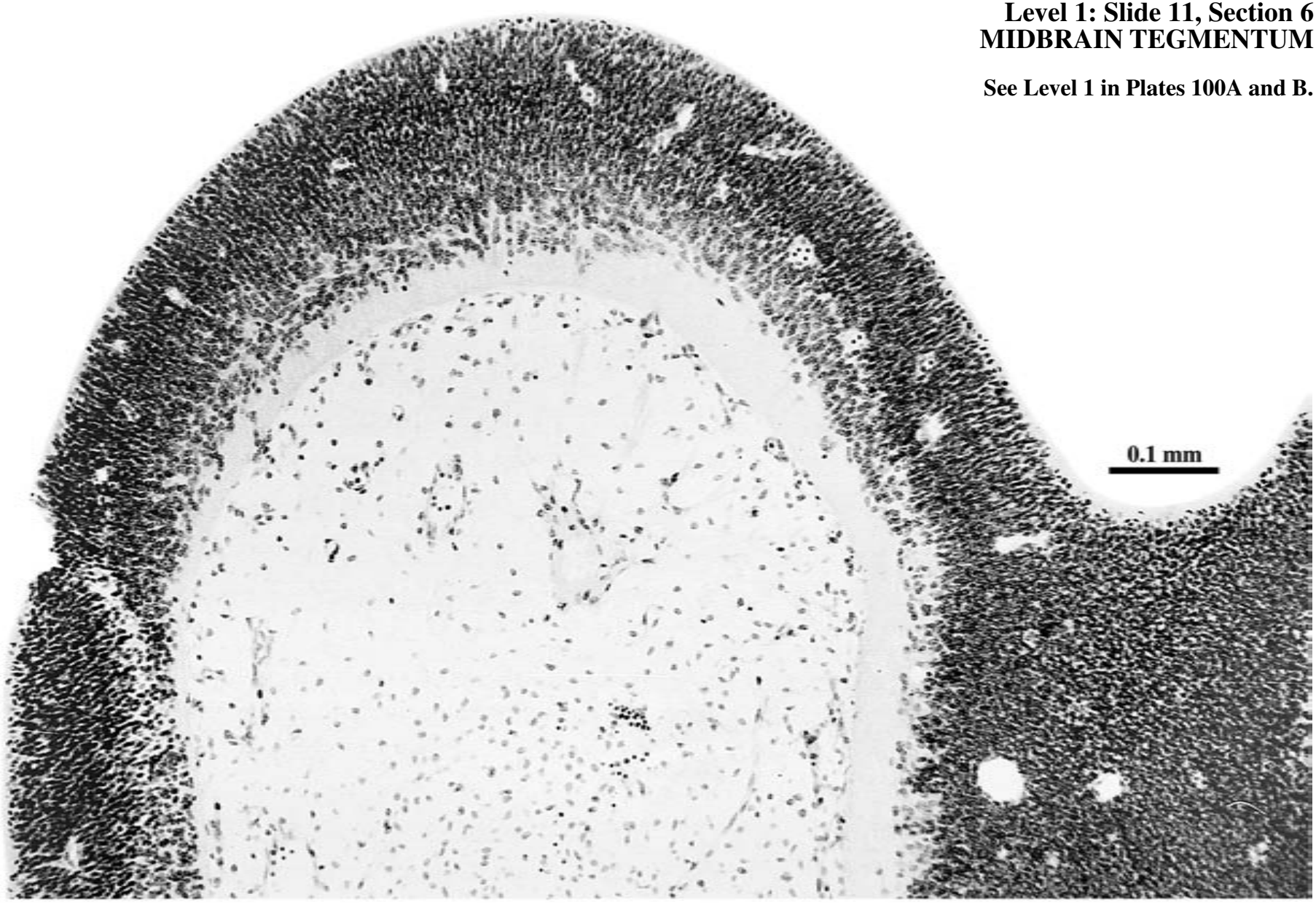


PLATE 108B

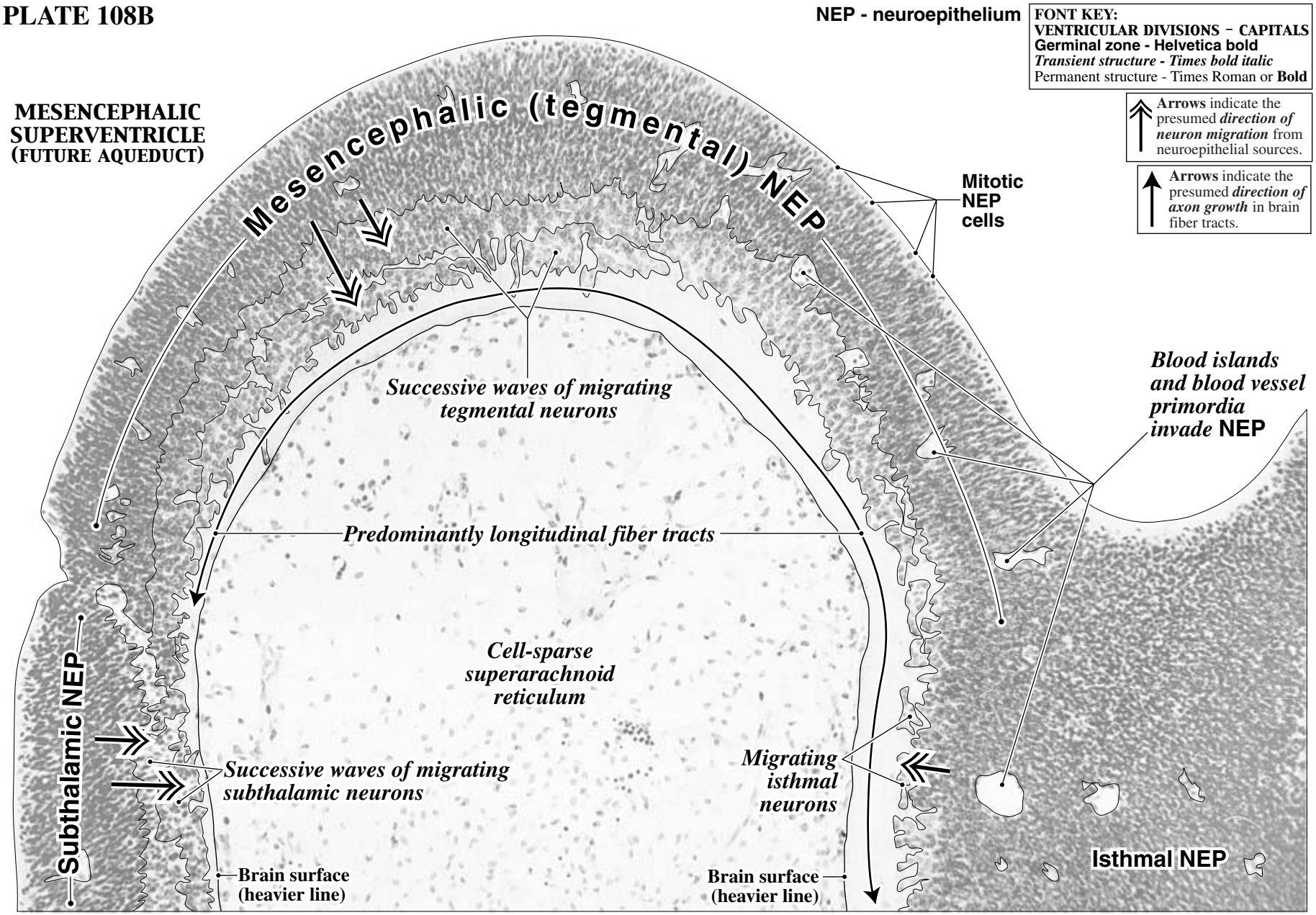

NEP - neuroepithelium
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the presumed direction of axon growth in brain fiber tracts.
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Mesencephalic (tegmental) NEP
Mitotic NEP cells
Blood islands and blood vessel primordia invade NEP
Successive waves of migrating tegmental neurons
Predominantly longitudinal fiber tracts
Cell-sparse superarachnoid reticulum
Subthalamic NEP
Successive waves of migrating subthalamic neurons
Migrating isthmal neurons
Isthmal NEP
Brain surface (heavier line)
Brain surface (heavier line)

PLATE 109A
GW5.5 Sagittal, CR 10.5 mm, C6516
Level 1: Slide 11, Section 6
ISTHMUS and CEREBELLUM
See Level 1 in Plates 100A and B.

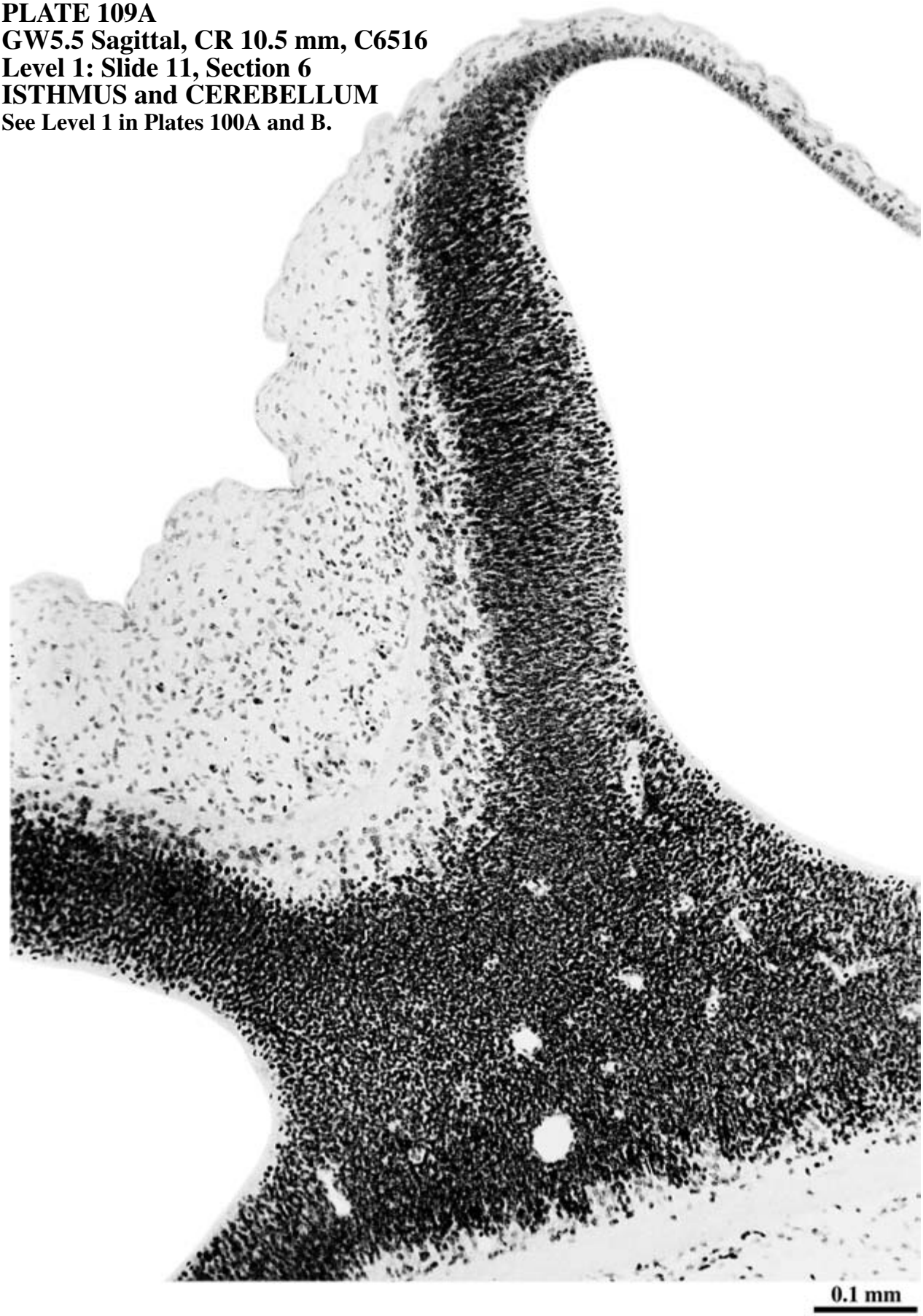


PLATE 109B

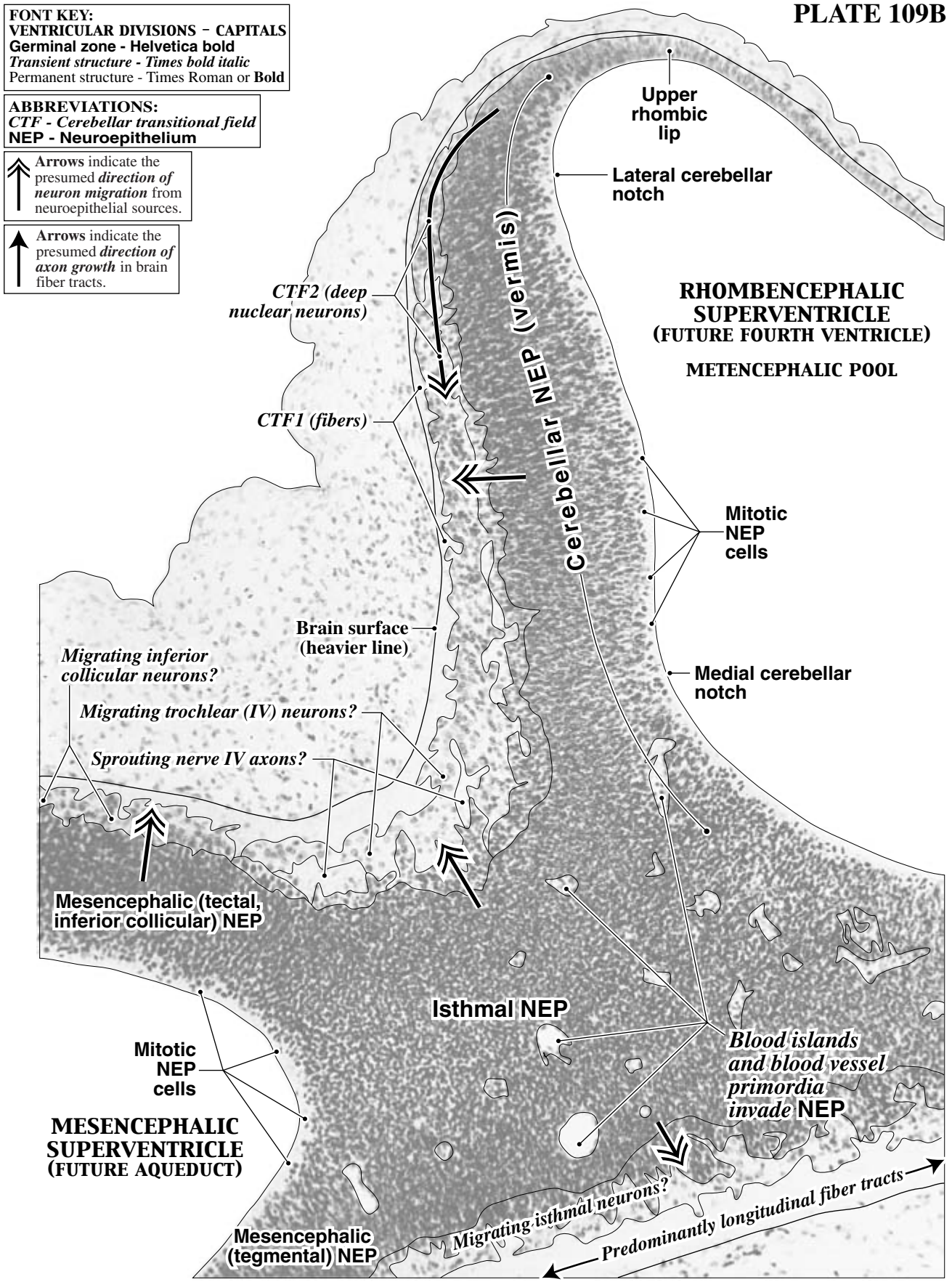
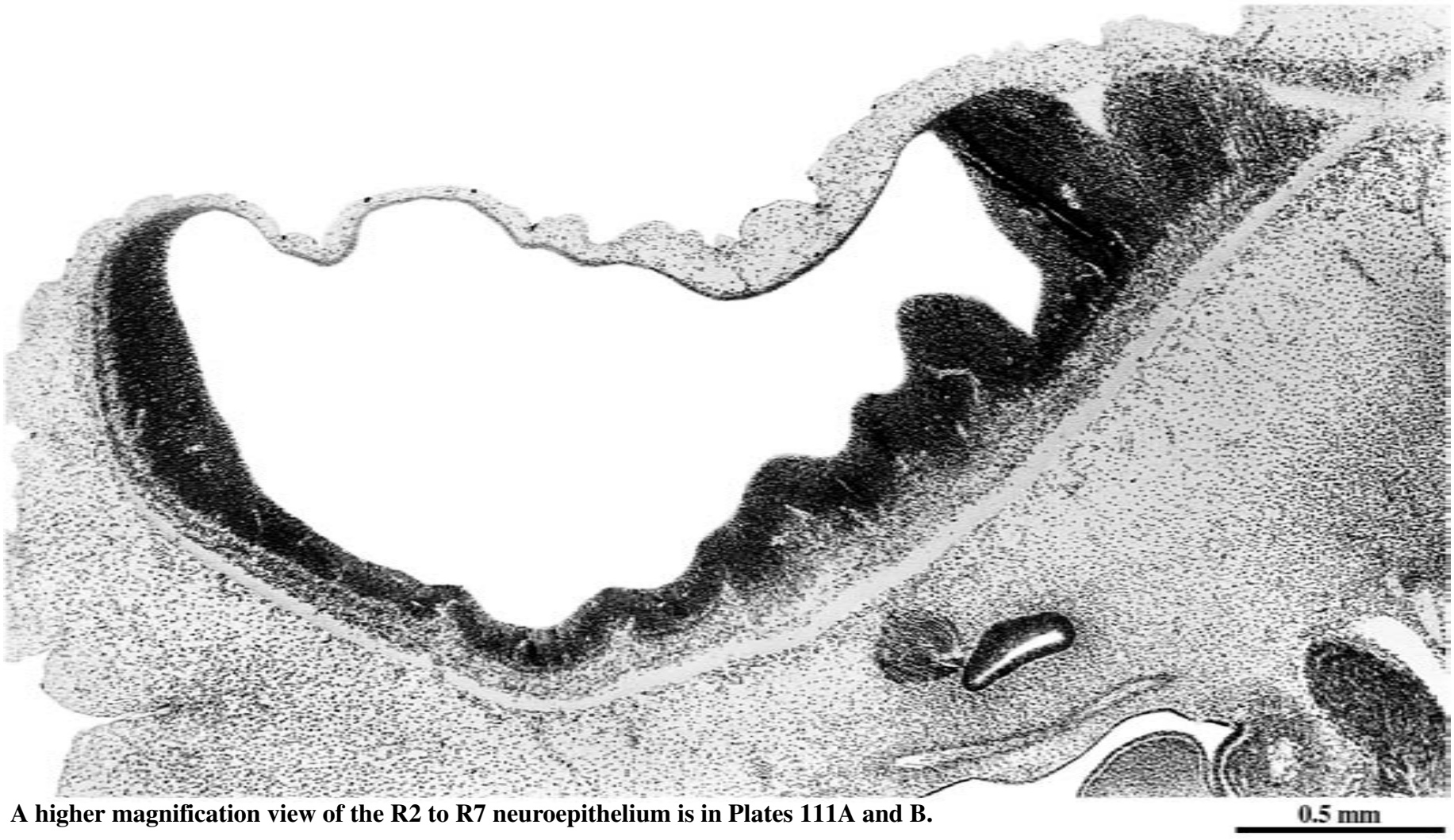

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
CTF - Cerebellar transitional field
NEP - Neuroepithelium
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Arrows indicate the presumed direction of axon growth in brain fiber tracts.
Upper rhombic lip
Lateral cerebellar notch
CTF2 (deep nuclear neurons)
CTF1 (fibers)
Cerebellar NEP (vermis)
RHOMBENCEPHALIC SUPERVENTRICLE
(FUTURE FOURTH VENTRICLE)
METENCEPHALIC POOL
Mitotic NEP cells
Brain surface (heavier line)
Migrating inferior collicular neurons?
Migrating trochlear (IV) neurons?
Sprouting nerve IV axons?
Medial cerebellar notch
Mesencephalic (tectal, inferior collicular) NEP
Isthmal NEP
Blood islands and blood vessel primordia invade NEP
Mitotic NEP cells
MESENCEPHALIC SUPERVENTRICLE
(FUTURE AQUEDUCT)
Migrating isthmal neurons?
Predominantly longitudinal fiber tracts
Mesencephalic (tegmental) NEP

PLATE 110A

GW5.5 Sagittal, CR 10.5 mm, C6516
Near Level 3: Slide 8, Section 10
PONS/MEDULLA



A higher magnification view of the R2 to R7 neuroepithelium is in Plates 111A and B.

See Level 3 in Plates 102A and B.

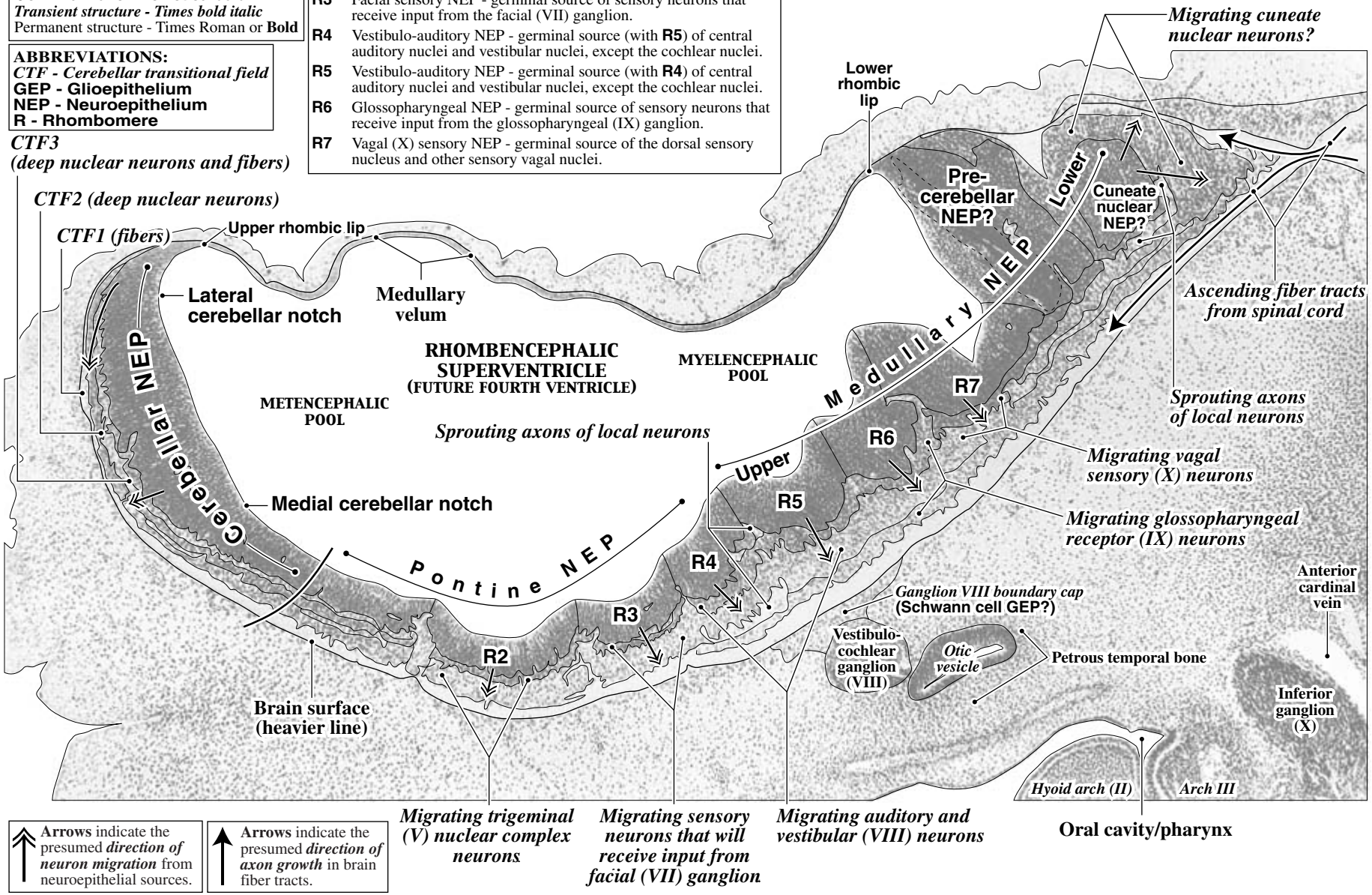
PLATE 110B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

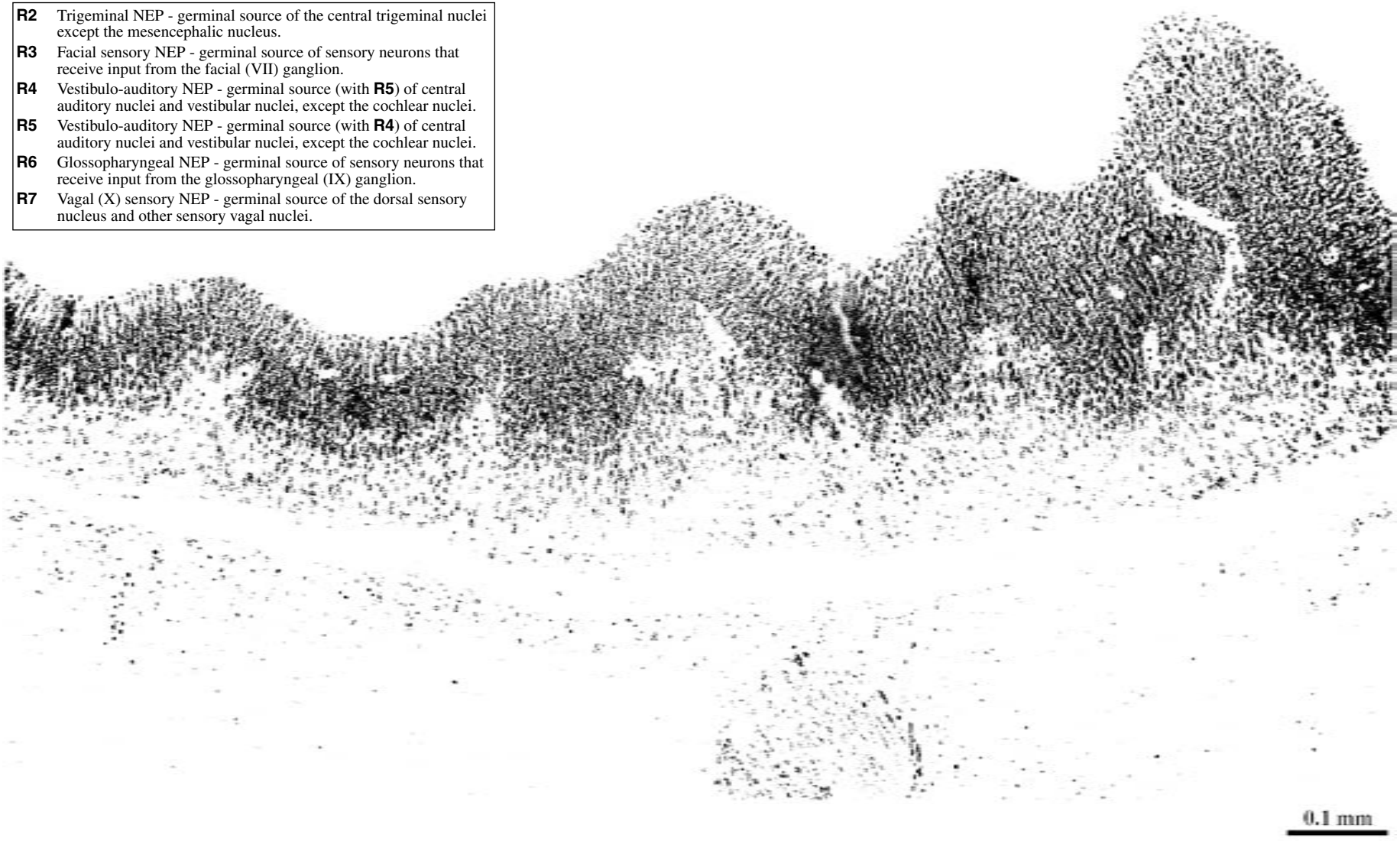
Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

PLATE 111A

GW5.5 Sagittal, CR 10.5 mm, C6516
Near Level 3: Slide 8, Section 10
PONS/MEDULLA

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

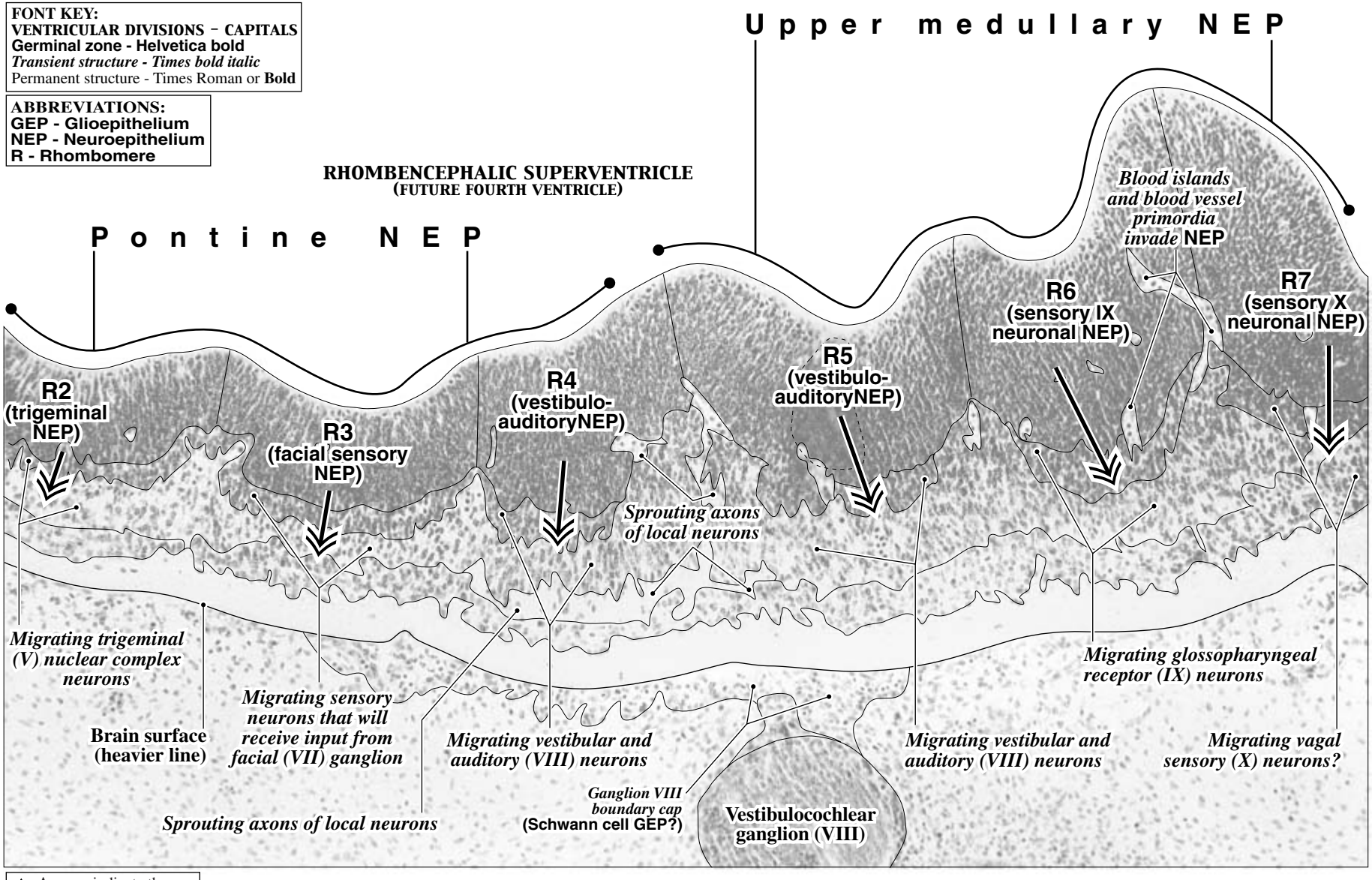


See Level 3 in Plates 102A and B.

PLATE 111B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 112A

GW5.5 Sagittal, CR 10.5 mm, C6516
Between Levels 4 and 5: Slide 7, Section 6
RHOMBENCEPHALON

See Level 4 in Plates 103A and B;
Level 5 in Plates 104A and B.

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

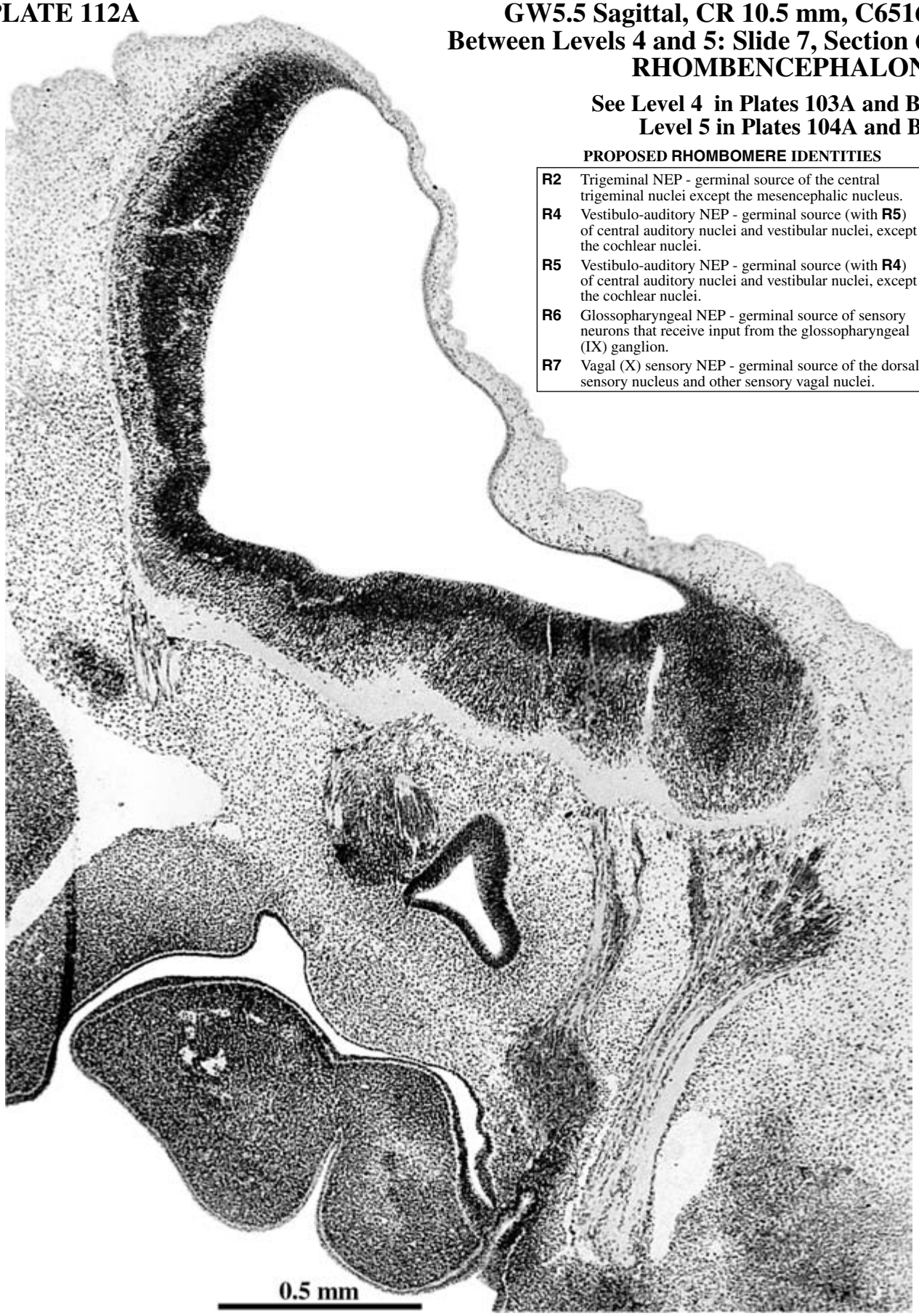
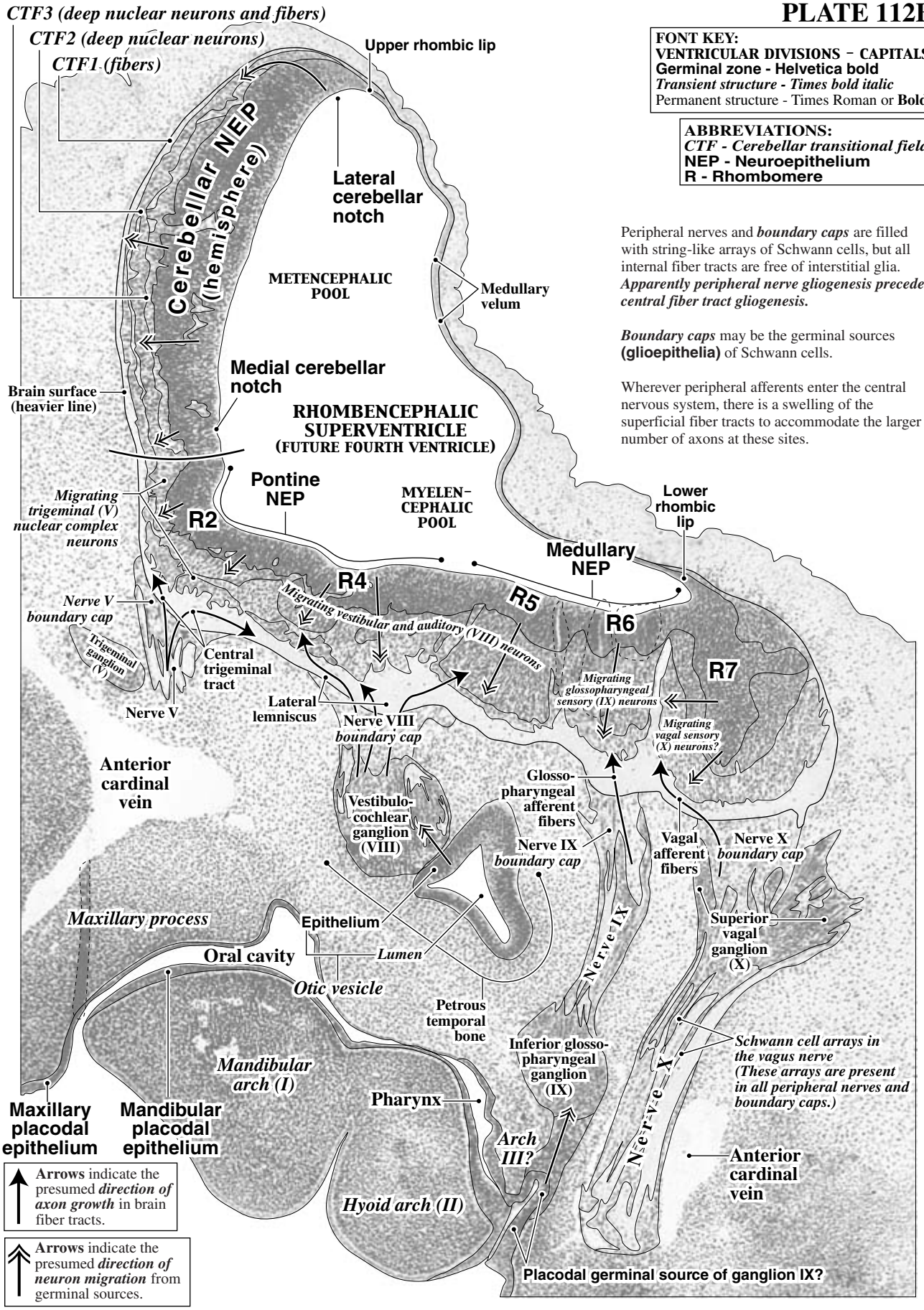


PLATE 112B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
NEP - Neuroepithelium
R - Rhombomere

Peripheral nerves and ***boundary caps*** are filled with string-like arrays of Schwann cells, but all internal fiber tracts are free of interstitial glia. ***Apparently peripheral nerve gliogenesis precedes central fiber tract gliogenesis.***

Boundary caps may be the germinal sources **(glioepithelia)** of Schwann cells.

Wherever peripheral afferents enter the central nervous system, there is a swelling of the superficial fiber tracts to accommodate the larger number of axons at these sites.

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PLATE 113A

GW5.5 Sagittal, CR 10.5 mm, C6516
Lateral to Level 5: Slide 6, Section 11
RHOMBENCEPHALON

See Level 5 in Plates 104A and B.

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

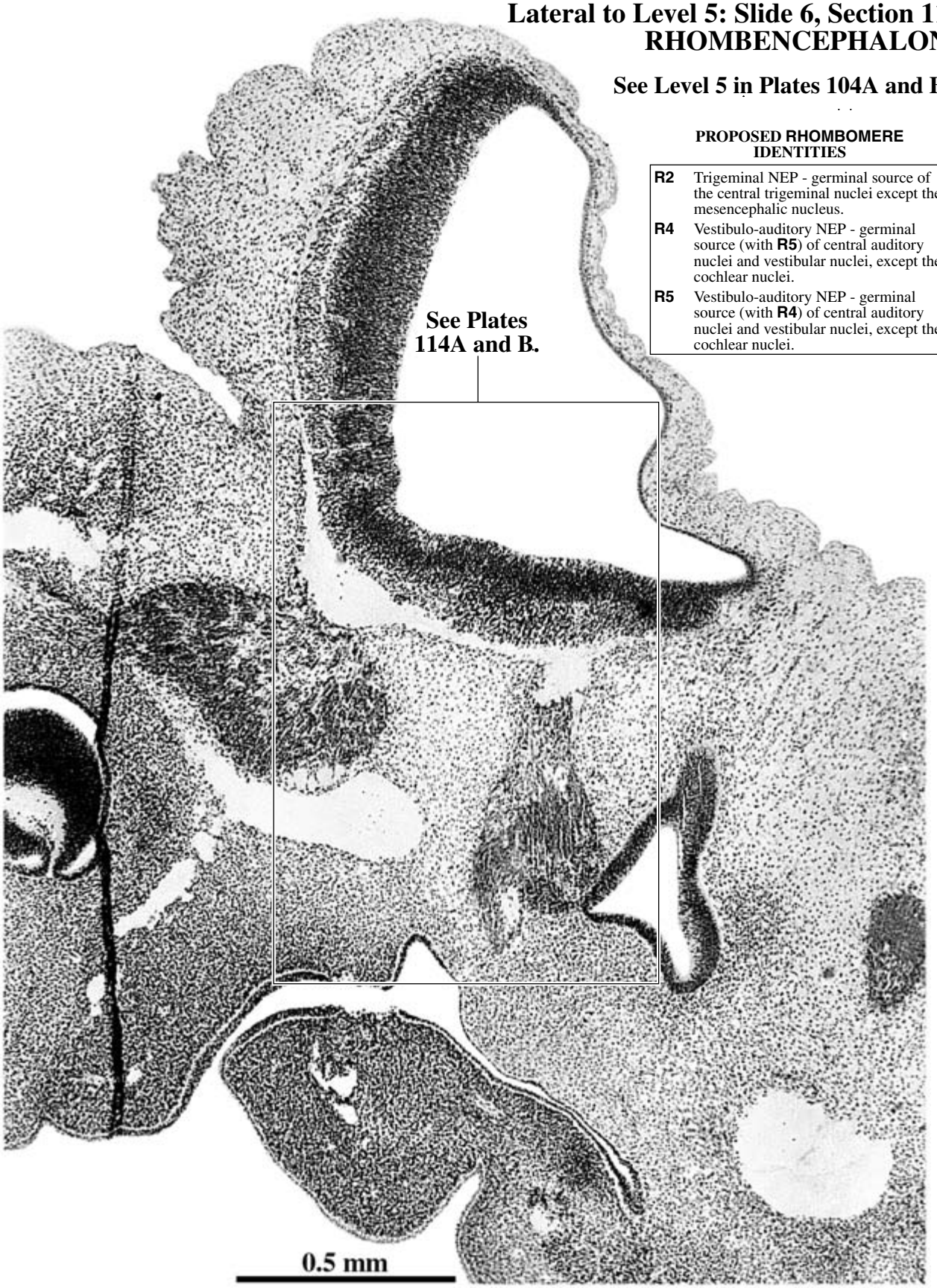
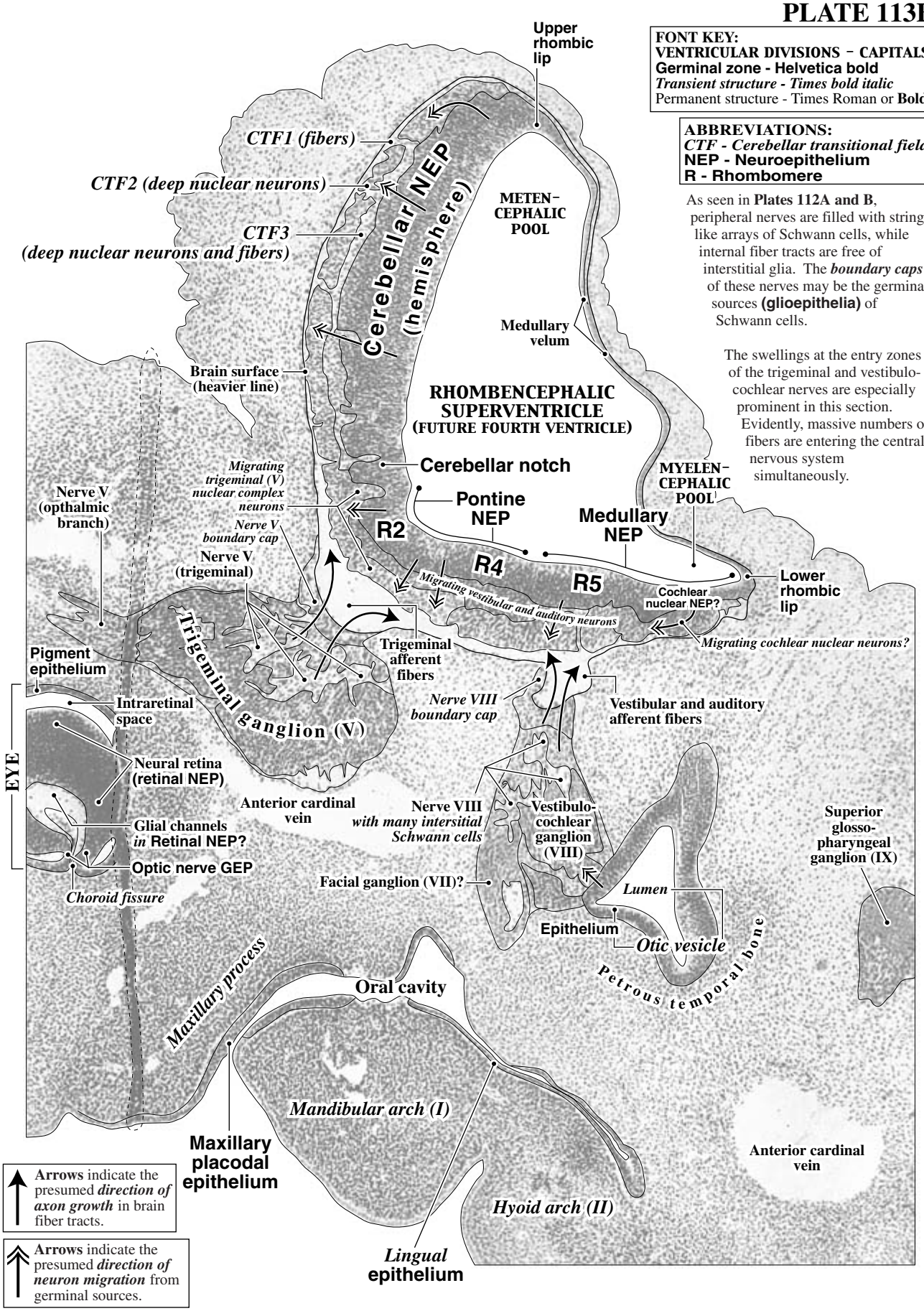


PLATE 113B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
NEP - Neuroepithelium
R - Rhombomere

As seen in **Plates 112A and B**, peripheral nerves are filled with string-like arrays of Schwann cells, while internal fiber tracts are free of interstitial glia. The ***boundary caps*** of these nerves may be the germinal sources **(glioepithelia)** of Schwann cells.

The swellings at the entry zones of the trigeminal and vestibulo-cochlear nerves are especially prominent in this section. Evidently, massive numbers of fibers are entering the central nervous system simultaneously.

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PLATE 114A

GW5.5 Sagittal, CR 10.5 mm, C6516
Lateral to Level 5: Slide 6, Section 11
ENTRY ZONES OF NERVES V AND VIII

See Level 5 in Plates 104A and B.

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

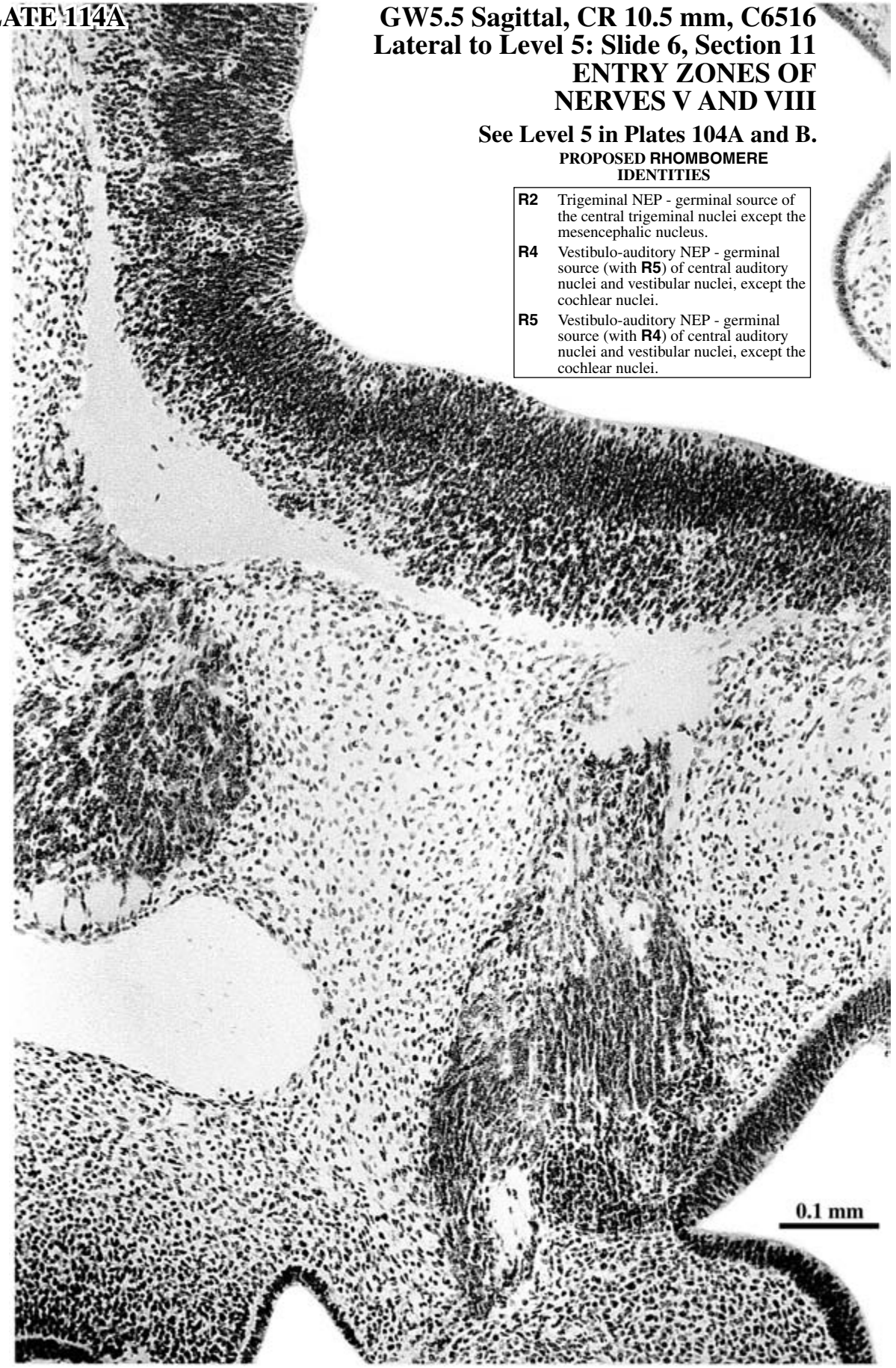
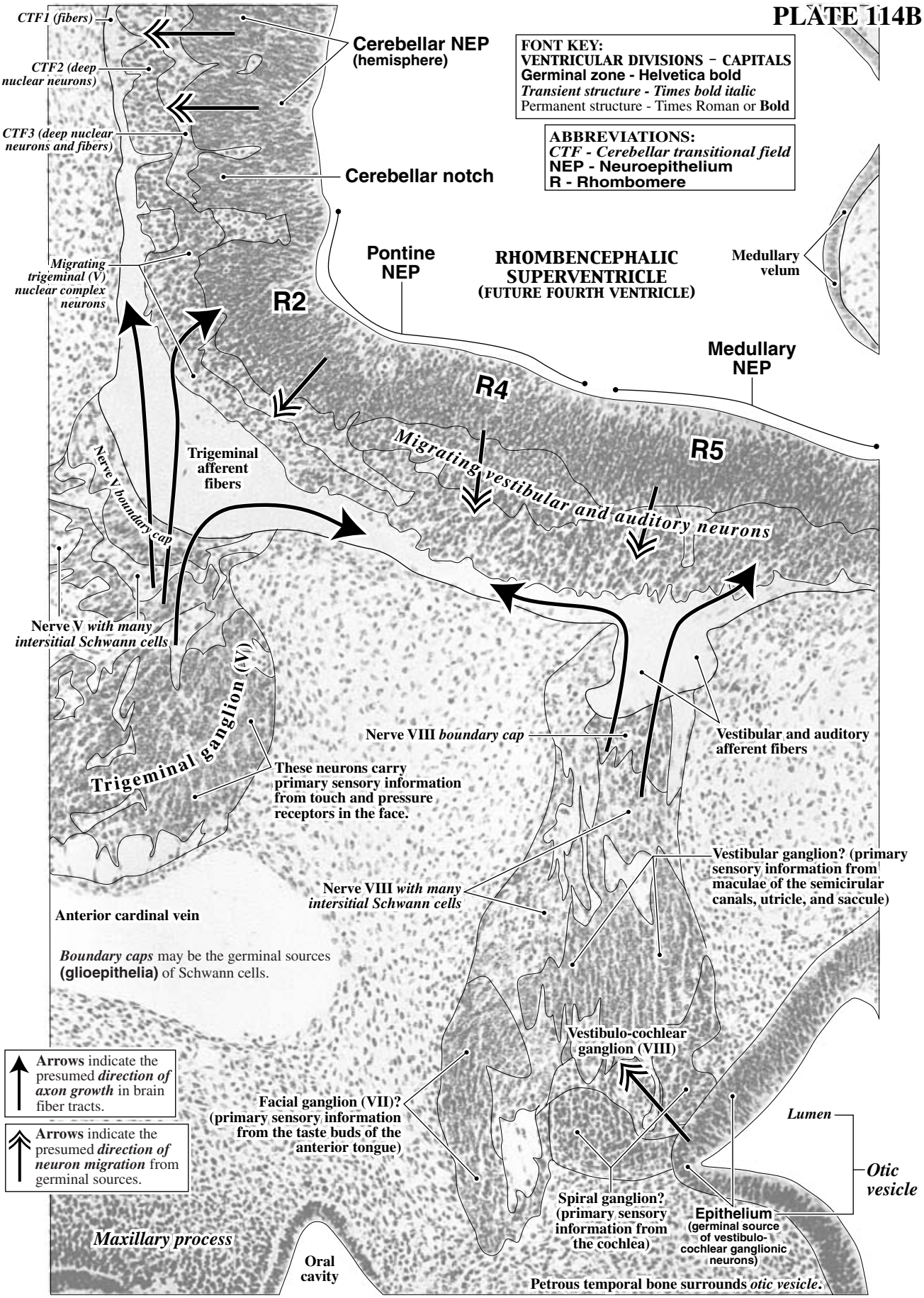


PLATE 114B


CTF1 (fibers)
CTF2 (deep nuclear neurons)
CTF3 (deep nuclear neurons and fibers)
Cerebellar NEP (hemisphere)
Cerebellar notch
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
CTF - Cerebellar transitional field
NEP - Neuroepithelium
R - Rhombomere
Pontine NEP
RHOMBENCEPHALIC SUPERVENTRICLE (FUTURE FOURTH VENTRICLE)
Medullary velum
Migrating trigeminal (V) nuclear complex neurons
R2
R4
R5
Medullary NEP
Trigeminal afferent fibers
Nerve V boundary cap
Migrating vestibular and auditory neurons
Nerve V with many intersitial Schwann cells
Trigeminal ganglion (V)
These neurons carry primary sensory information from touch and pressure receptors in the face.
Nerve VIII boundary cap
Vestibular and auditory afferent fibers
Vestibular ganglion? (primary sensory information from maculae of the semicirular canals, utricle, and saccule)
Nerve VIII with many intersitial Schwann cells
Anterior cardinal vein
Boundary caps may be the germinal sources (glioepithelia) of Schwann cells.
Vestibulo-cochlear ganglion (VIII)
Facial ganglion (VII)? (primary sensory information from the taste buds of the anterior tongue)
Lumen
Otic vesicle
Spiral ganglion? (primary sensory information from the cochlea)
Epithelium (germinal source of vestibulo-cochlear ganglionic neurons)
Maxillary process
Oral cavity
Petrous temporal bone surrounds otic vesicle.
Arrows indicate the presumed direction of axon growth in brain fiber tracts.
Arrows indicate the presumed direction of neuron migration from germinal sources.

PART IX: GW5 CORONAL

Carnegie Collection specimen #8314 (designated here as C8314) with a 7.1 mm crown-rump length (CR) is estimated to be at gestational week (GW) 5. C8314 was fixed in formalin, embedded in a celloidin/paraffin mix, and was cut in 8 μm transverse sections that were stained with azan. Sections of the prosencephalon and anterior mesencephalon are cut in the coronal plane, but the plane shifts to predominantly horizontal in the posterior mesencephalon, pons and medulla. We photographed 39 sections at low magnification from the frontal prominence to the posterior tips of the mesencephalon and rhombencephalon. Eleven of these sections are illustrated in **Plates 115AB to 124AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of C8314's brain and eye (**Figure 8**), and to show each illustrated section *in situ* (*insets,* **Plates 115A to 124A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures.

At this stage of development, the forebrain is a unitary prosencephalon because a telencephalon cannot be clearly distinguished from the diencephalon. There are no paired telencephalic vesicles. The most anterior brain sections are tentatively identified as the future telencephalon, while sections of the optic vesicle and posterior to it are more clearly identified as diencephalic. All parts of the prosencephalic neuroepithelium are rapidly increasing their pool of neuronal and glial stem cells as they expand the shorelines of the enlarging prosencephalic superventricle. Cell migration is virtually absent. The olfactory placode has not yet invaginated, but forms a thick epithelium in the anterolateral surface of the head. The evaginated optic vesicle forms a C-shaped curve around the developing lens, defining an inner retinal neuroepithelium and an outer pigment epithelium. The eye is much closer to the diencephalon than at GW5.5 (**Part VII**) and does not yet form a stalk-like extension that will be the optic nerve.

The mesencephalon contains a stockbuilding neuroepithelium in the pretectum and tectum; cell migration has not yet begun. The tegmental and isthmal neuroepithelia are also stockbuilding their stem cell populations. Only a few pioneer neurons have migrated out. The subpial fiber band is very thin in the tegmentum, but thickens slightly in the isthmus.

The most prominent neuroepithelial structures in the rhombencephalon are the laterally-placed rhombomeres. These are crescent-shaped evaginations of stockbuilding neuroepithelium separated by narrow mounds jutting into the ventricular lumen. Blood islands and sprouting pioneer axons form clefts in between the evaginations. The rhombomeres are associated with the entry zones of sensory cranial nerves V, VII, VIII, IX, and X. In the coronal plane, the trigeminal ganglion (sensory axons of V) can be easily associated with rhombomere 2, and the vestibulocochlear ganglion (source of VIII axons) with rhombomeres 4 and 5. The subpial fiber band is thicker where sensory afferent axons enter the brain. A thin, definite layer of migrating neurons lines the superficial border of each rhombomere as neuronal and glial progeny move into a small parenchyma. Medial pontine and medullary neuroepithelia are thinner, and may actually be shrinking as more neurons and glia migrate outward. The small stockbuilding cerebellar neuroepithelium is only identifiable in the most posterior sections of the rhombencephalon; the few neurons accumulating outside it are probably the earliest-generated deep nuclear neurons.

C8314 Computer-aided 3-D Brain Reconstructions

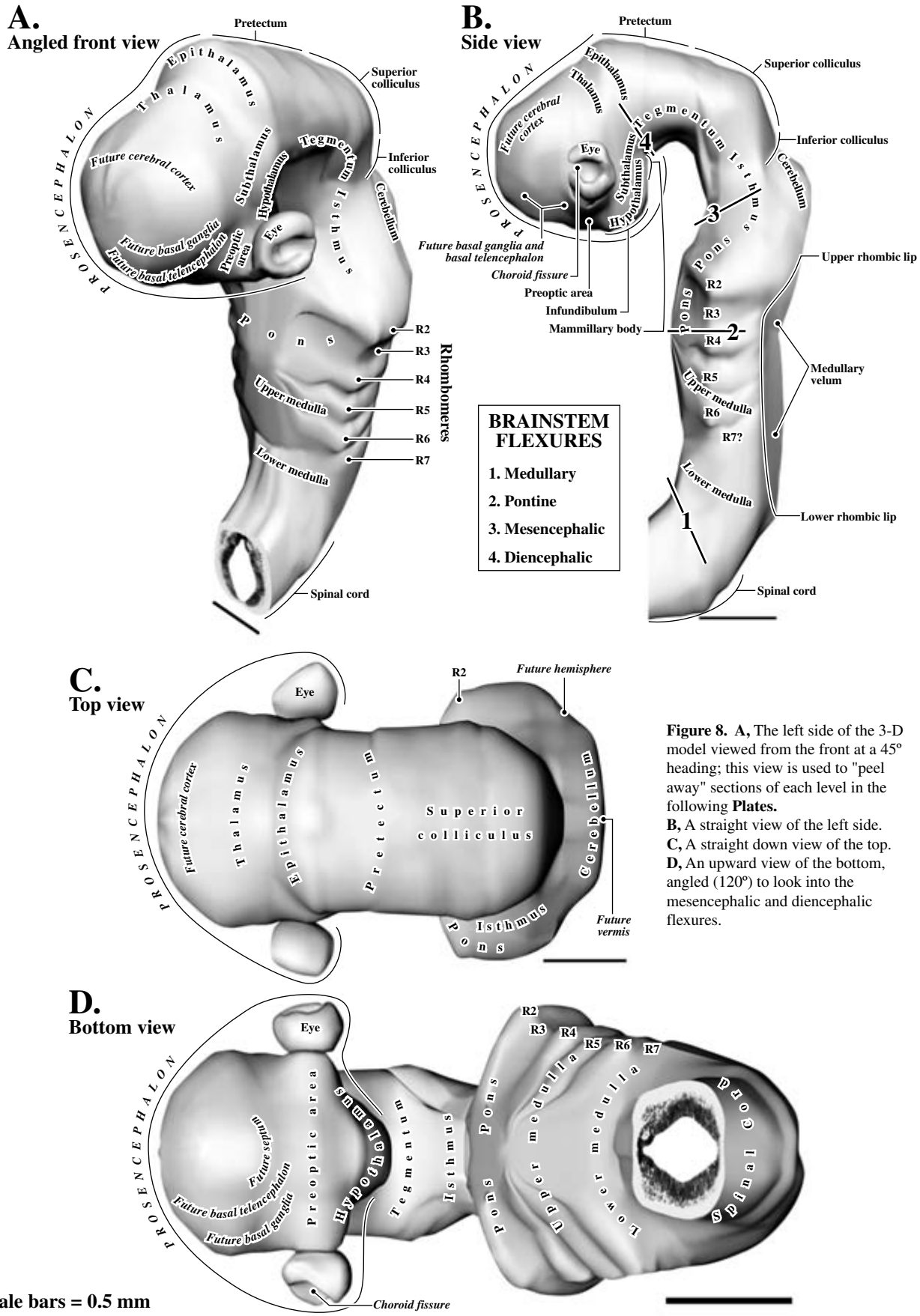


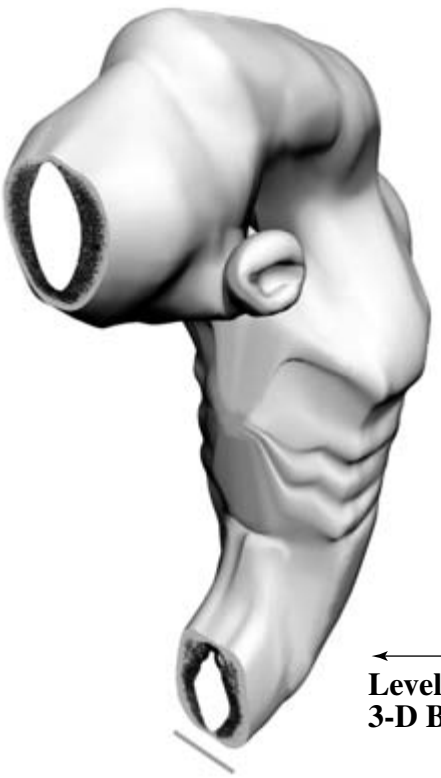
Figure 8. A, The left side of the 3-D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.**
B, A straight view of the left side.
C, A straight down view of the top.
D, An upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures.

Scale bars = 0.5 mm

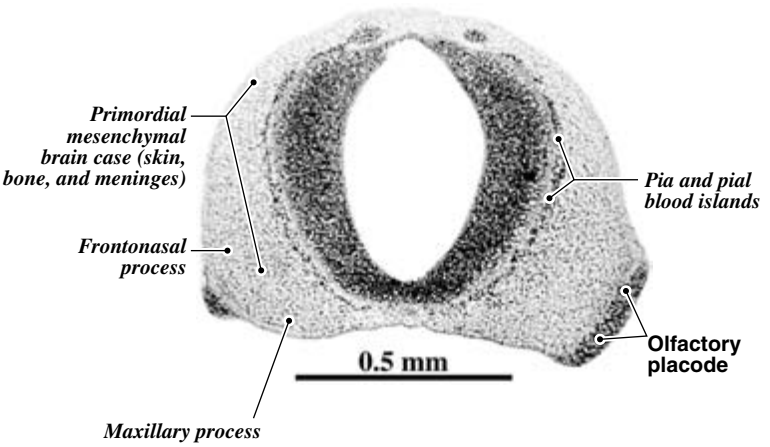
PLATE 115A

Peripheral neural and non-neural structures labeled

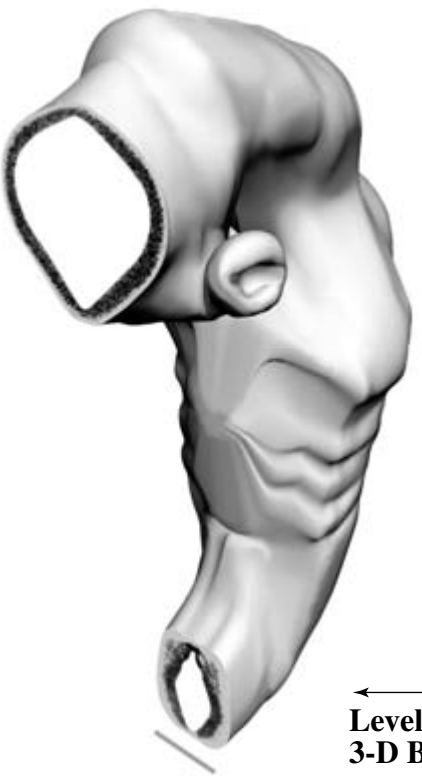
GW5 Coronal
CR 8 mm
C8314



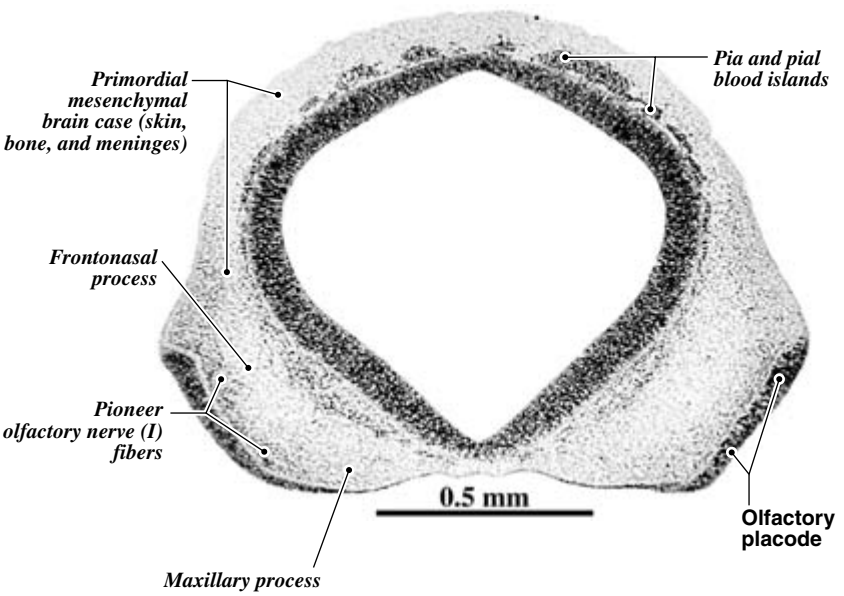
Level 1: Section 12



Level 1: Computer-aided 3-D Brain Reconstruction



Level 2: Section 42

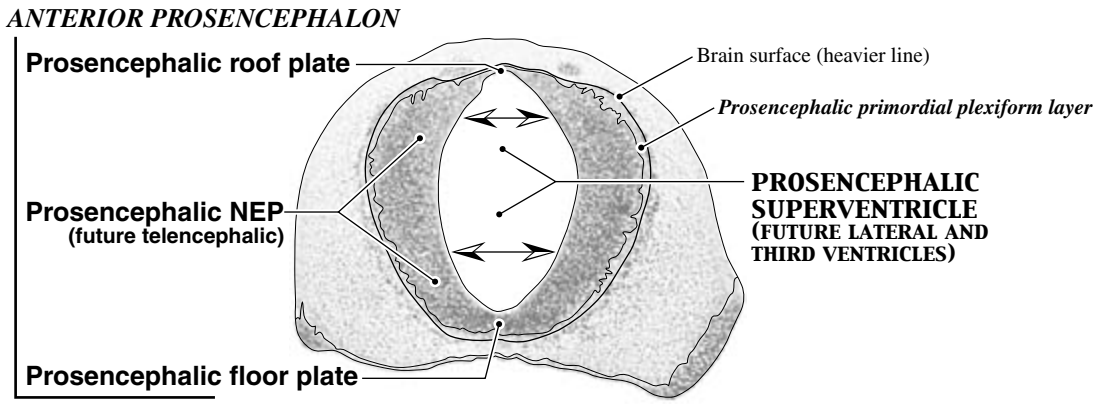


Level 2: Computer-aided 3-D Brain Reconstruction

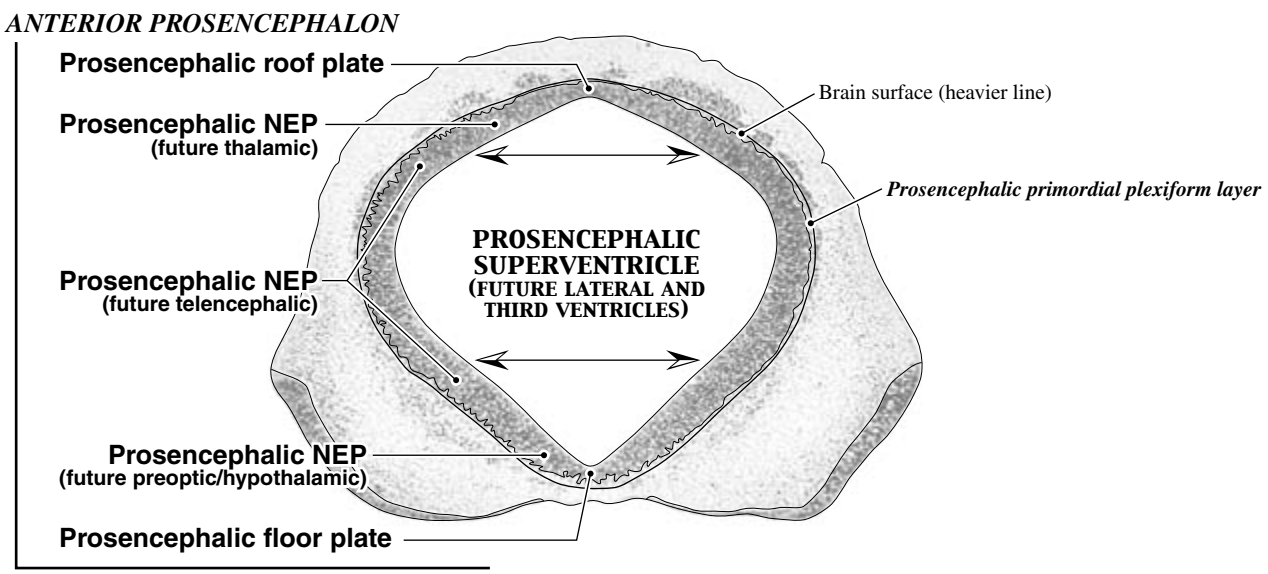
Central neural structures labeled

PLATE 115B

Level 1: Section 12



Level 2: Section 42



NEP - Neuroepithelium

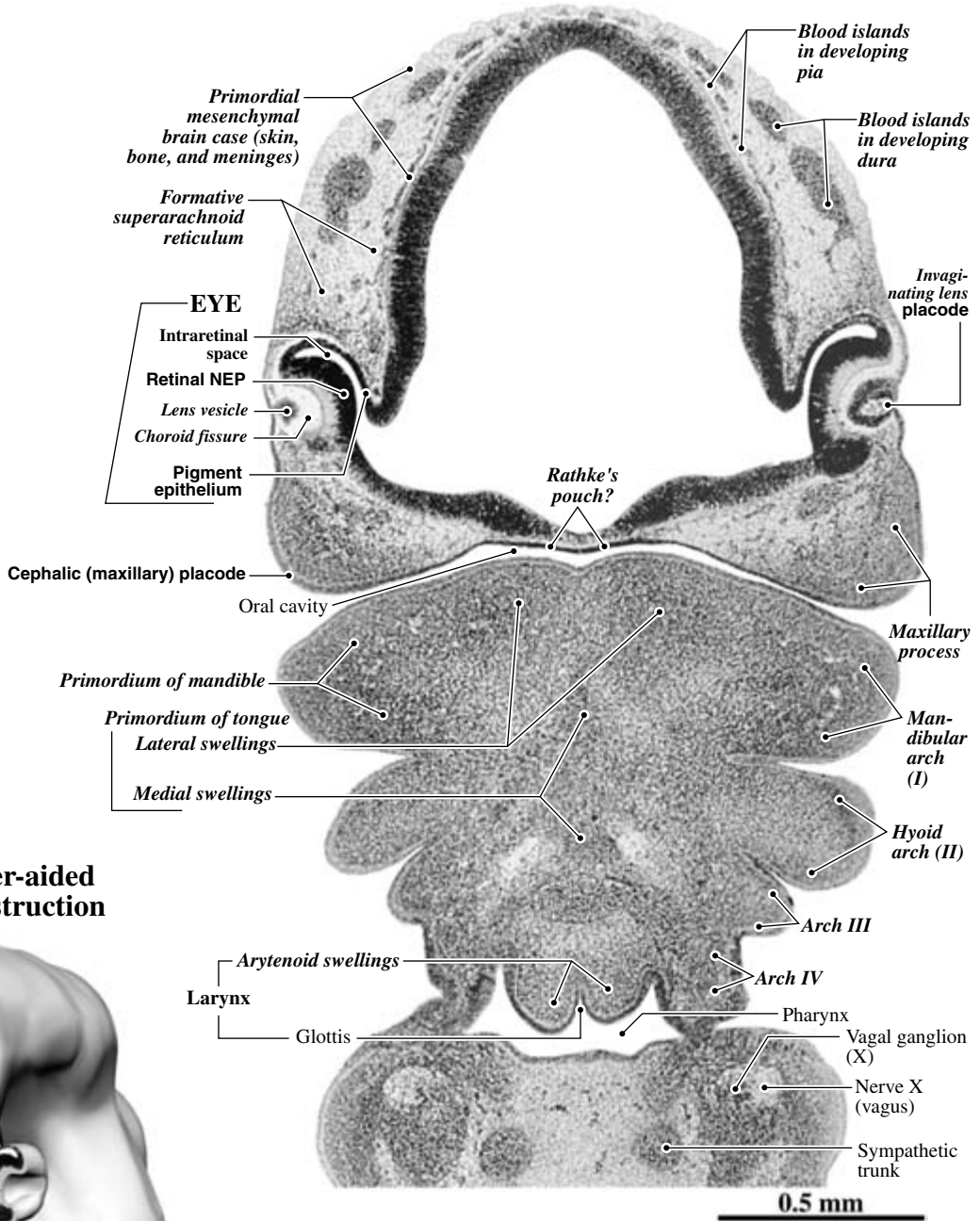
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

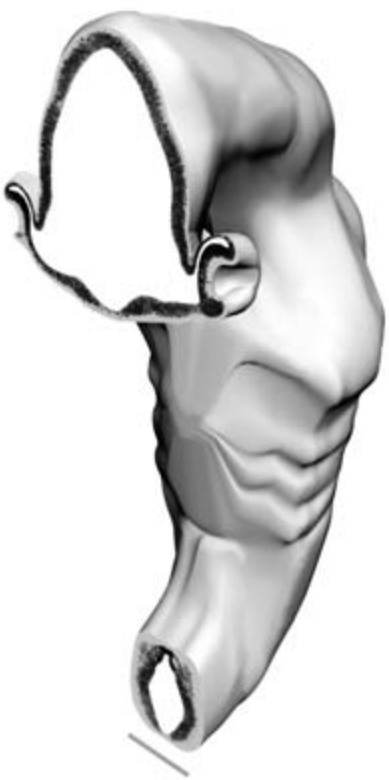
PLATE 116A

Peripheral neural and non-neural structures labeled

GW5 Coronal
CR 8 mm
C8314
Level 3:
Section 82

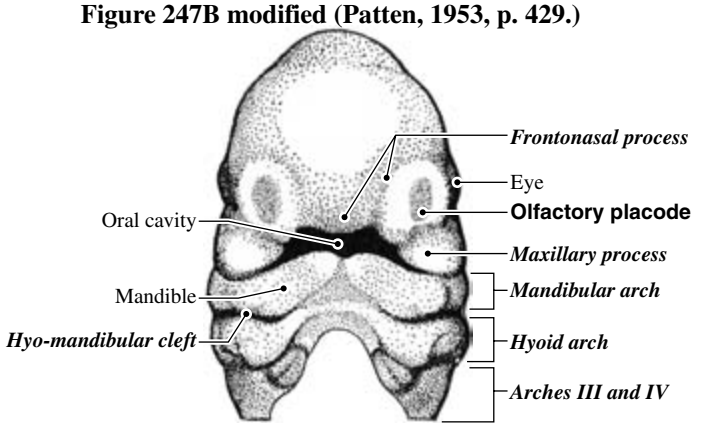


Level 3: Computer-aided 3-D Brain Reconstruction



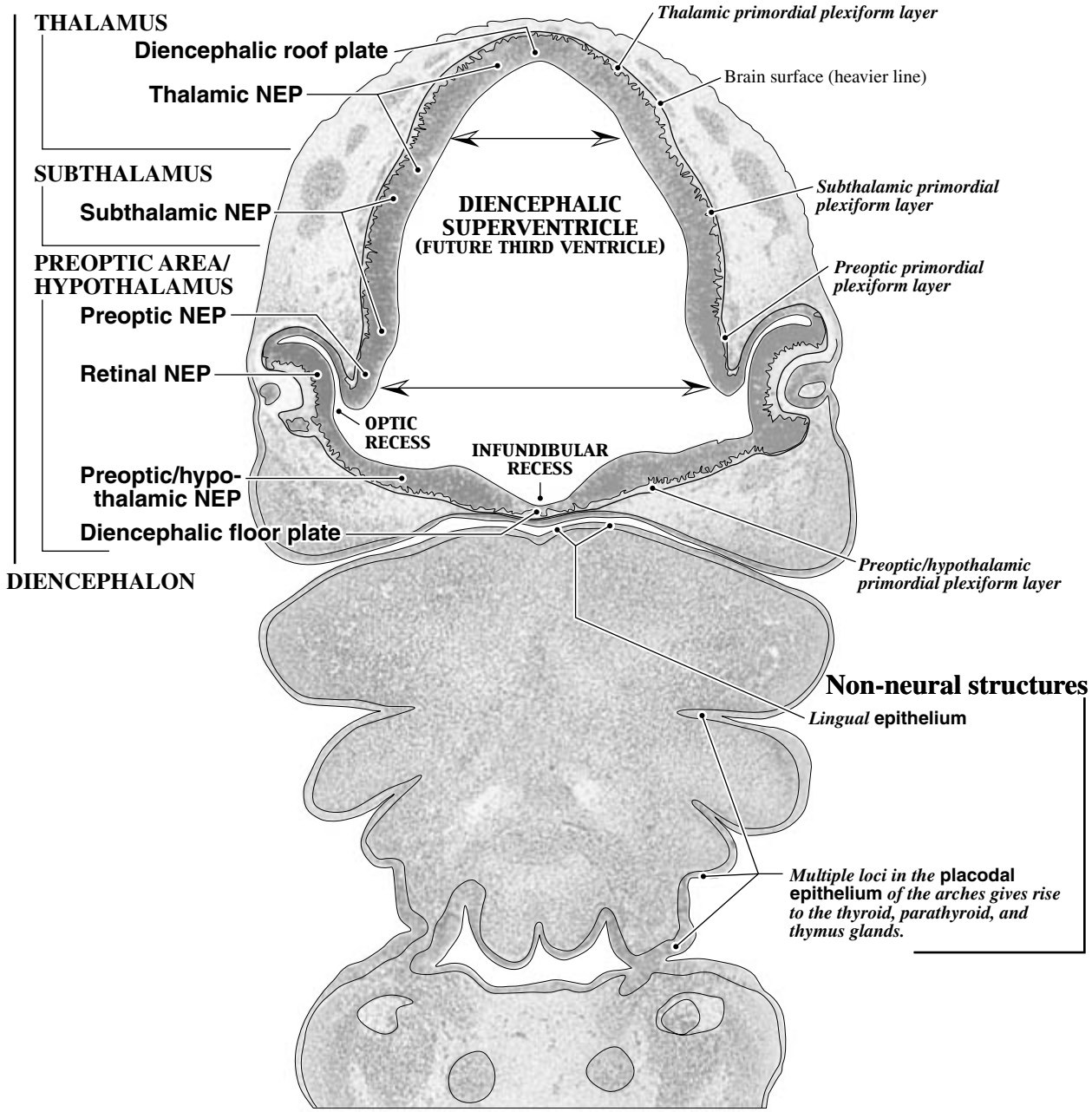
The GW5 Face and Neck

Figure 247B modified (Patten, 1953, p. 429.)



Central neural structures labeled

PLATE 116B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

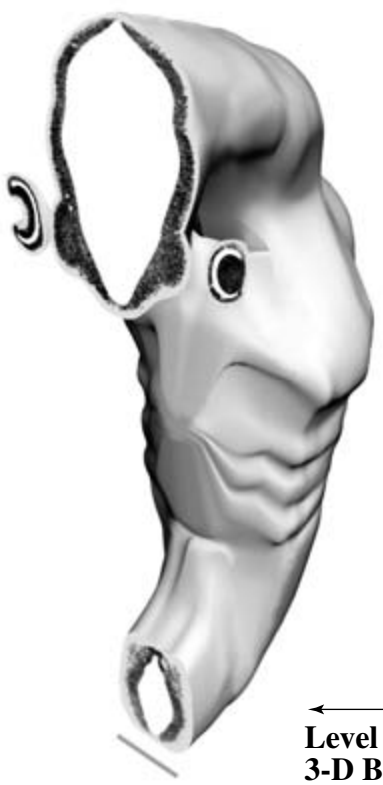
NEP - Neuroepithelium

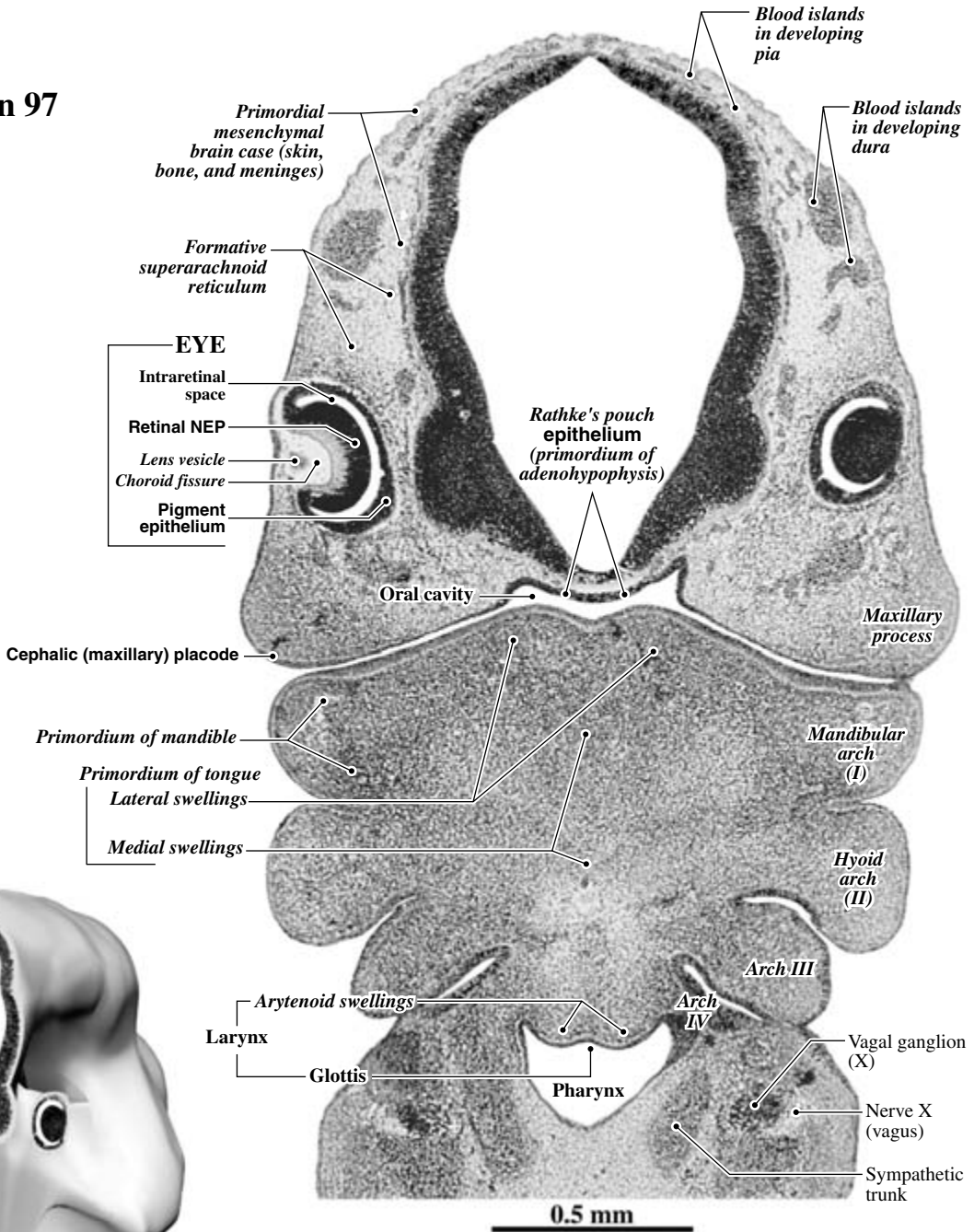
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 117A

Peripheral neural and non-neural structures labeled

GW5 Coronal
CR 8 mm
C8314
Level 4: Section 97

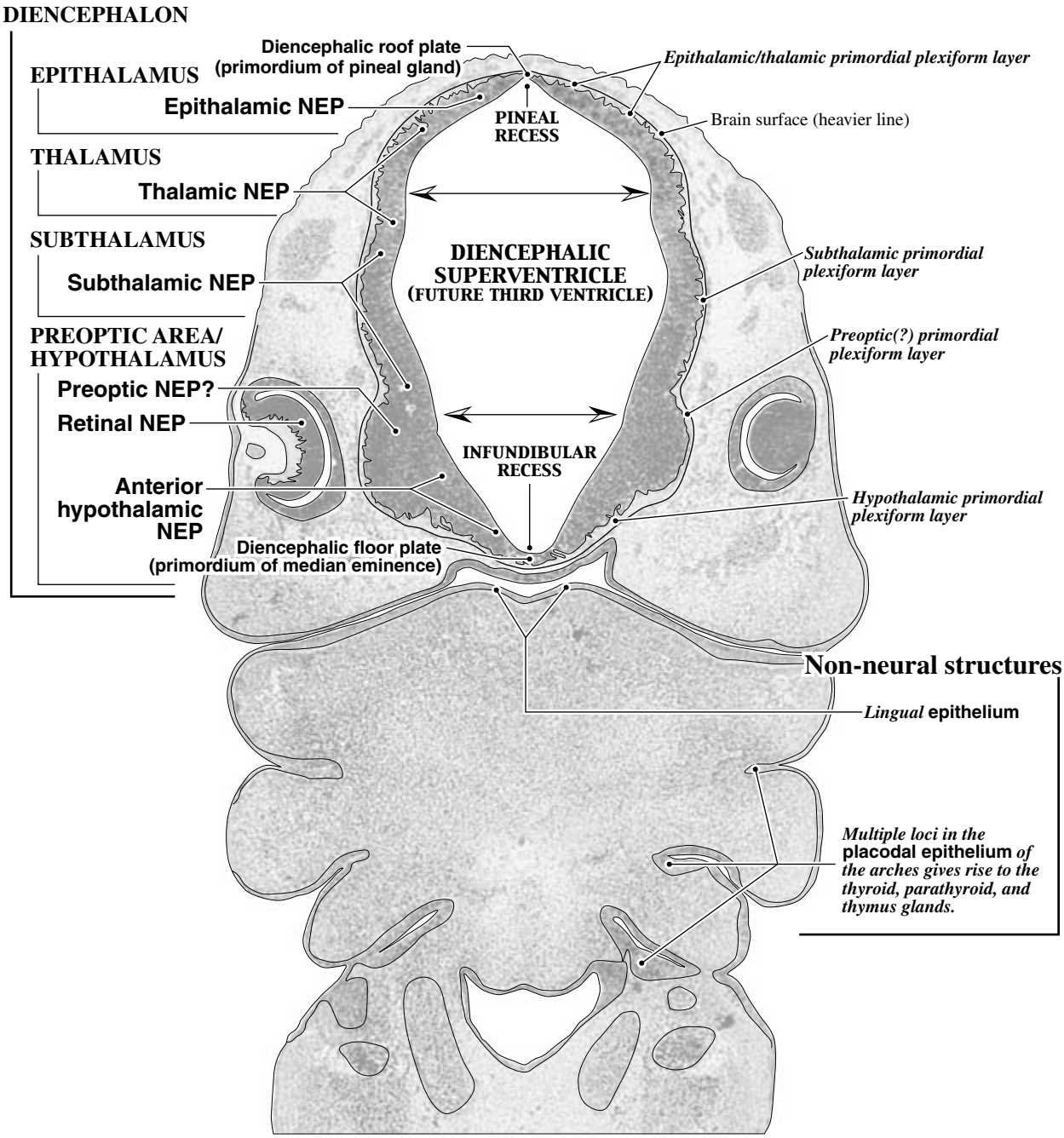




Level 4: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 117B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

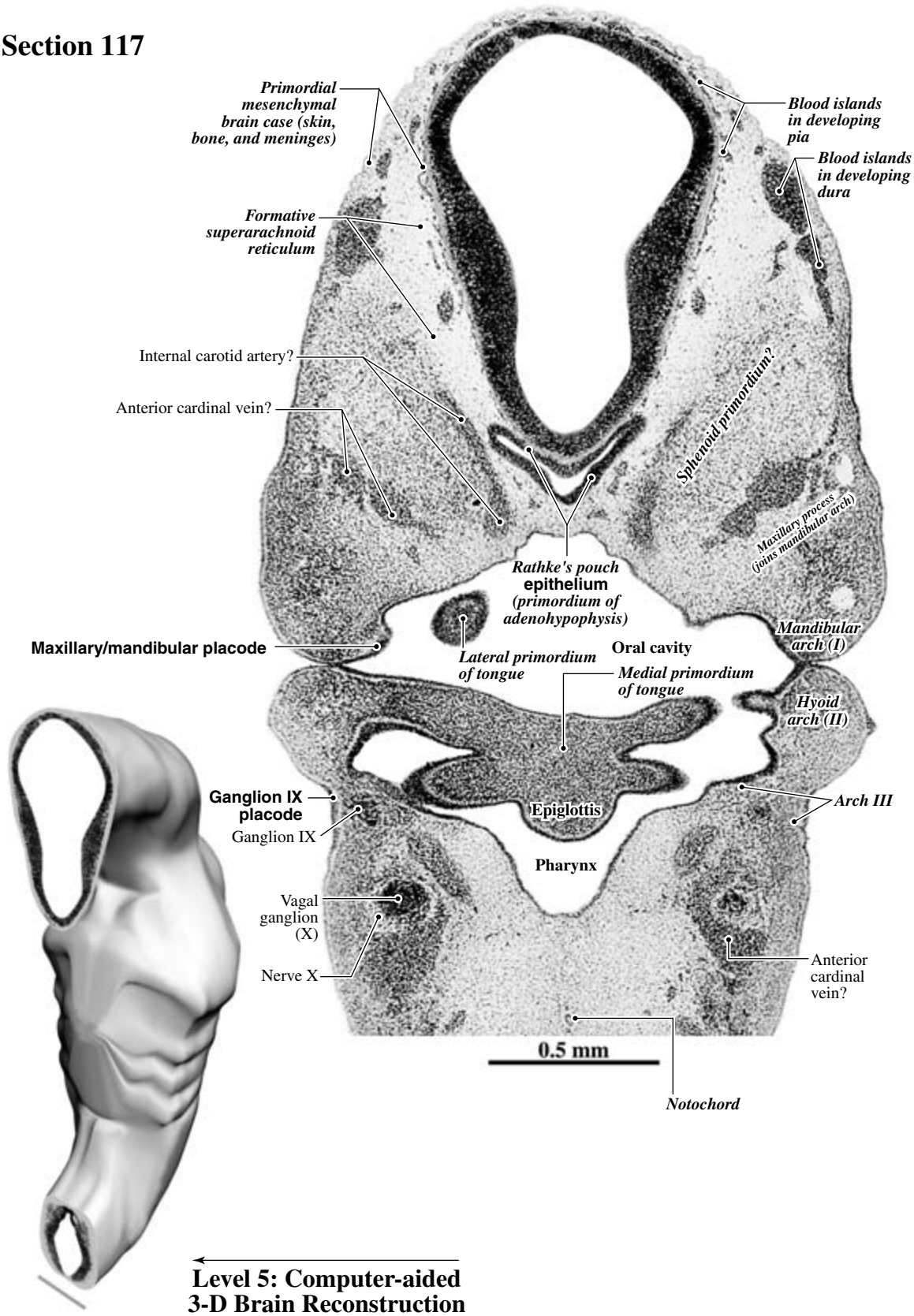
NEP - Neuroepithelium

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 118A

Peripheral neural and non-neural structures labeled

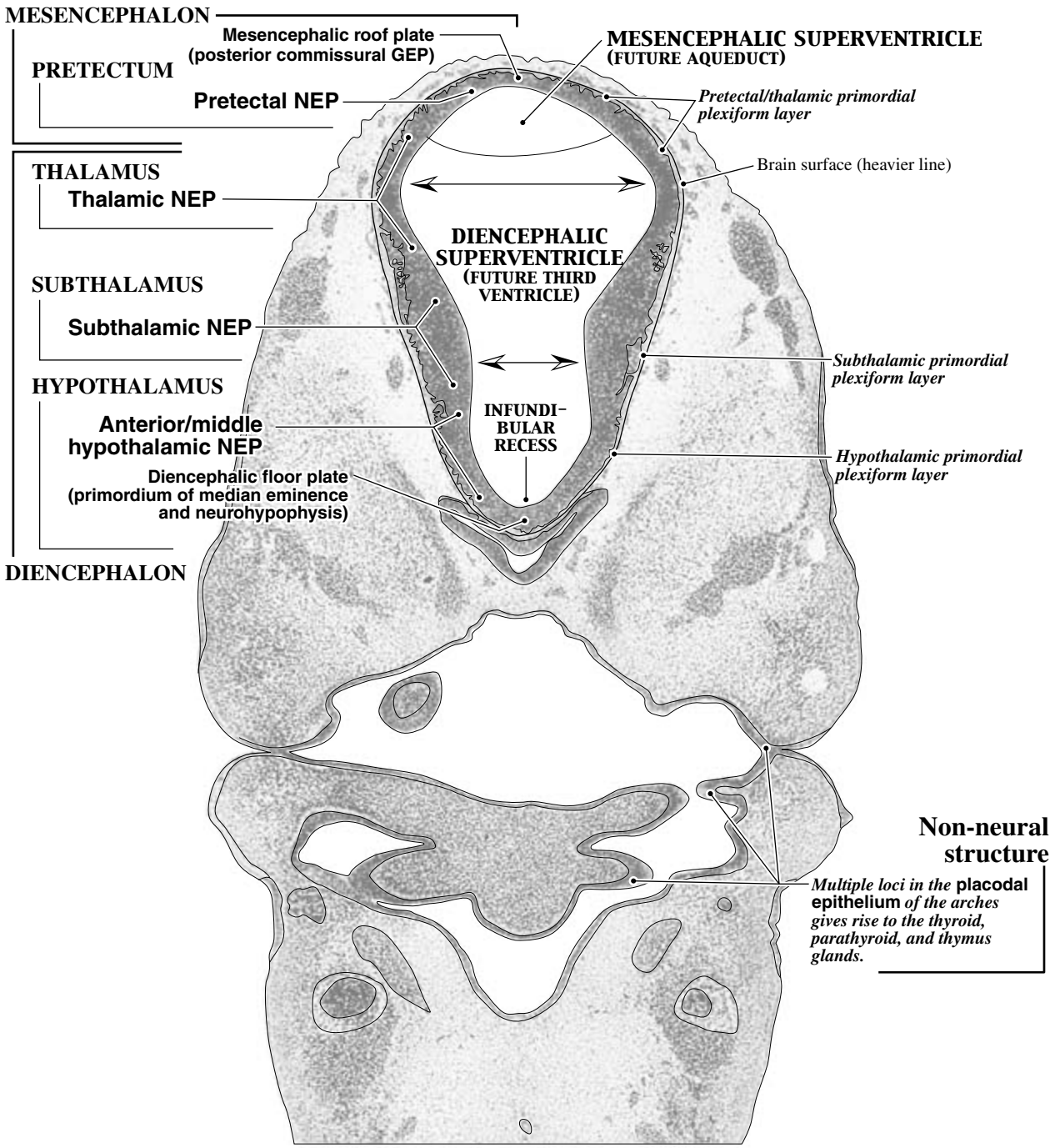
GW5 Coronal
CR 8 mm
C8314
Level 5: Section 117



Level 5: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 118B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

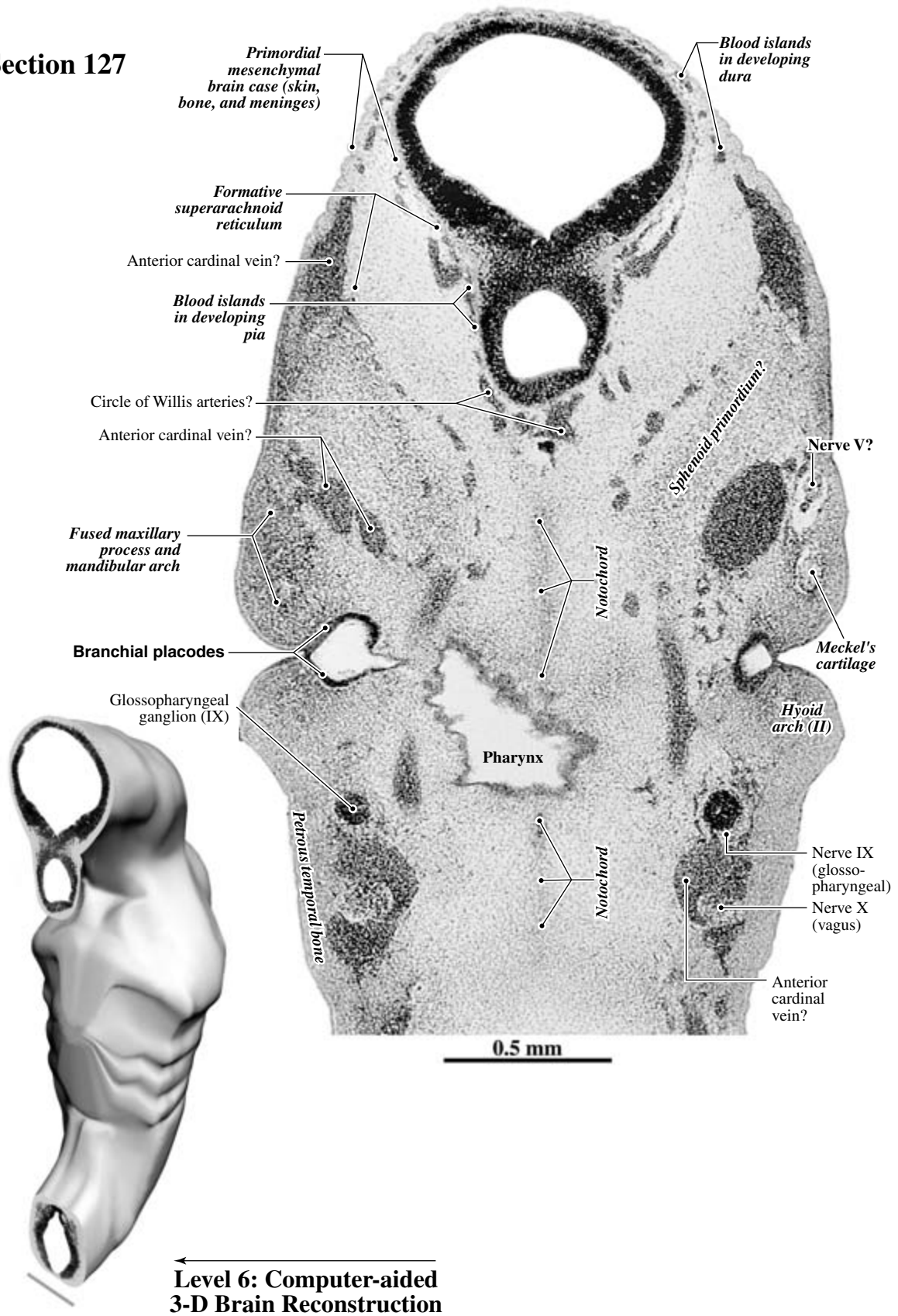
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 119A

GW5 Coronal
CR 8 mm
C8314
Level 6: Section 127

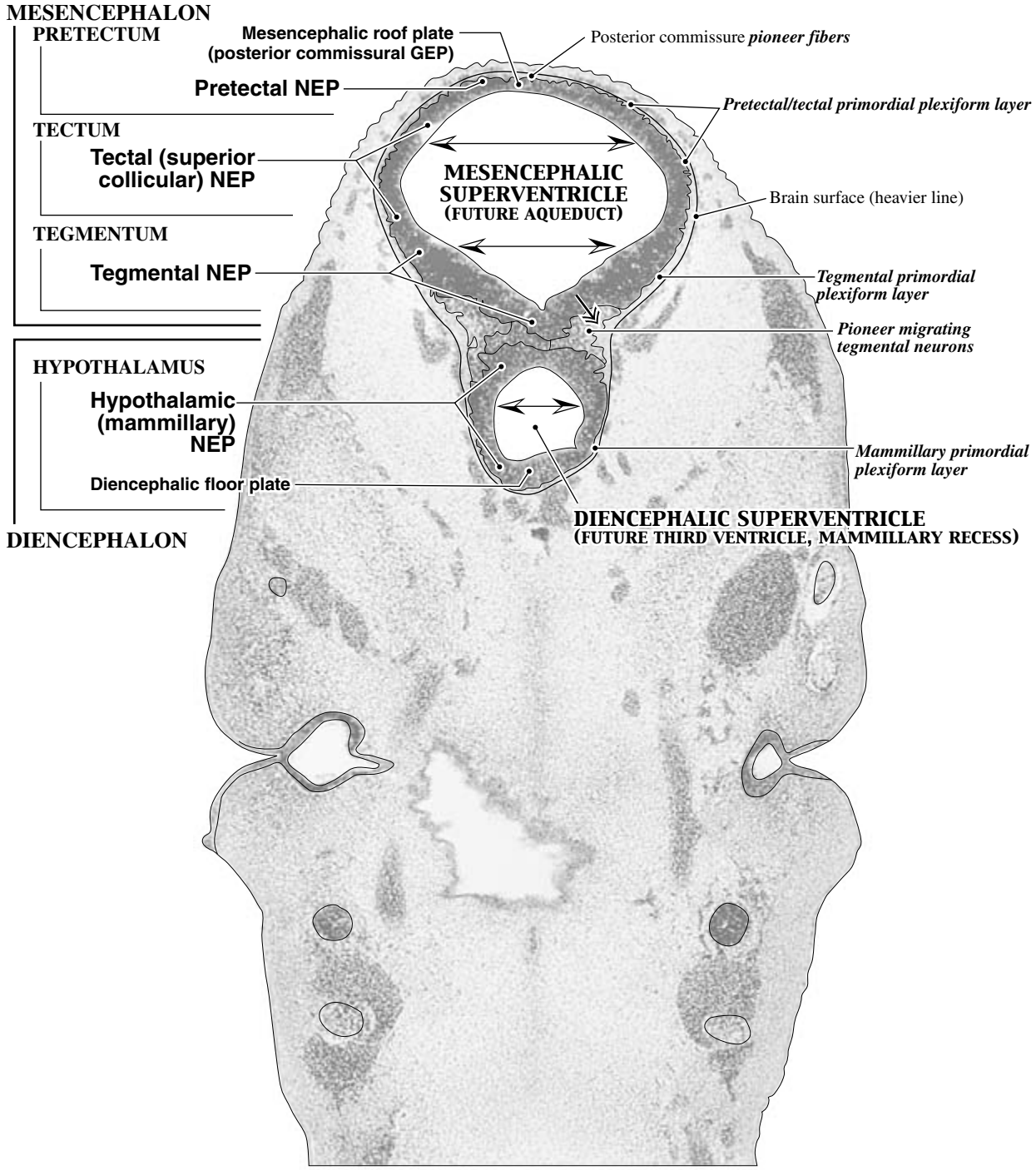
Peripheral neural and non-neural structures labeled



Level 6: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 119B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

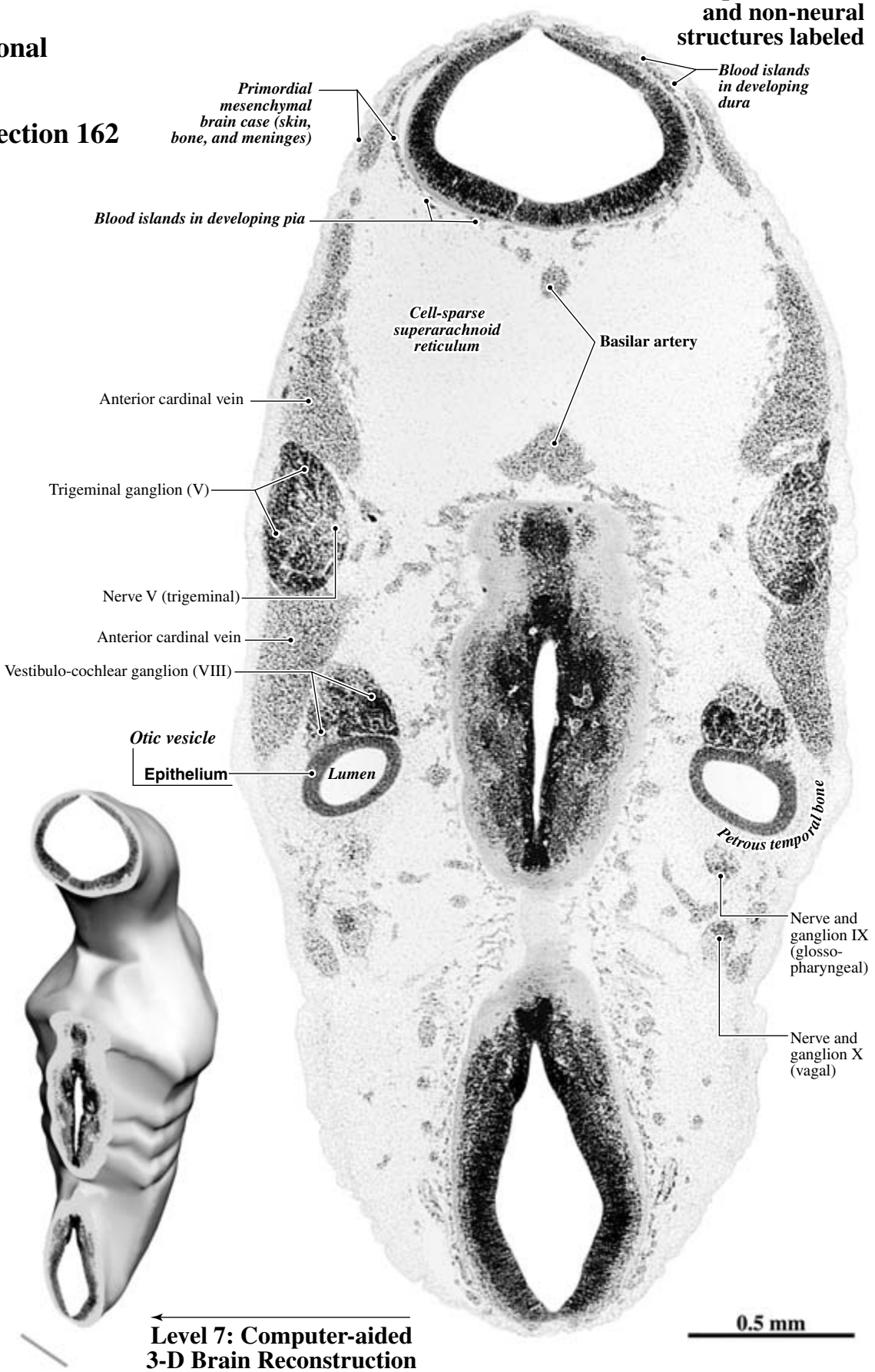
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 120A

GW5 Coronal
CR 8 mm
C8314
Level 7: Section 162

Peripheral neural and non-neural structures labeled



Level 7: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 120B

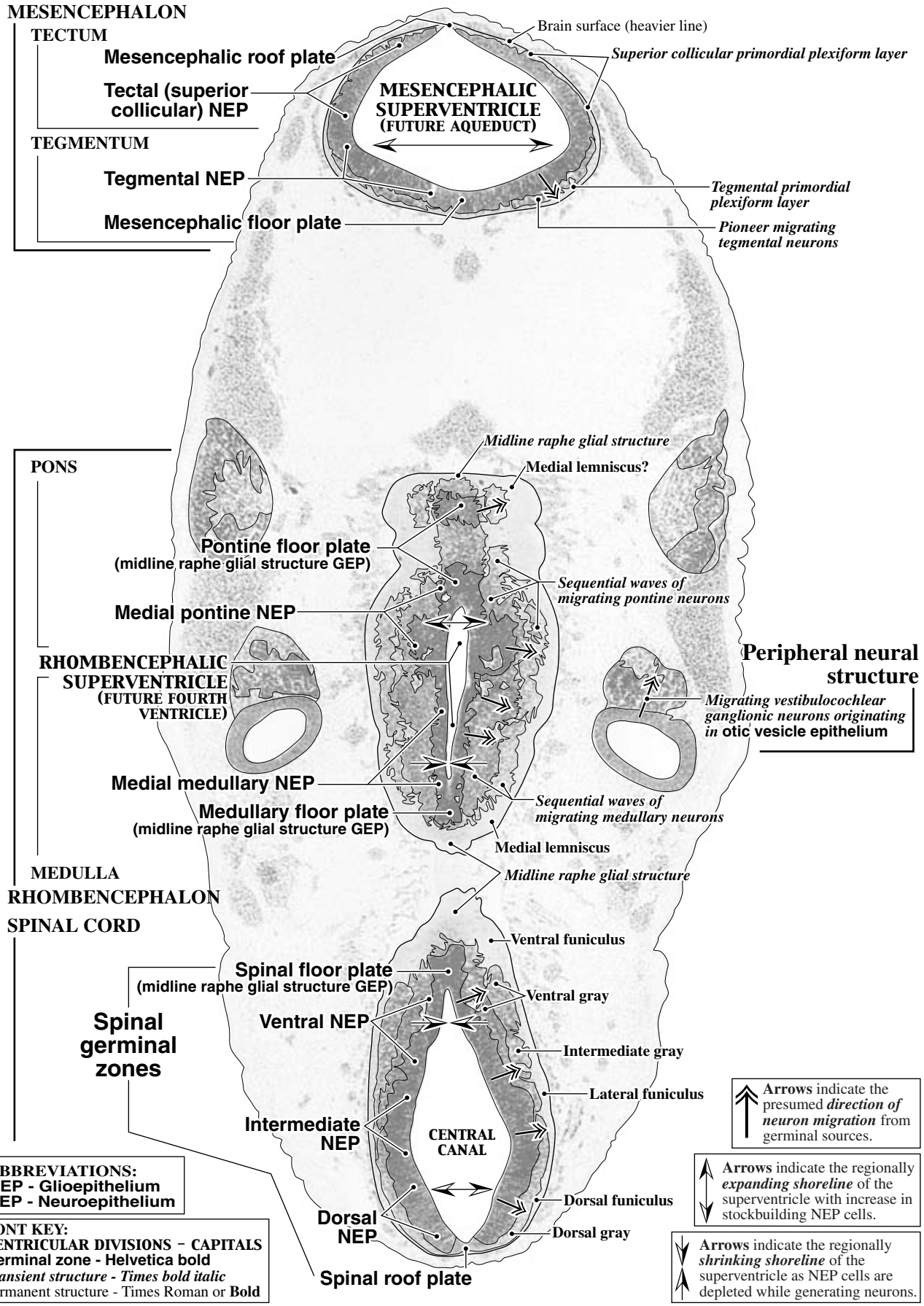
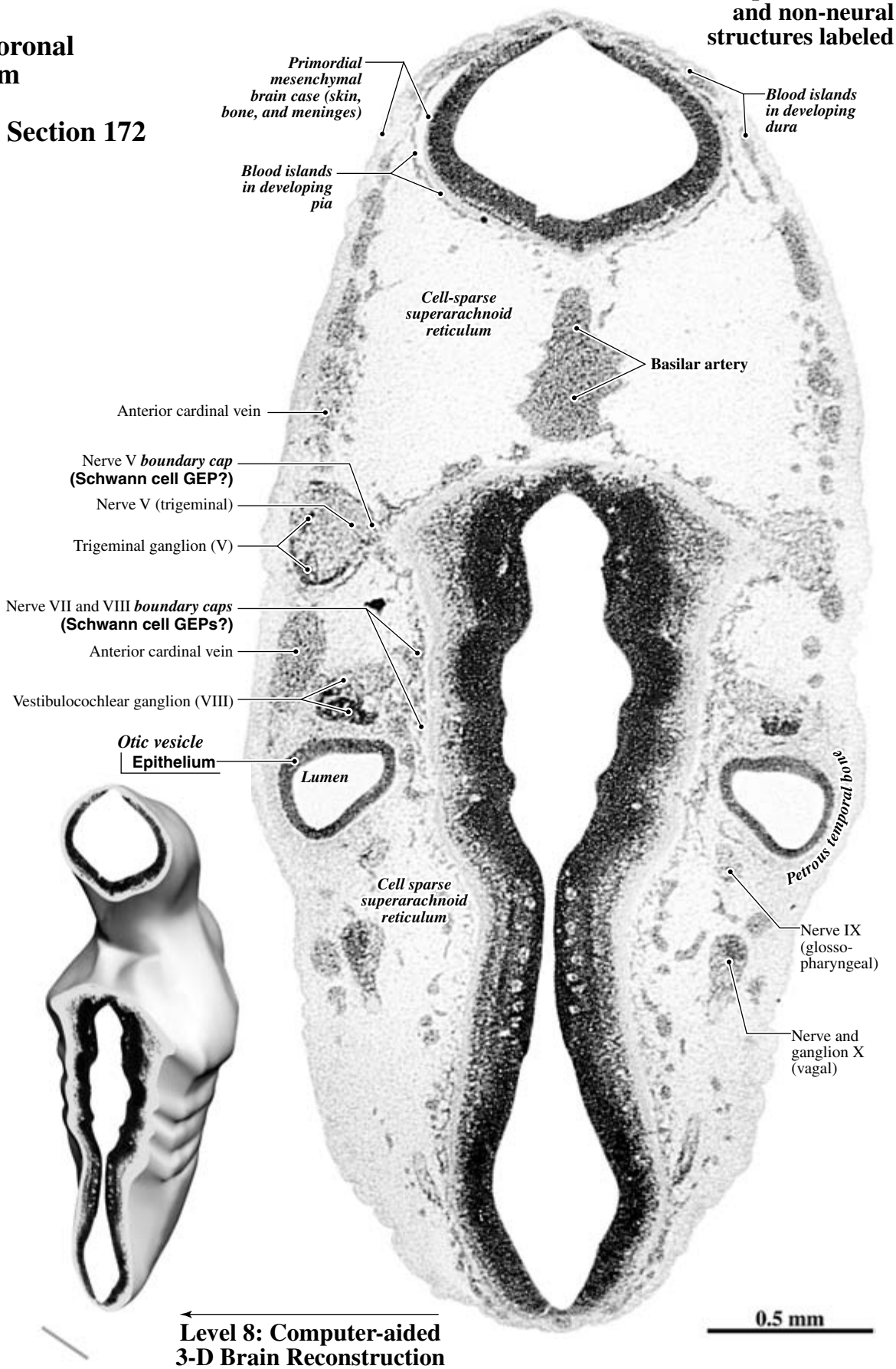


PLATE 121A

GW5 Coronal
CR 8 mm
C8314
Level 8: Section 172

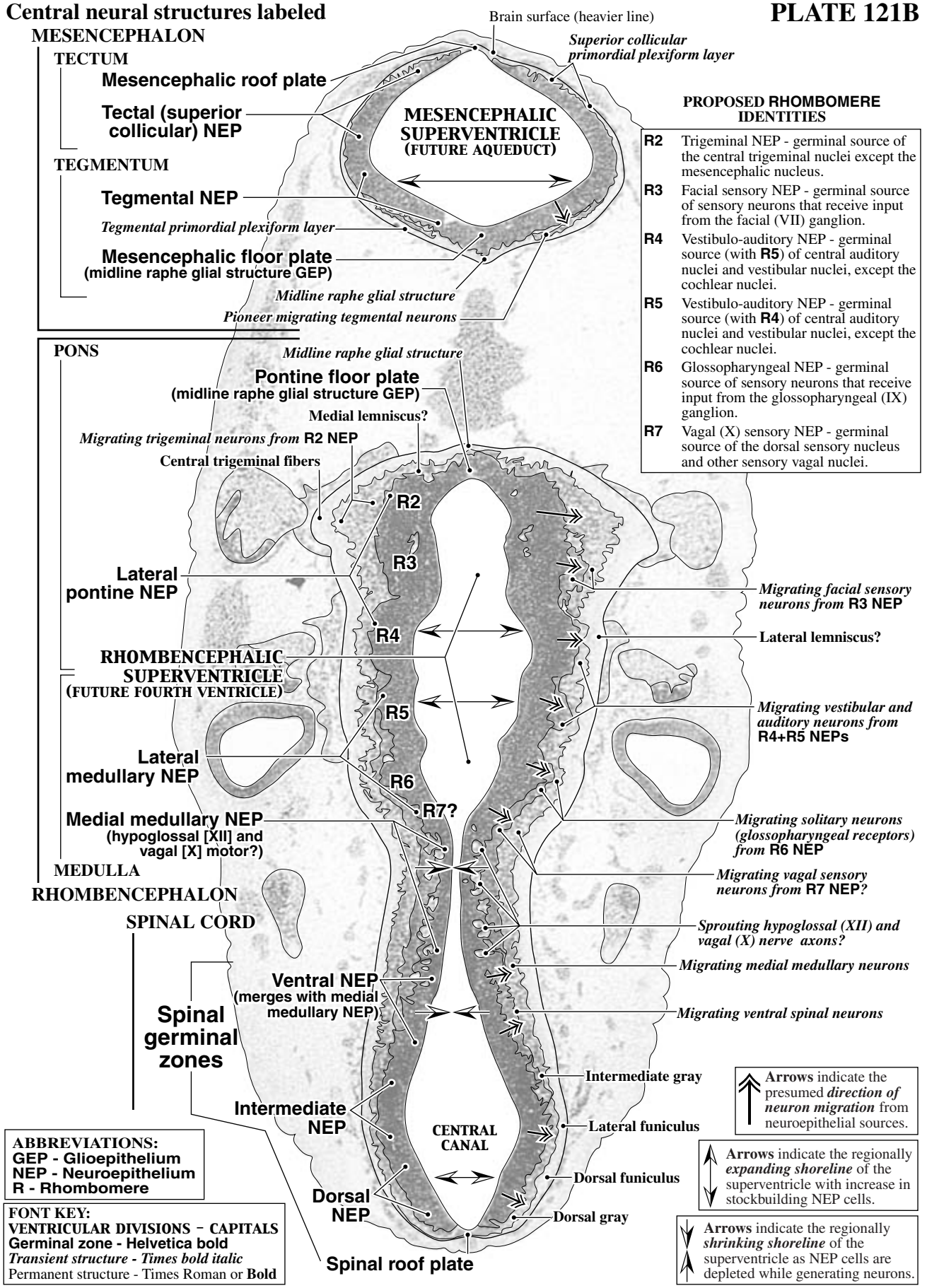
Peripheral neural and non-neural structures labeled



Level 8: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 121B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

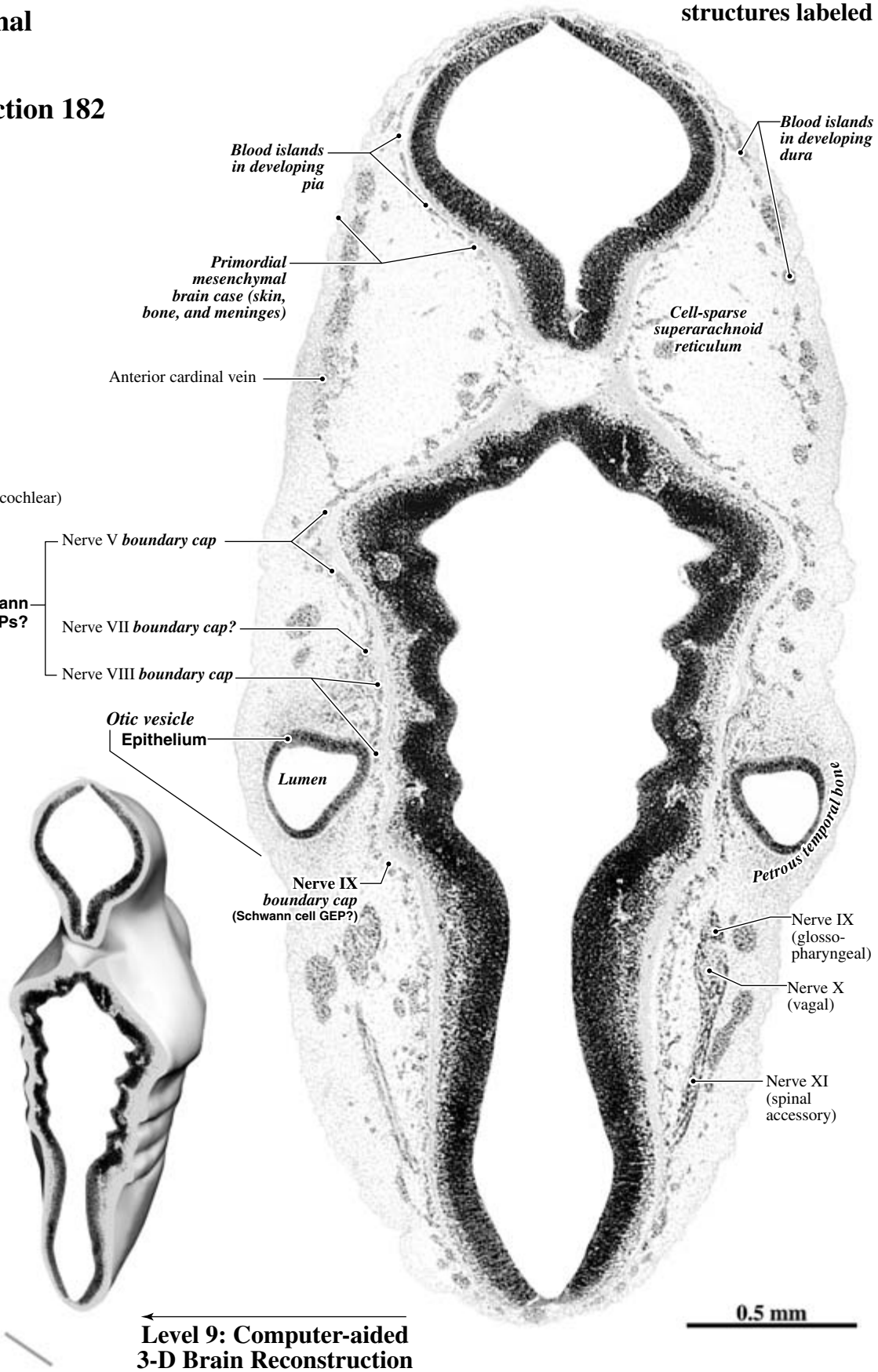
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 122A

Peripheral neural and non-neural structures labeled

GW5 Coronal
CR 8 mm
C8314
Level 9: Section 182



Level 9: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 122B

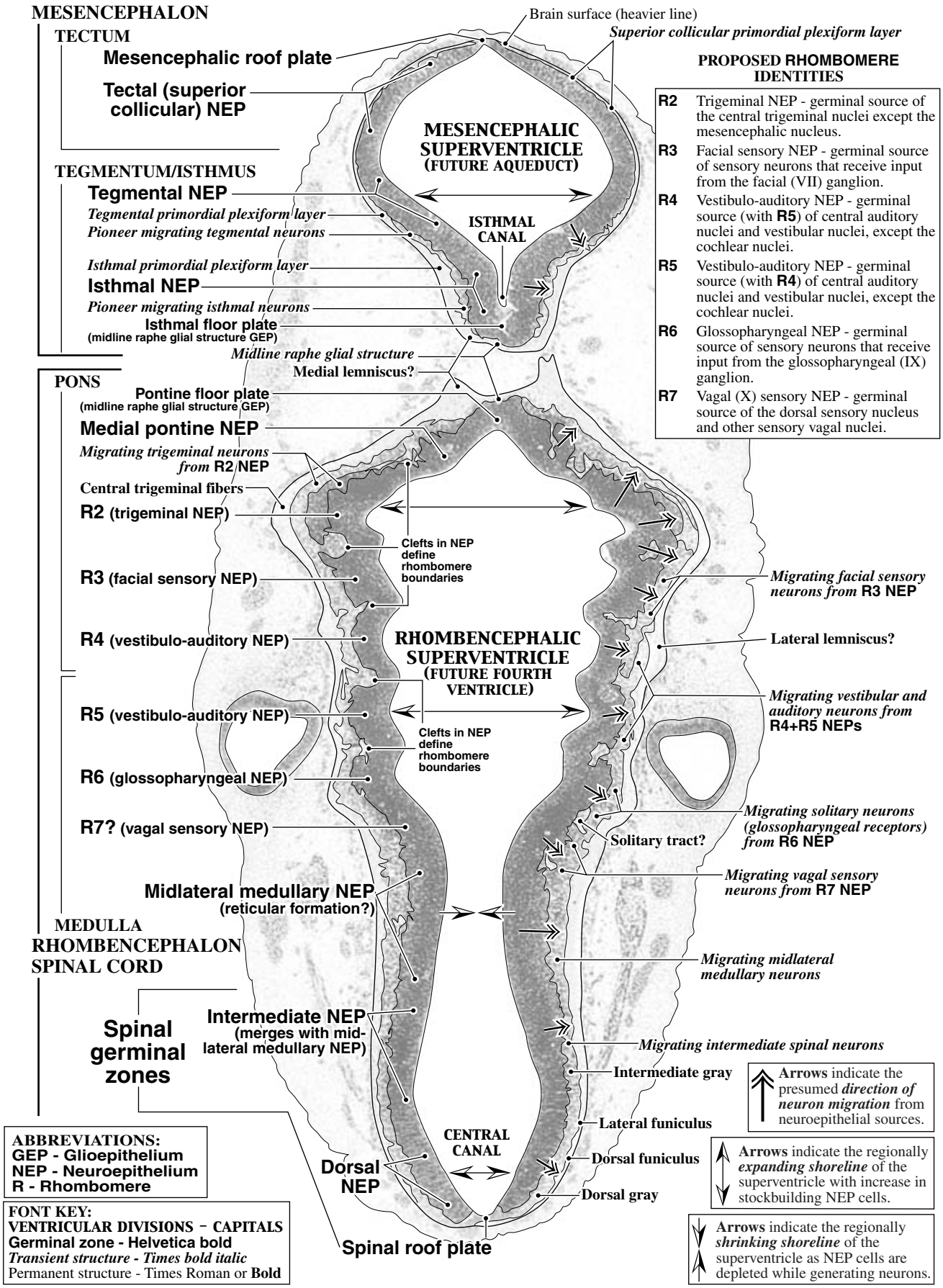
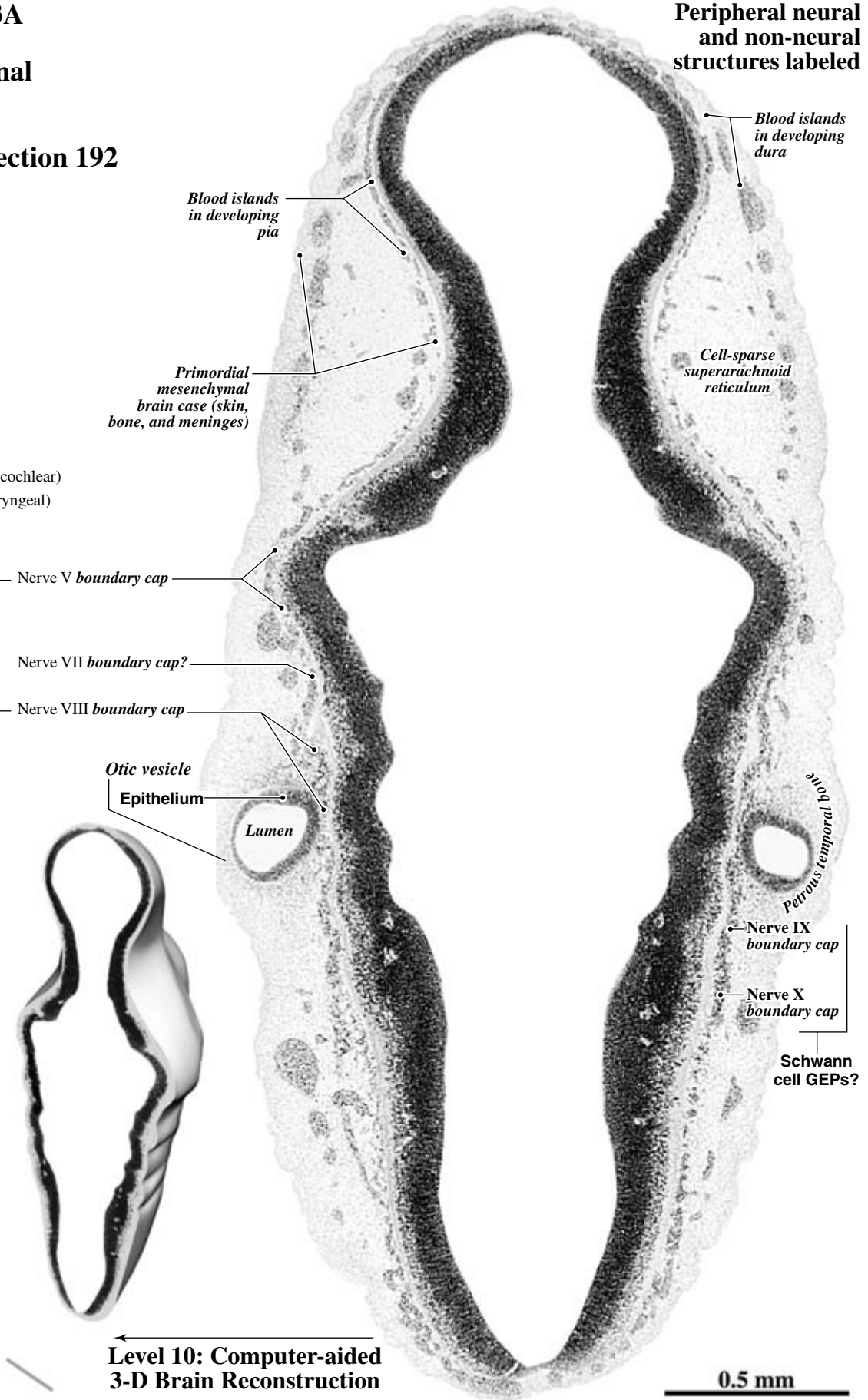


PLATE 123A

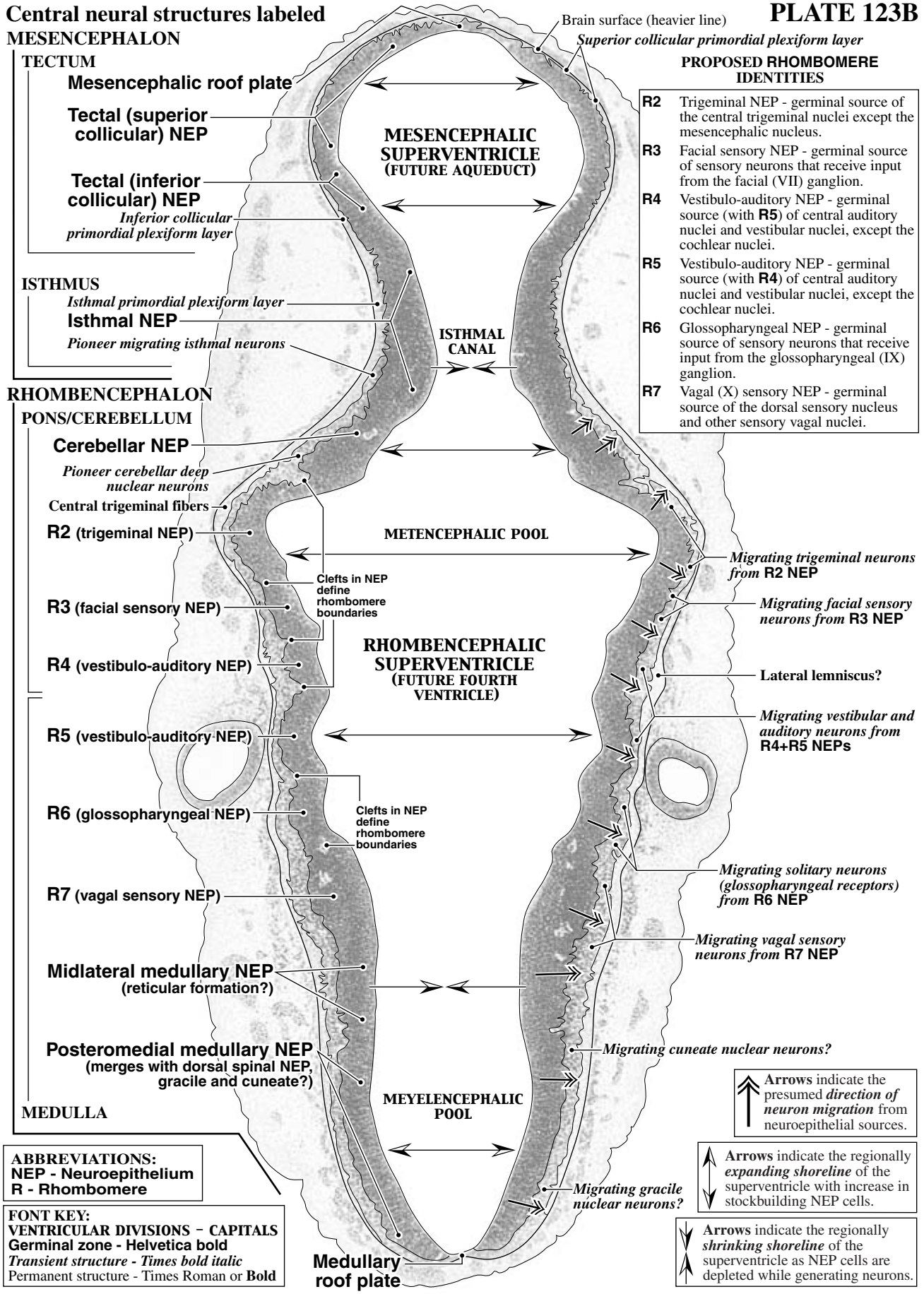
GW5 Coronal
CR 8 mm
C8314
Level 10: Section 192

Peripheral neural and non-neural structures labeled



Central neural structures labeled

PLATE 123B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

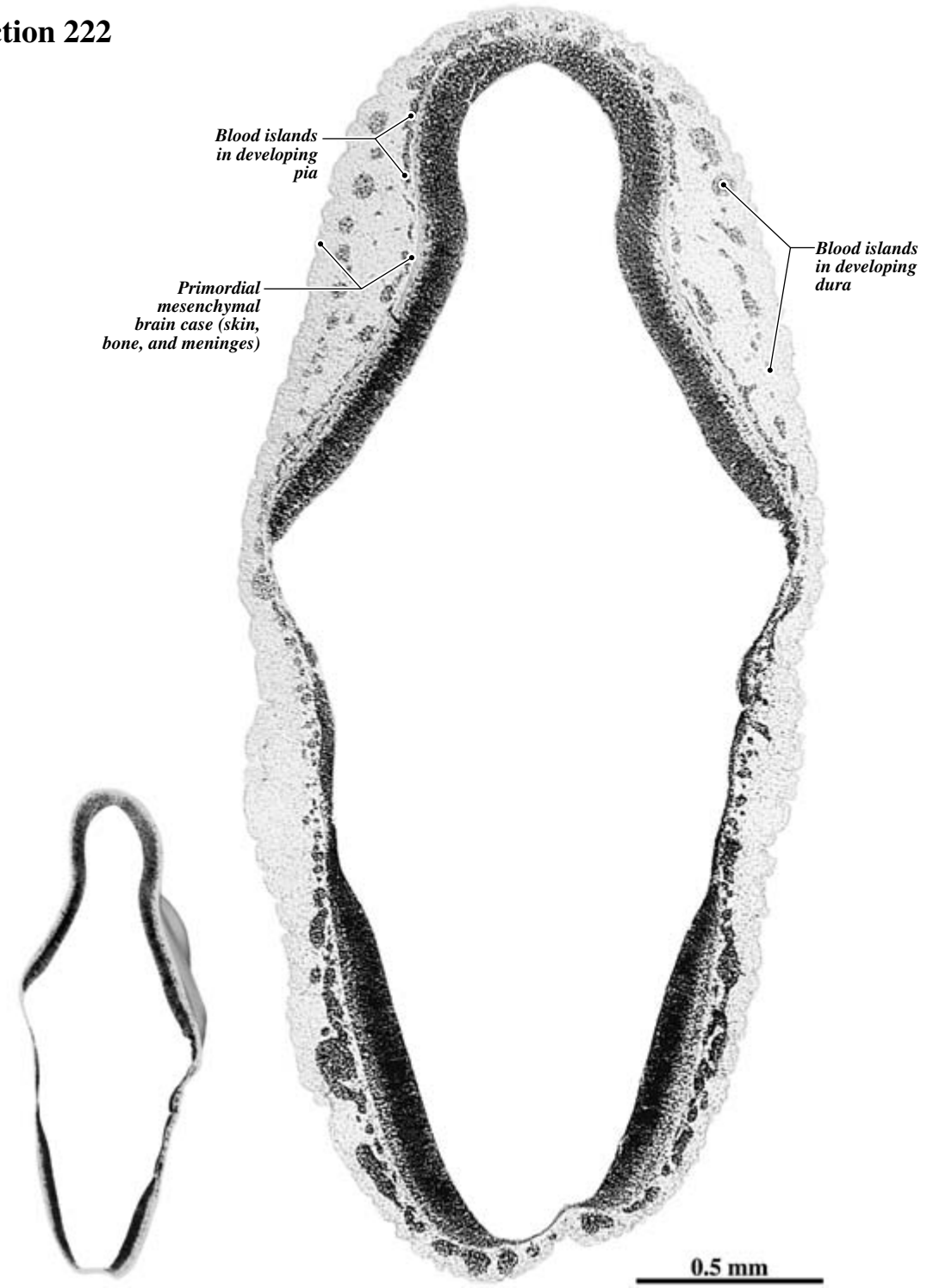
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

Arrows indicate the regionally ***shrinking shoreline*** of the superventricle as NEP cells are depleted while generating neurons.

PLATE 124A

GW5 Coronal
CR 8 mm
C8314
Level 11: Section 222

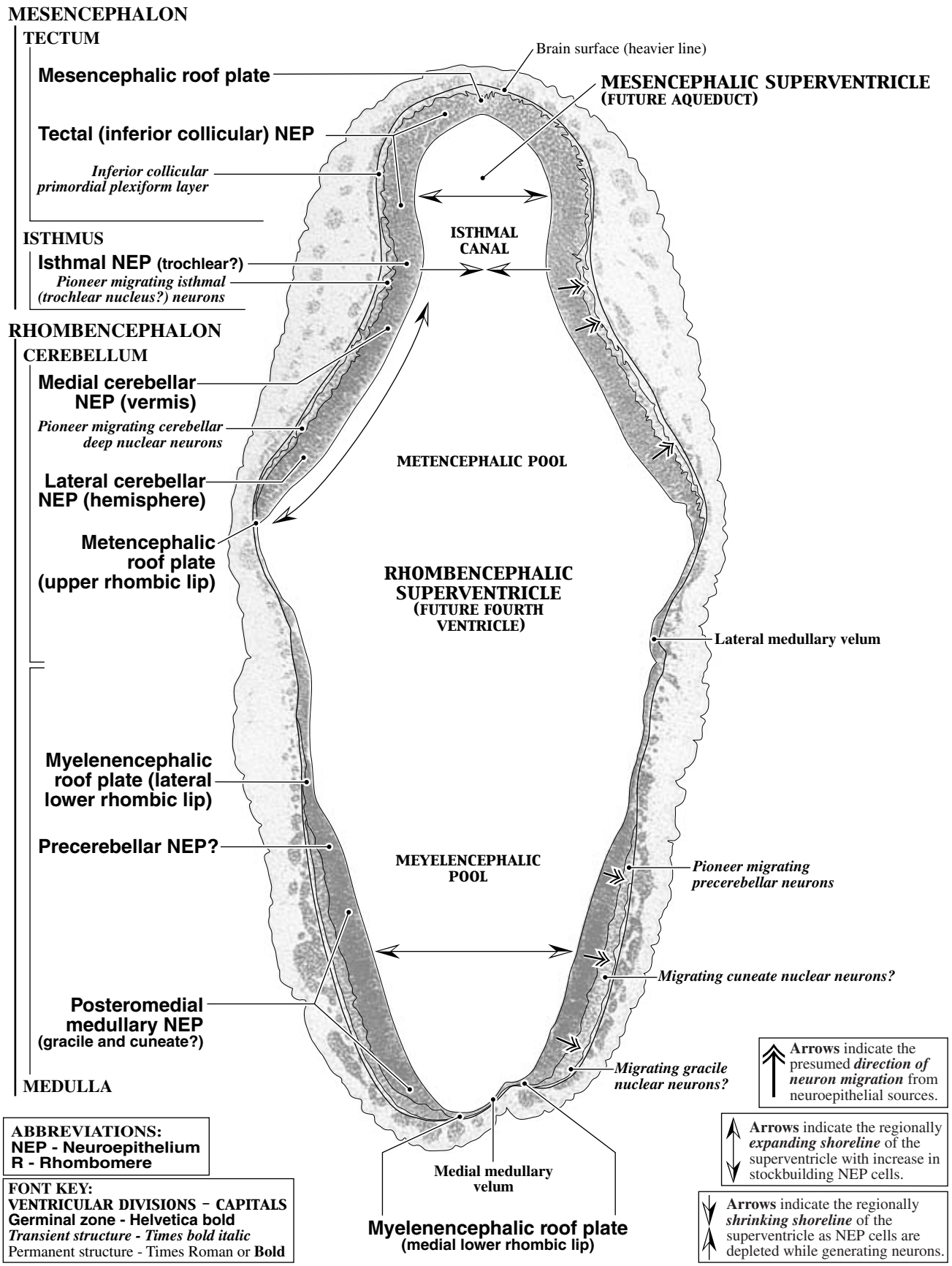
Peripheral neural and non-neural structures labeled



Level 11: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 124B



PART X: GW5 SAGITTAL

Carnegie Collection specimen #8966 (designated here as C8966) with a 7.1 mm crown-rump length (CR) is estimated to be at gestational week (GW) 5. C8966 was preserved in Zenker's fixative, embedded in a celloidin/ paraffin mix, and was cut in 10-μm sagittal sections that were stained with hematoxylin and eosin. Various orientations of the computer-aided 3-D reconstruction of C8314's brain are used to show the gross external features of a GW5 brain (**Figure 9**). Like most sagittally cut specimens, C8966's sections are not parallel to the midline; **Figure 9** shows the approximate rotations in front (**B**) and back views (**C**). We photographed 29 sections at low magnification from the left to right sides of the brain. Seven of the sections, mainly from the left side of the brain, are illustrated in **Plates 125AB to 131AB**. Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify the approximate midline, non-neural structures, peripheral neural structures, and brain ventricular divisions; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 132AB to 133AB** show high-magnification views of the rhombencephalon.

The anterior part of the prosencephalic superventricle is tentatively identified as the future telencephalic superventricle, an enlargement of the diencephalic superventricle. The prosencephalic neuroepithelium is stockbuilding its various populations of neuronal and glial stem cells. The presumptive basal ganglionic and basal telencephalic neuroepithelia do not form mounds in the floor of the telencephalon. There is a definite lamina terminalis in the ventral prosencephalon that marks the site of closure of the anterior neuropore. The olfactory epithelium, in an anterolateral placode, is already producing nerve fibers.

The mesencephalon, arching between the mesencephalic and diencephalic flexures, is characterized by stockbuilding neuroepithelia surrounding an expanding mesencephalic superventricle. Cells have not yet migrated from the tectal and pretectal neuroepithelia. A few cells are migrating outside the tegmental and isthmal neuroepithelia. There is a very thin subpial fiber band.

The rhombencephalon is the largest brain structure. Rhombomeres 2 through 7 form well-defined swellings in the lateral neuroepithelium. The rotation of C8966's sections does not clearly show all the entry points of the cranial sensory nerves. However, rhombomere 2 is clearly associated with incoming axons from the trigeminal ganglion (V afferents), and rhombomeres 4 and 5 with the vestibulocochlear ganglion (VIII afferents). The association of rhombomere 3 with a tentatively identifiable facial ganglion (VII afferents) is less clear. Each rhombomere has a thin layer of pioneer migrating neurons, most are receptors for incoming sensory axons. However, there are many fewer fibers entering the brain from these ganglia than at GW5.5, and no fibrous swellings are in the very thin subpial fiber band. Sections near the midline show that rhombomeres do not extend into the medial pontine and medullary neuroepithelia. There is a thicker layer of migrating cells outside the medullary neuroepithelium, and the subpial fiber band is thicker as the brain blends with the spinal cord. The cerebellum stands out as the most immature and smallest rhombencephalic structure. In spite of that, a cerebellar notch can be identified laterally where the cerebellar and pontine neuroepithelia join. The most lateral sections cut the cerebellar neuroepithelium tangentially, allowing a few indistinct layers in the cerebellar transitional field to be identified.

EXTERNAL FEATURES OF THE GW5 BRAIN

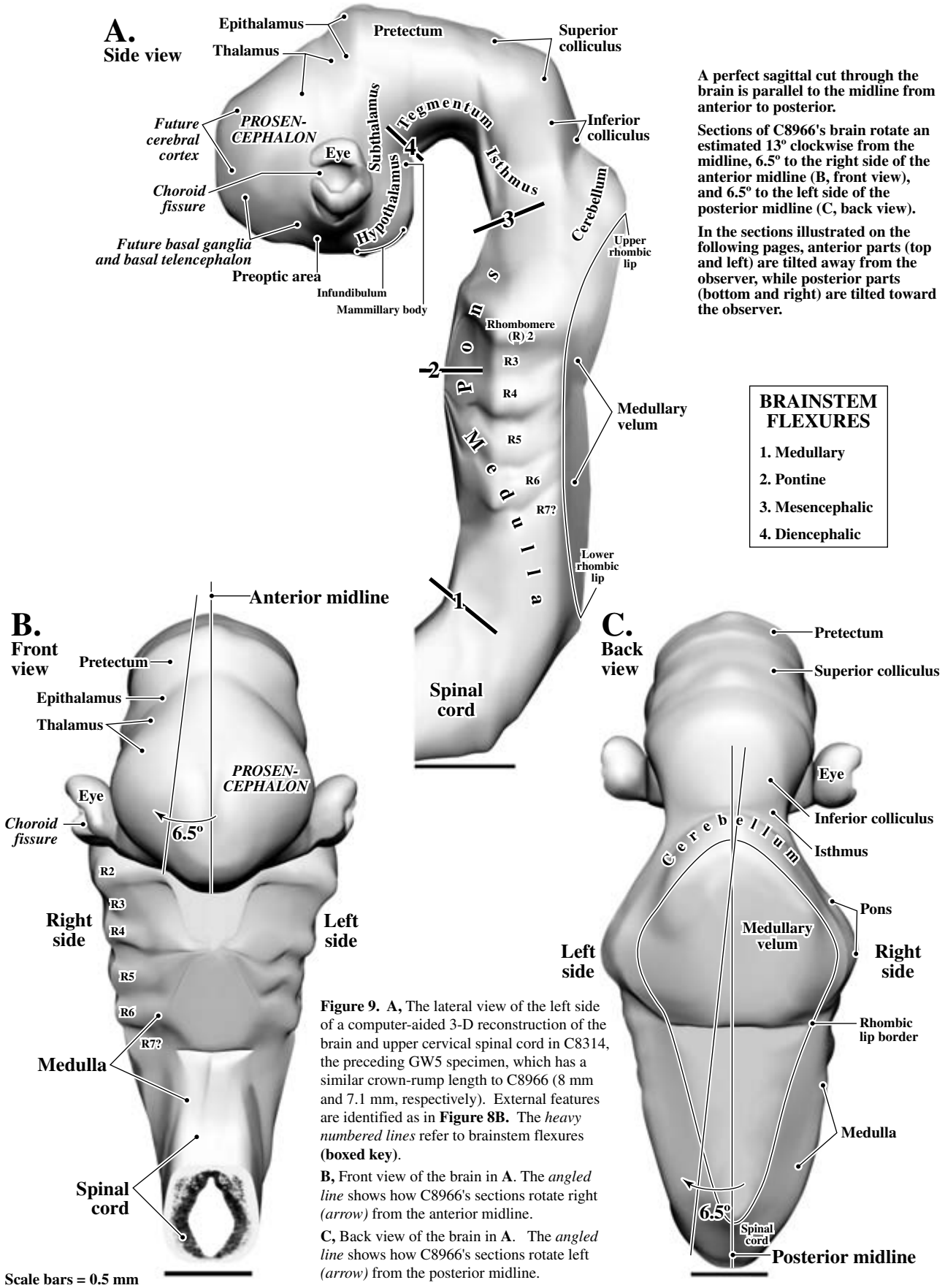


Figure 9. A, The lateral view of the left side of a computer-aided 3-D reconstruction of the brain and upper cervical spinal cord in C8314, the preceding GW5 specimen, which has a similar crown-rump length to C8966 (8 mm and 7.1 mm, respectively). External features are identified as in **Figure 8B.** The *heavy numbered lines* refer to brainstem flexures **(boxed key)**.

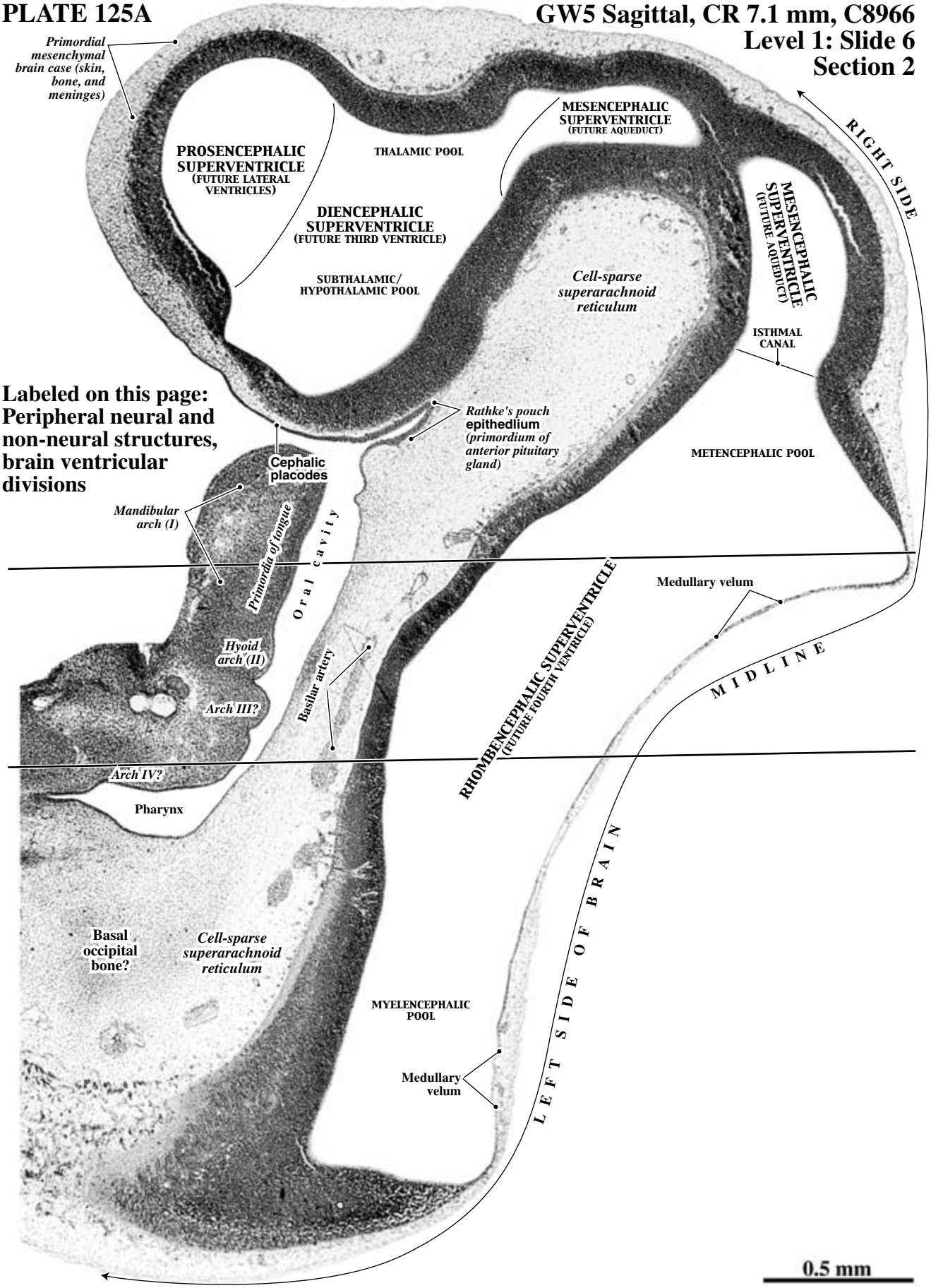
B, Front view of the brain in **A**. The *angled line* shows how C8966's sections rotate right *(arrow)* from the anterior midline.

C, Back view of the brain in **A**. The *angled line* shows how C8966's sections rotate left *(arrow)* from the posterior midline.

Scale bars = 0.5 mm

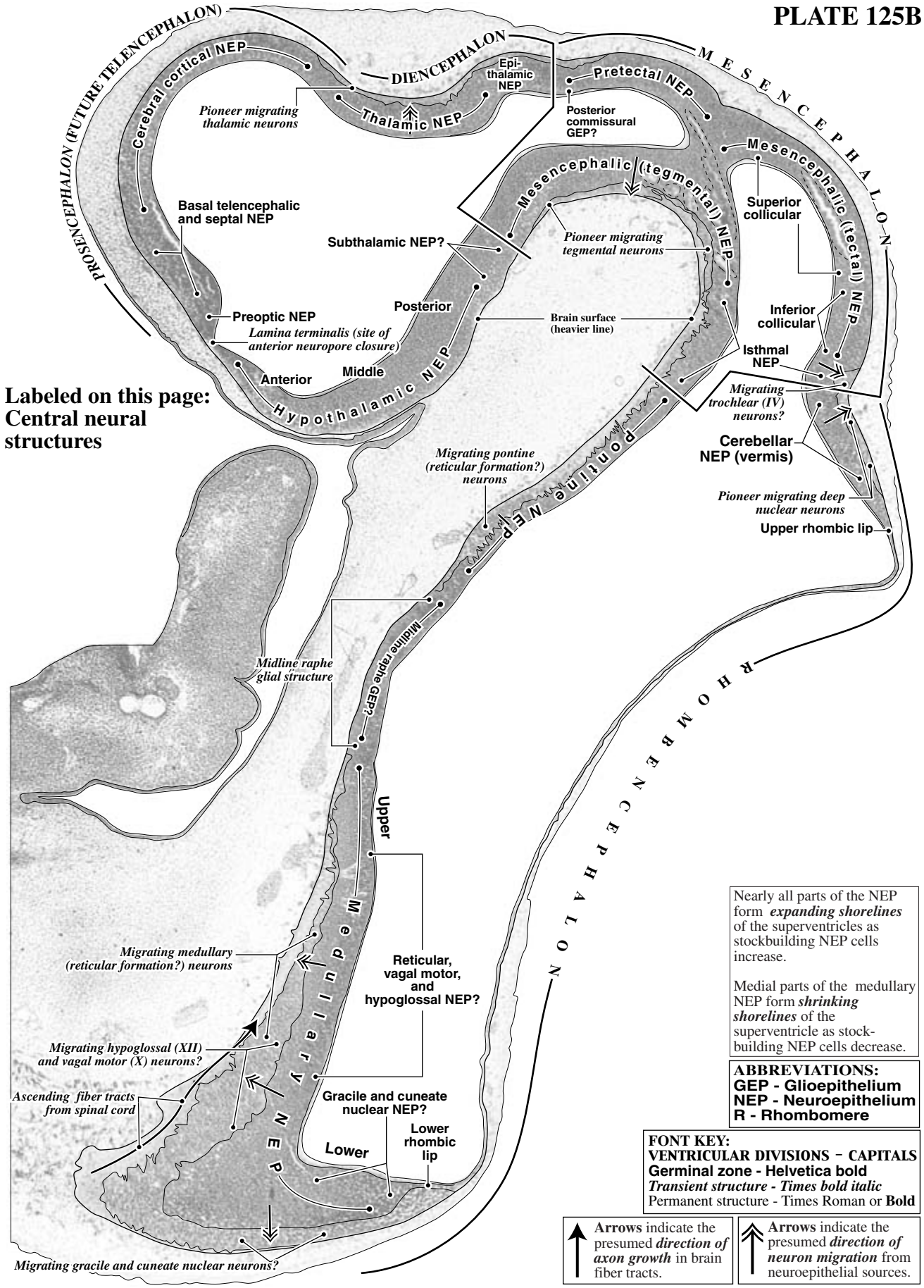
PLATE 125A

GW5 Sagittal, CR 7.1 mm, C8966
Level 1: Slide 6
Section 2



Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 125B



Labeled on this page: Central neural structures

Nearly all parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

Medial parts of the medullary NEP form ***shrinking shorelines*** of the superventricle as stock-building NEP cells decrease.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

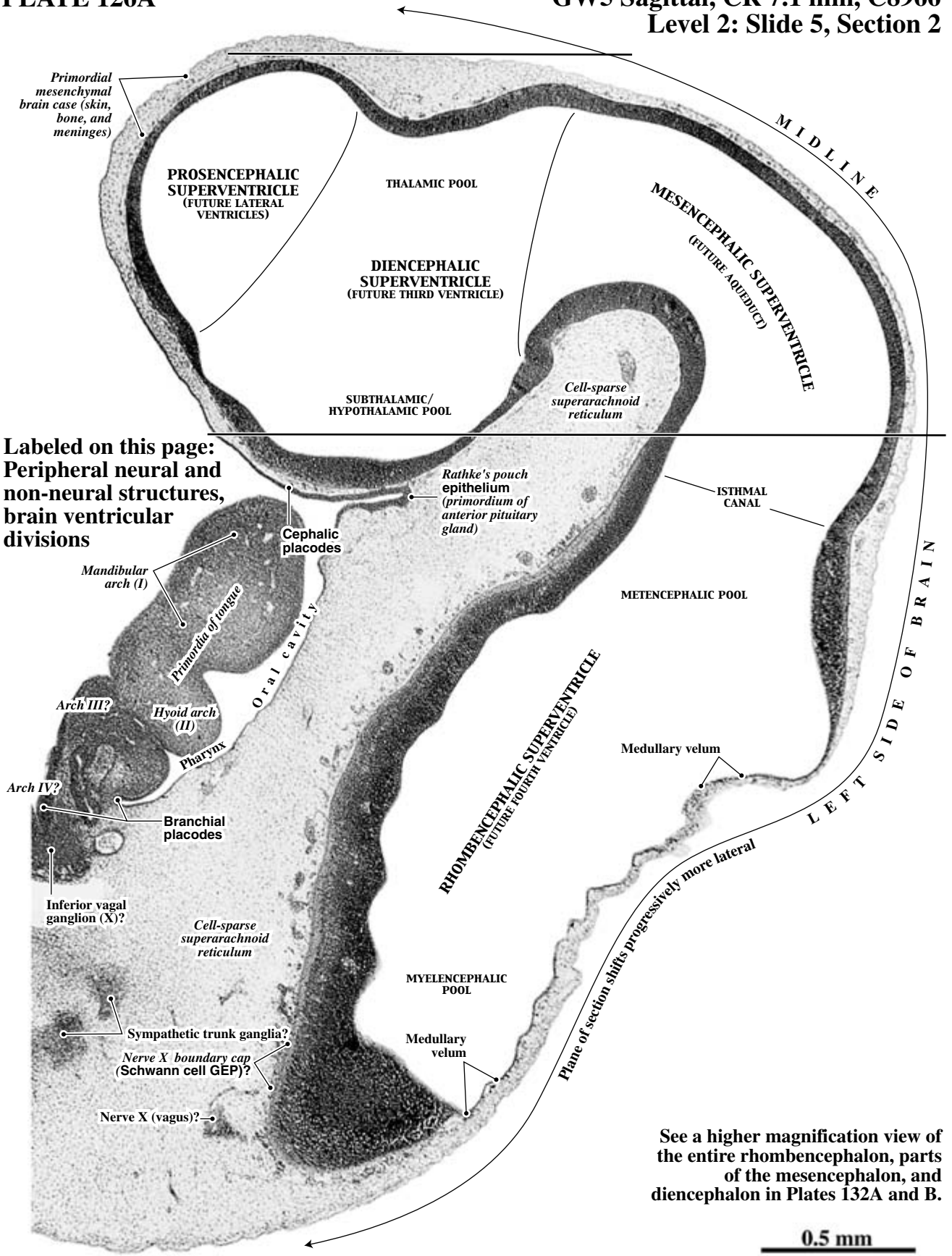
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 126A

GW5 Sagittal, CR 7.1 mm, C8966
Level 2: Slide 5, Section 2



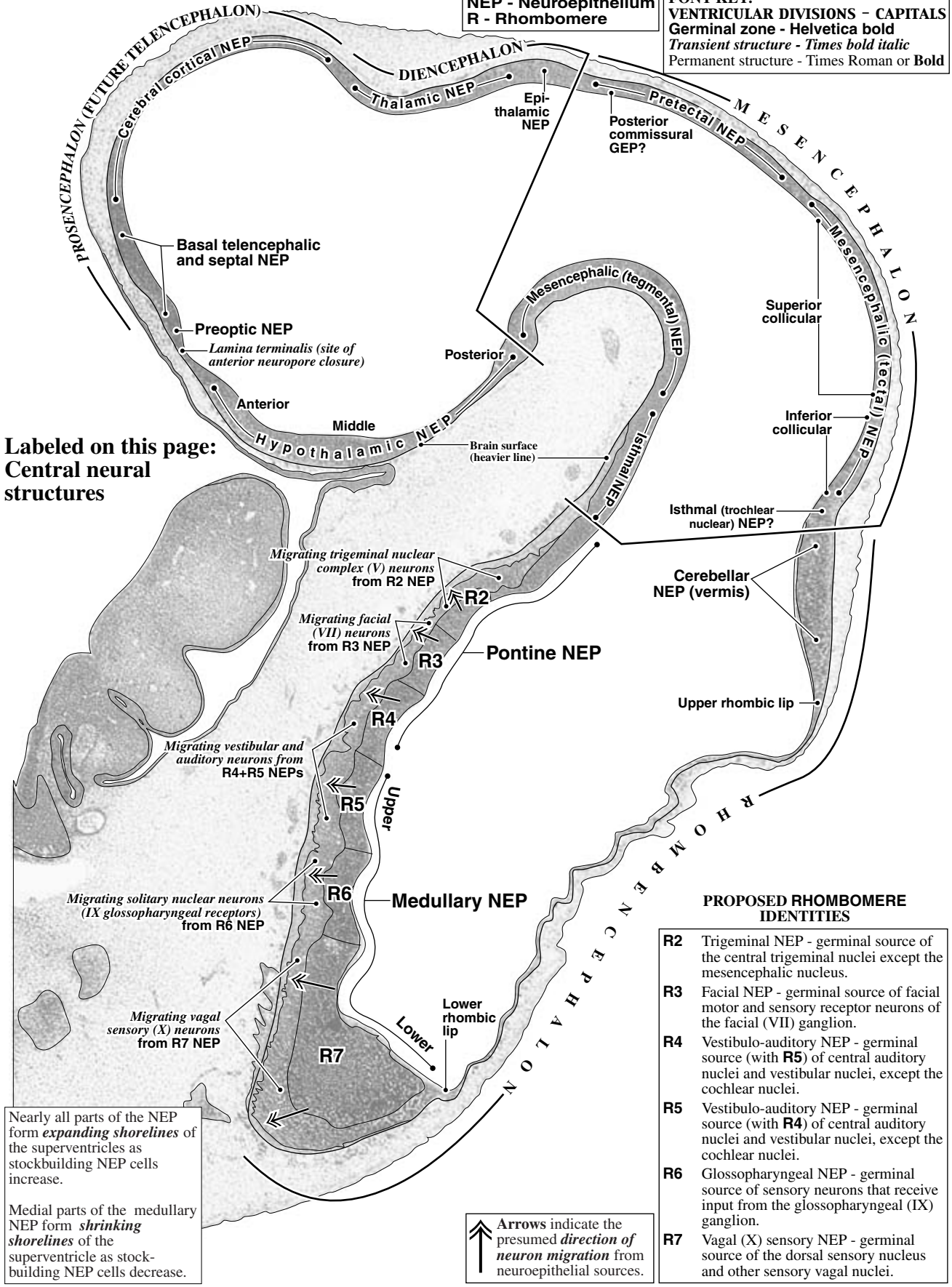
Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

See a higher magnification view of the entire rhombencephalon, parts of the mesencephalon, and diencephalon in Plates 132A and B.

PLATE 126B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**



Labeled on this page:
Central neural structures

Nearly all parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

Medial parts of the medullary NEP form ***shrinking shorelines*** of the superventricle as stock-building NEP cells decrease.

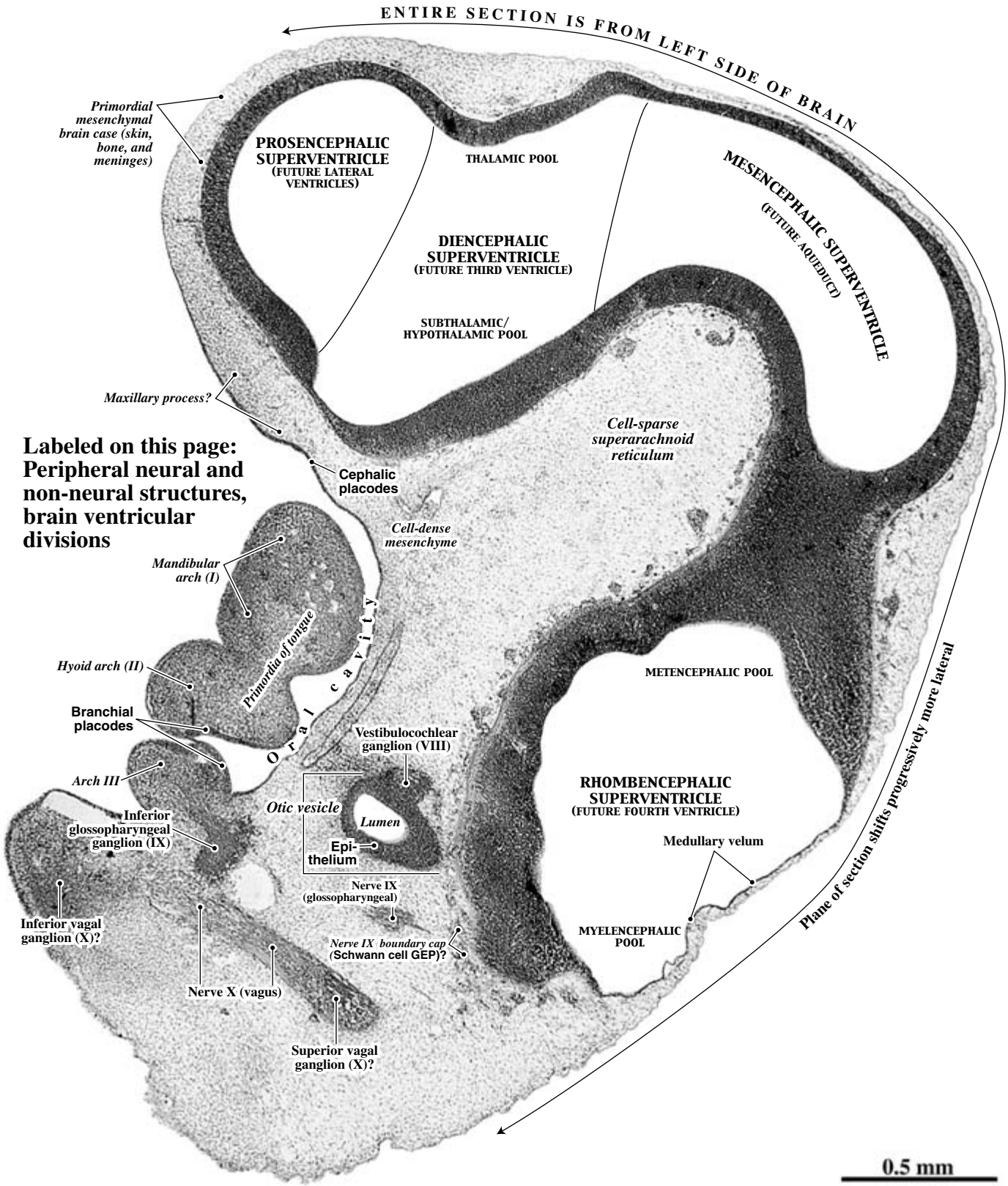
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

PLATE 127A

GW5 Sagittal, CR 7.1 mm, C8966
Level 3: Slide 4, Section 7



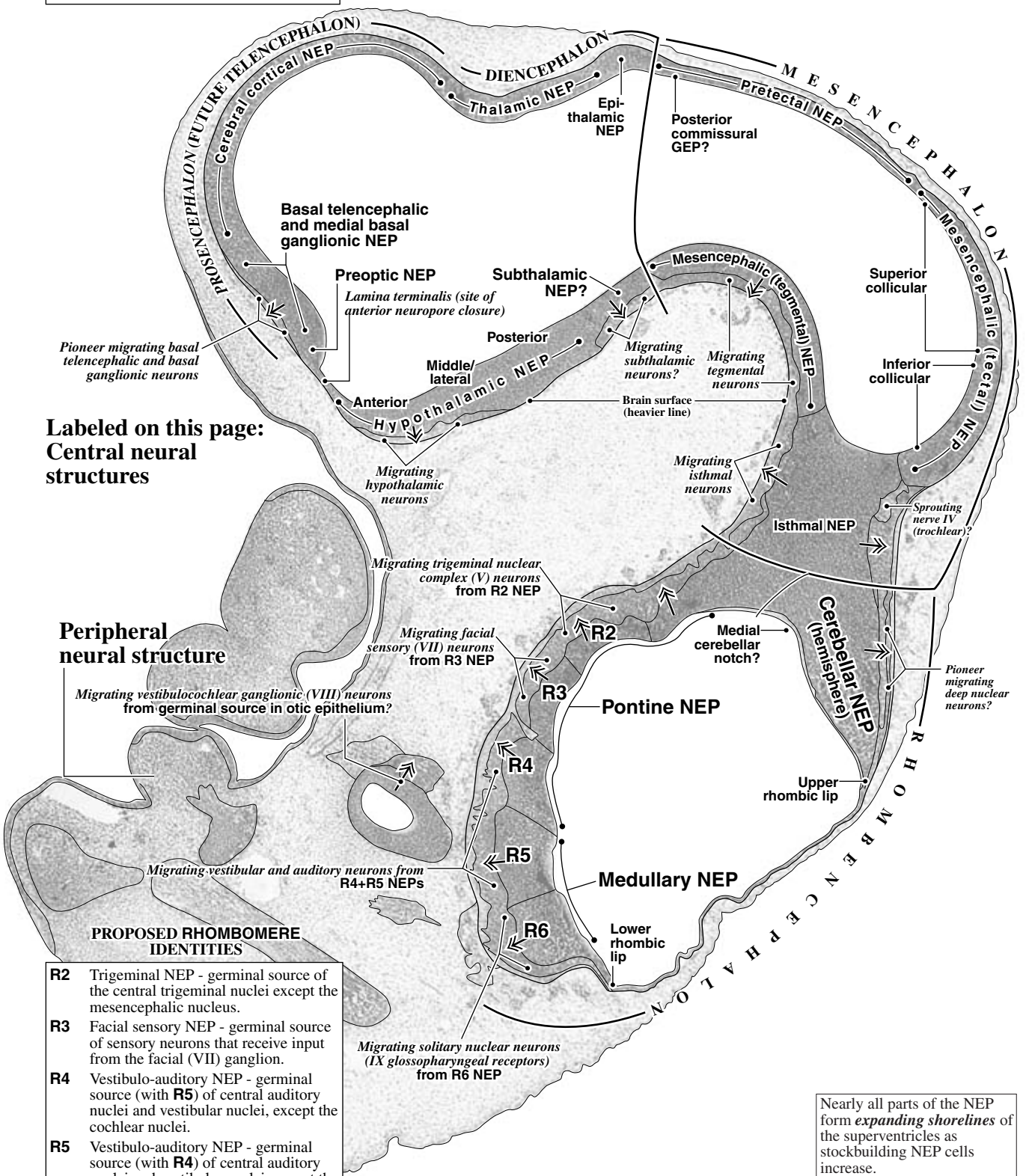
Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 127B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.



Labeled on this page: Central neural structures

Peripheral neural structure

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

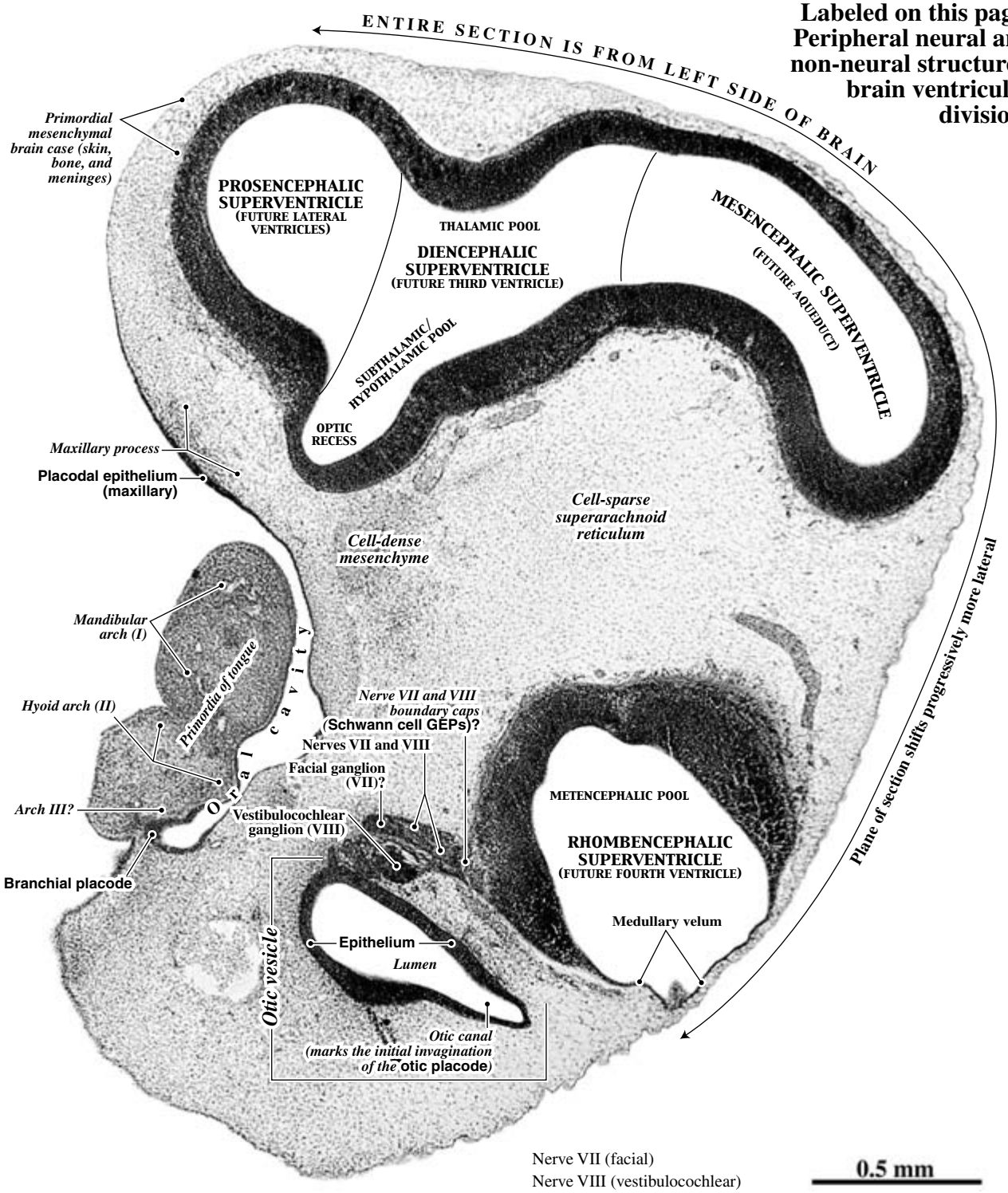
Nearly all parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

Medial parts of the medullary NEP form ***shrinking shorelines*** of the superventricle as stock-building NEP cells decrease.

PLATE 128A

GW5 Sagittal, CR 7.1 mm, C8966
Level 4: Slide 3, Section 24

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



See a higher magnification view of the rhombencephalon from this section in Plates 133A and B.

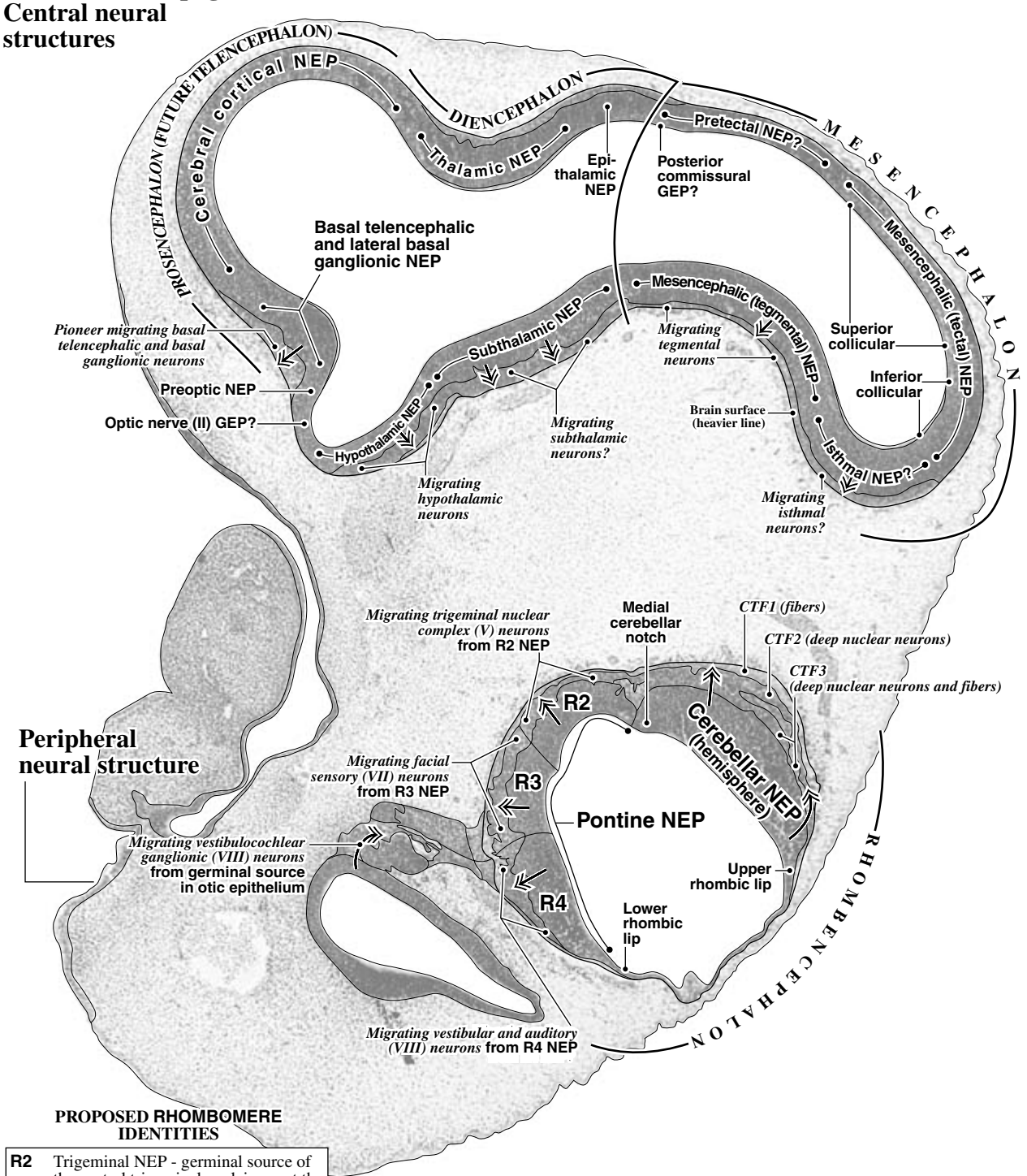
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PLATE 128B

Labeled on this page:
Central neural structures



PROPOSED RHOMBOMERE IDENTITIES

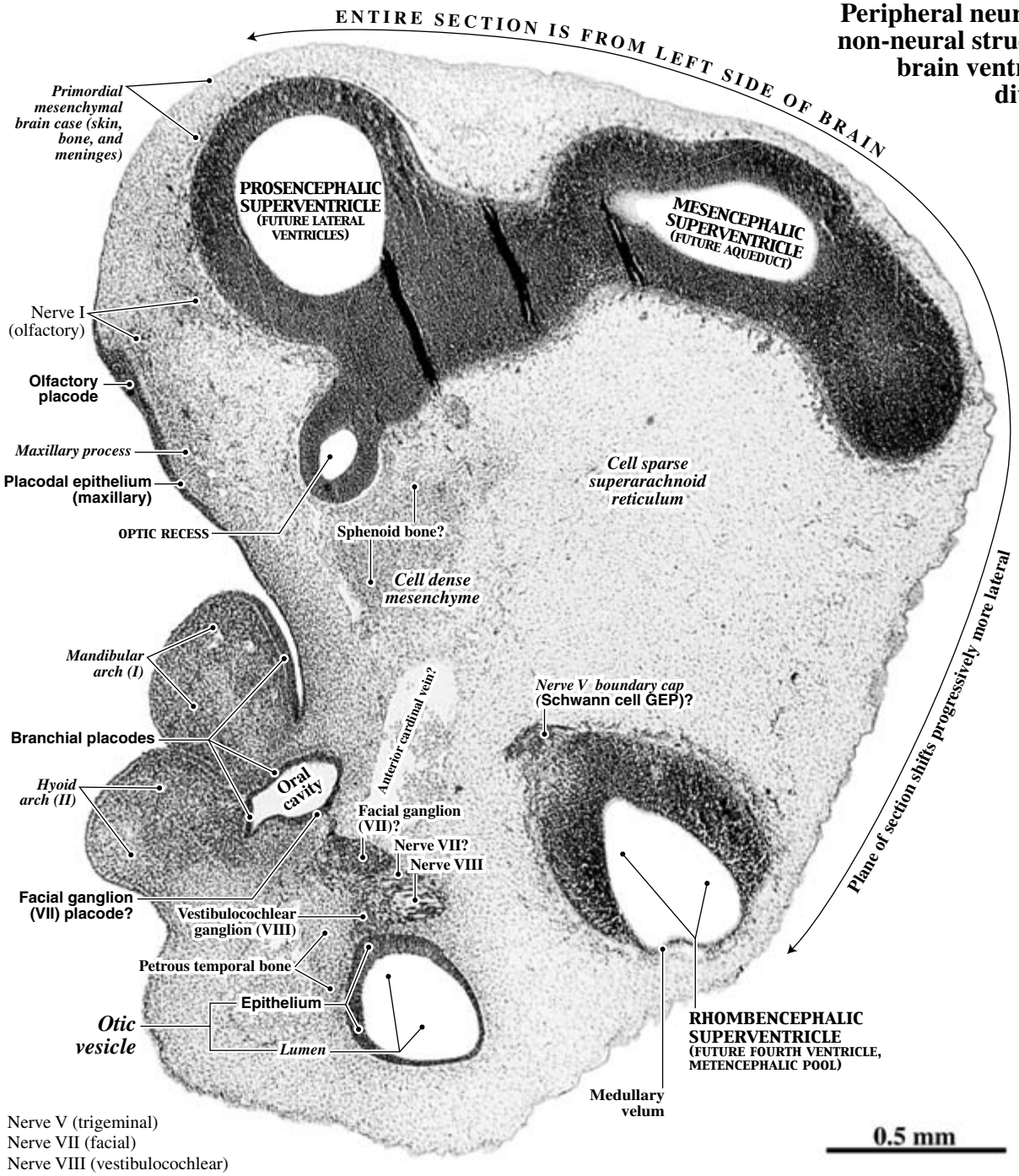
R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

All parts of the NEP in this section form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

PLATE 129A

GW5 Sagittal, CR 7.1 mm, C8966
Level 5: Slide 3, Section 12

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)

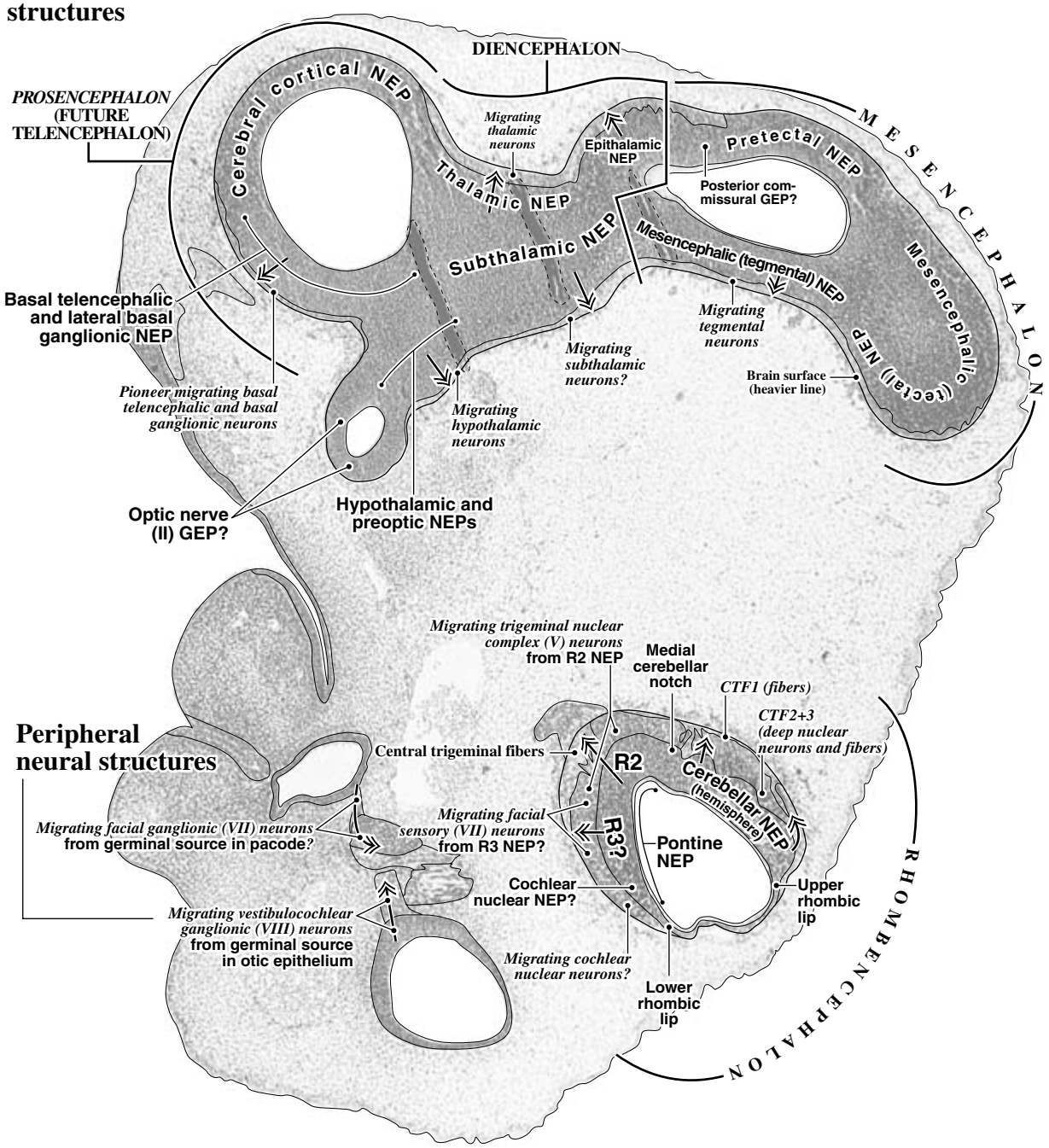
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PLATE 129B

Labeled on this page:
Central neural structures



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.

All parts of the NEP in this section form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

PLATE 130A

GW5 Sagittal, CR 7.1 mm, C8966
Level 6: Slide 3, Section 5

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

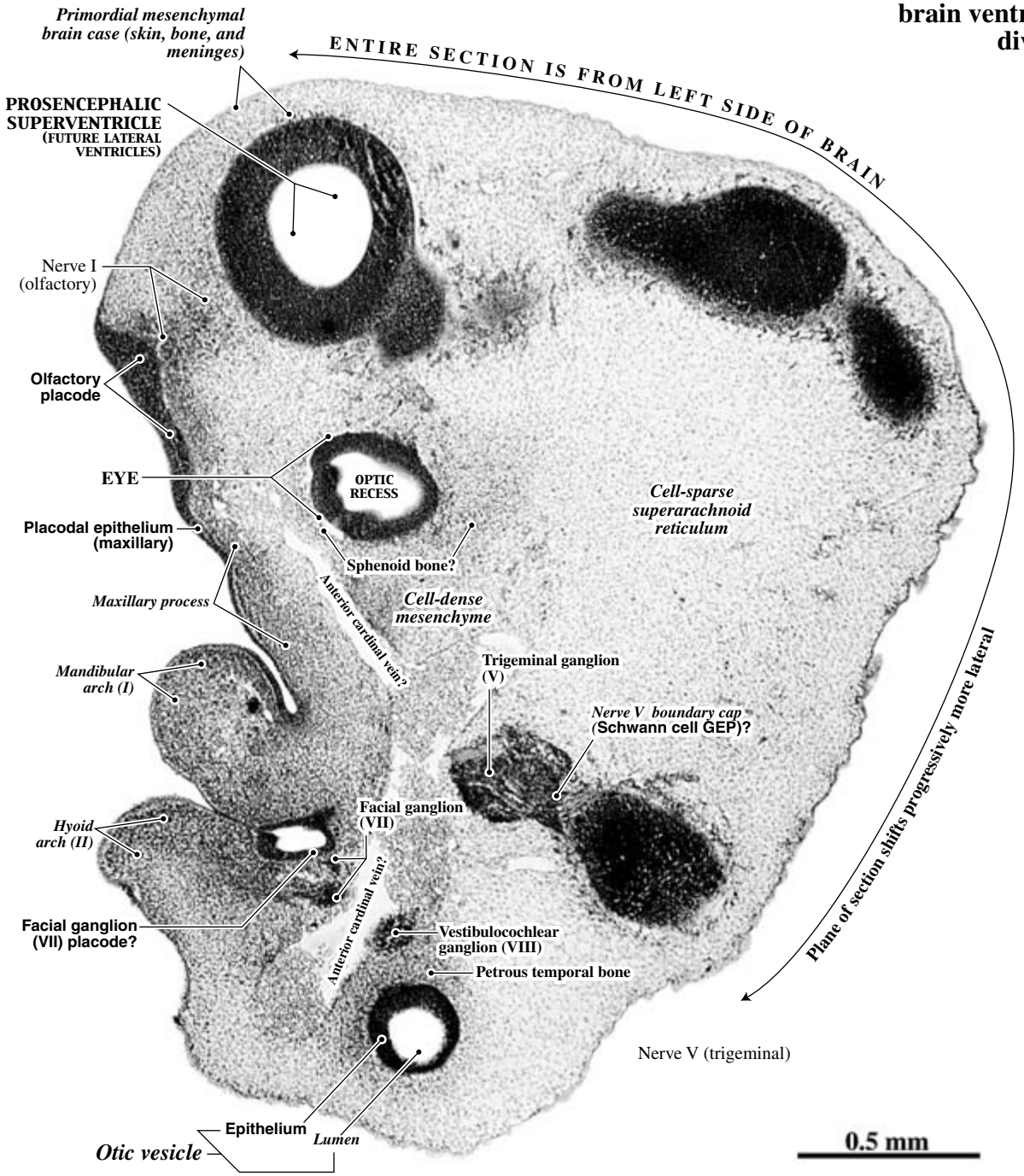
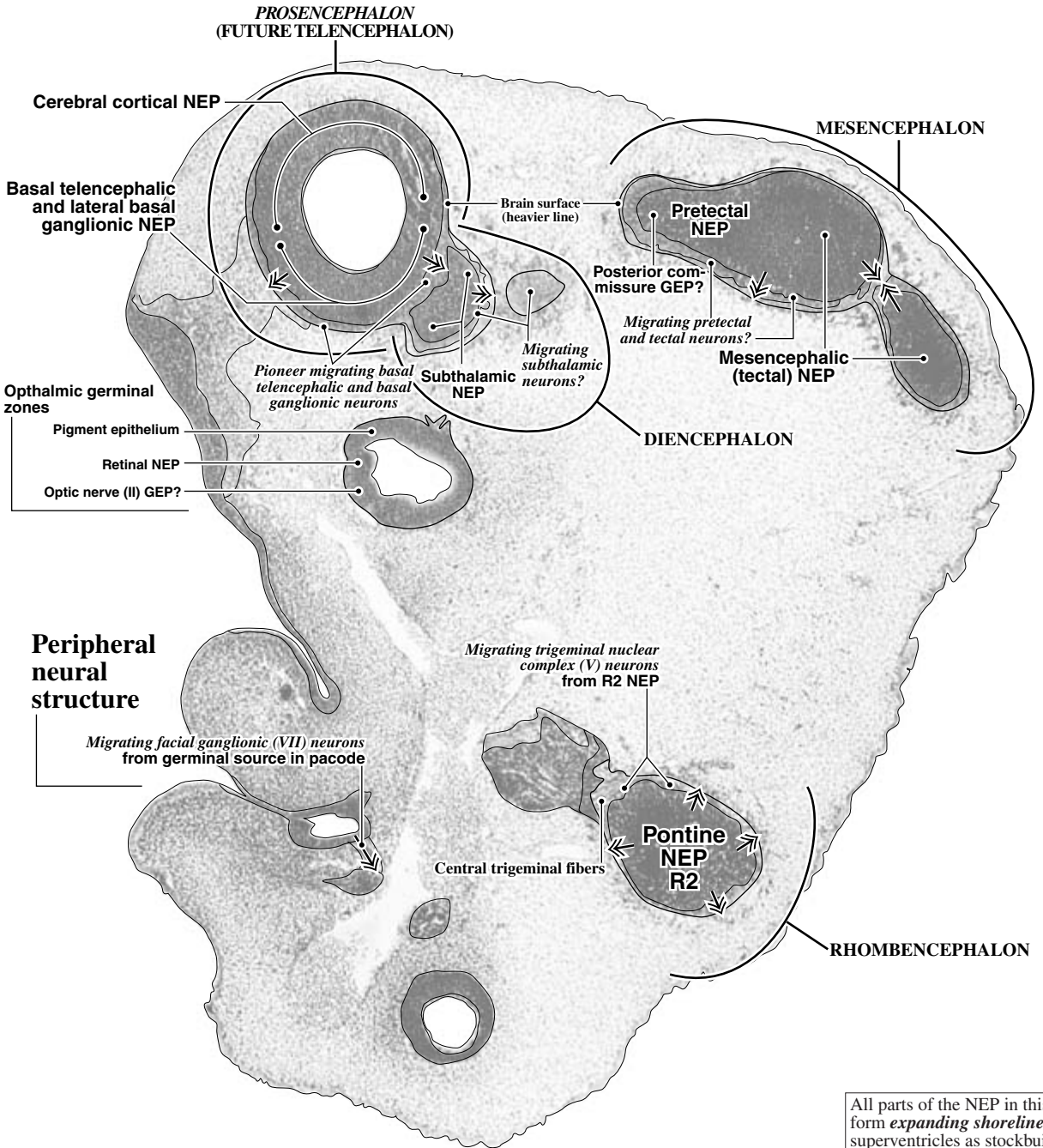


PLATE 130B

Labeled on this page:
Central neural structures



All parts of the NEP in this section form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

PROPOSED RHOMBOMERE IDENTITY

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 131A

GW5 Sagittal, CR 7.1 mm, C8966
Level 7: Slide 2, Section 22

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

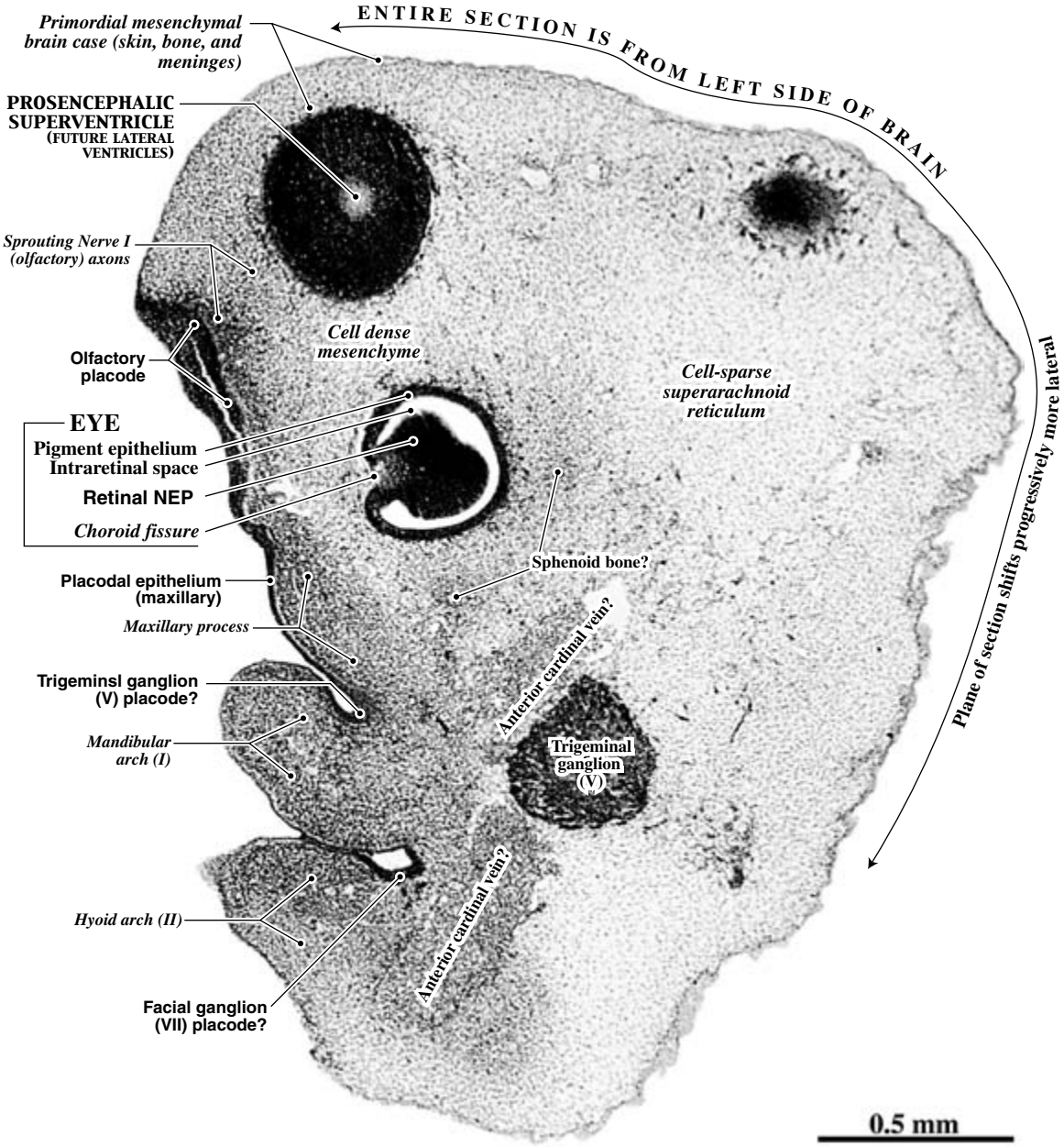
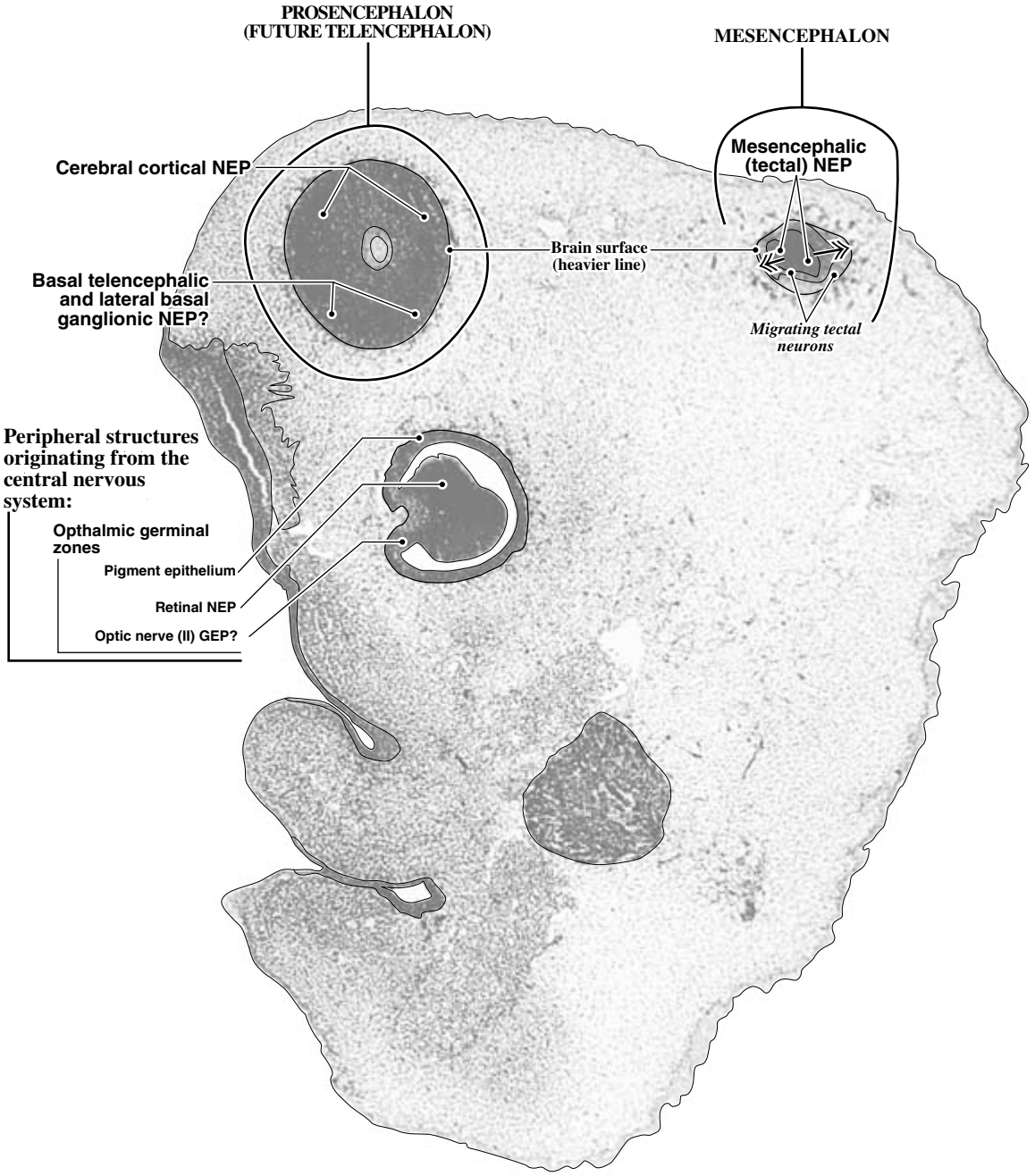


PLATE 131B

Labeled on this page:
Central neural structures



All parts of the NEP in this section form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 132A
GW5 Sagittal, CR 7.1 mm, C8966
Level 2: Slide 5, Section 2

See Level 2 in Plates 126A and B.

HYPOTHALAMUS, MESENCEPHALON, AND RHOMBENCEPHALON

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

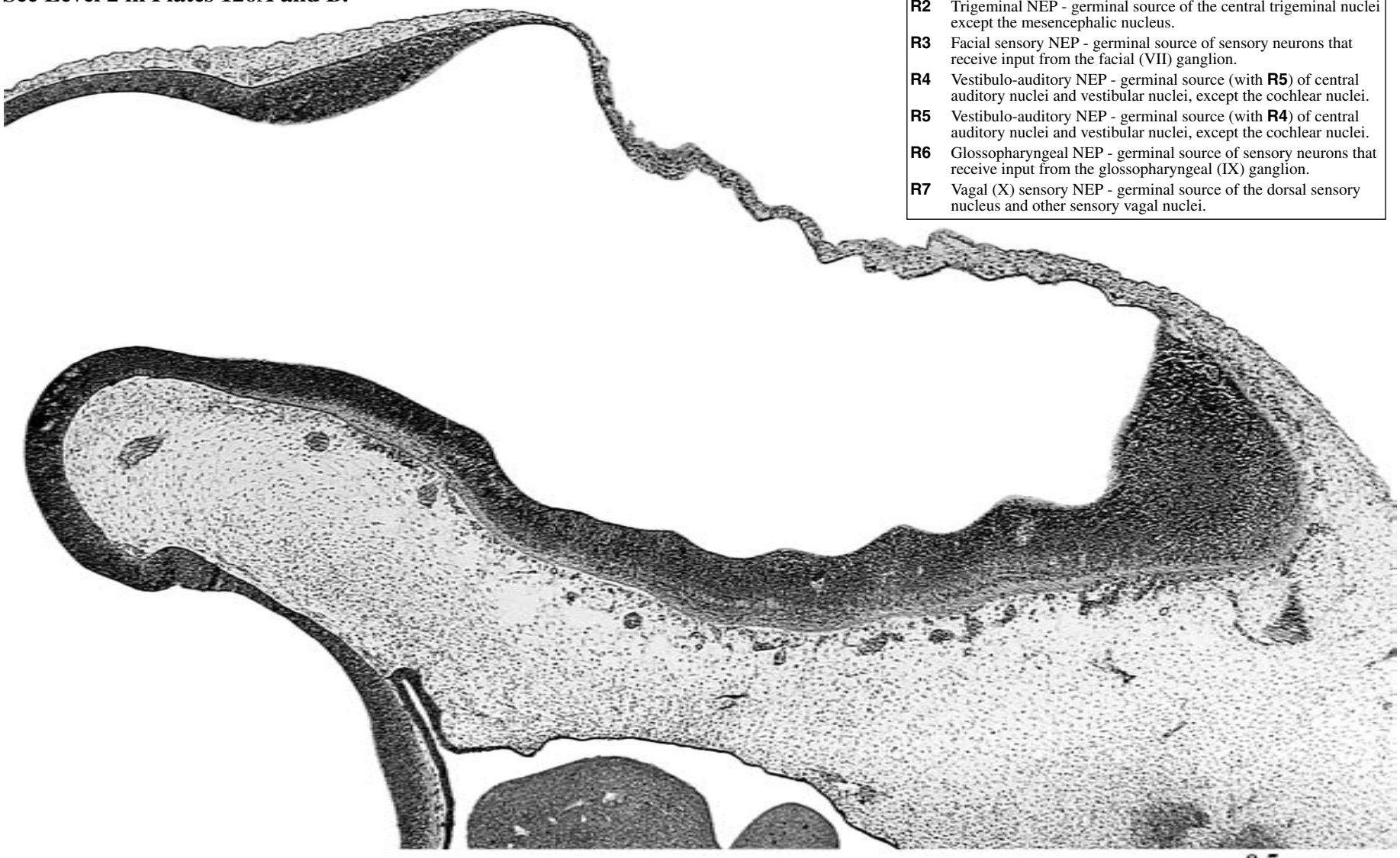


PLATE 132B

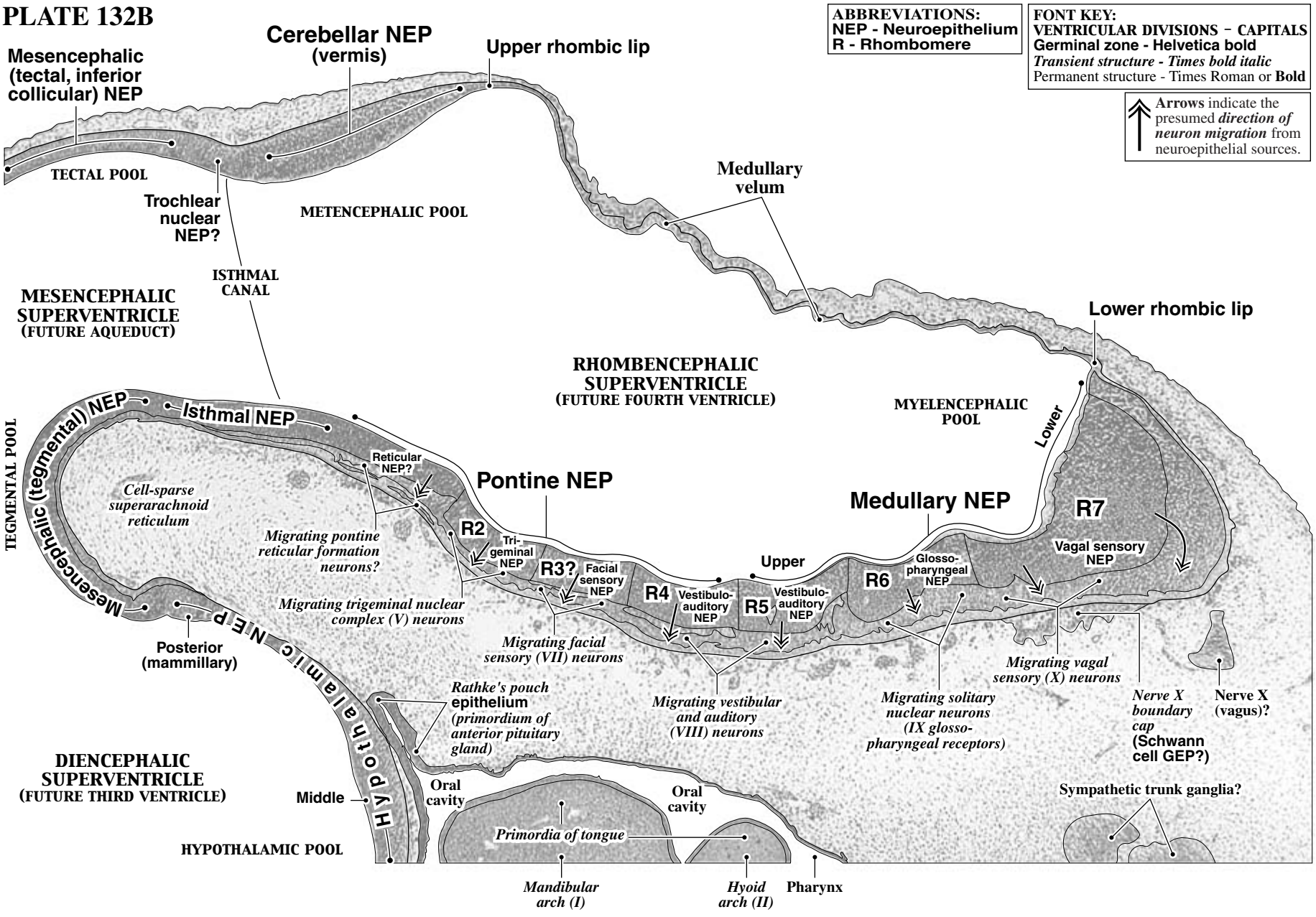
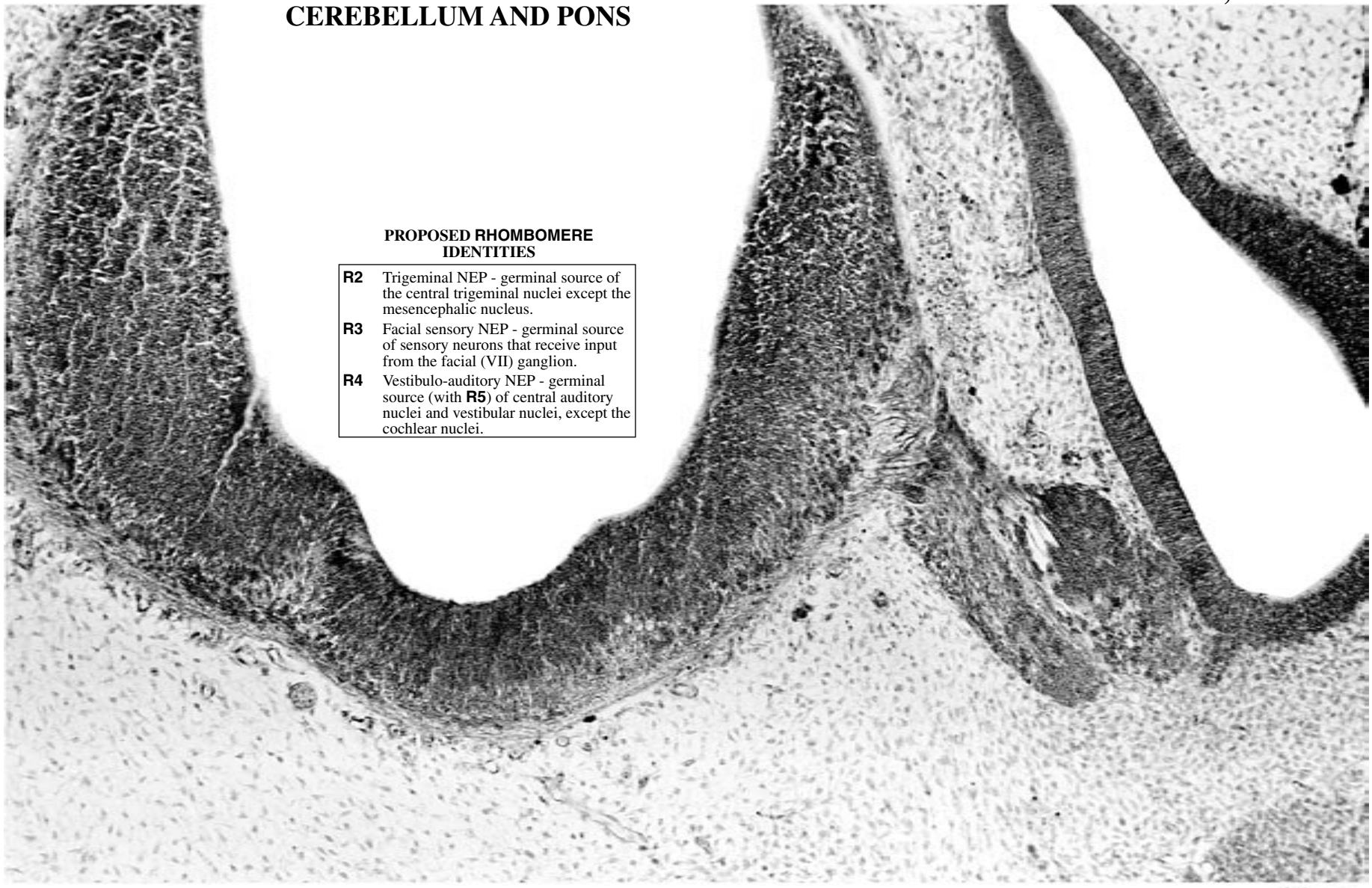

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Cerebellar NEP
(vermis)
Upper rhombic lip
Mesencephalic
(tectal, inferior
collicular) NEP
TECTAL POOL
Trochlear
nuclear
NEP?
METENCEPHALIC POOL
Medullary
velum
ISTHMAL
CANAL
MESENCEPHALIC
SUPERVENTRICLE
(FUTURE AQUEDUCT)
Lower rhombic lip
RHOMBENCEPHALIC
SUPERVENTRICLE
(FUTURE FOURTH VENTRICLE)
MYELENCEPHALIC
POOL
Lower
TEGMENTAL POOL
Mesencephalic (tegmental) NEP
Isthmal NEP
Reticular
NEP?
Pontine NEP
Medullary NEP
R7
Cell-sparse
superarachnoid
reticulum
Migrating pontine
reticular formation
neurons?
R2
Tri-
geminal
NEP
R3?
Facial
sensory
NEP
Upper
R4
Vestibulo-
auditory
NEP
R5
Vestibulo-
auditory
NEP
R6
Glosso-
pharyngeal
NEP
Vagal sensory
NEP
Migrating trigeminal nuclear
complex (V) neurons
Migrating facial
sensory (VII) neurons
Migrating vestibular
and auditory
(VIII) neurons
Migrating solitary
nuclear neurons
(IX glosso-
pharyngeal receptors)
Migrating vagal
sensory (X) neurons
Nerve X
boundary
cap
(Schwann
cell GEP?)
Nerve X
(vagus)?
Posterior
(mammillary)
Hypothalamic NEP
Rathke's pouch
epithelium
(primordium of
anterior pituitary
gland)
DIENCEPHALIC
SUPERVENTRICLE
(FUTURE THIRD VENTRICLE)
Middle
Oral
cavity
Oral
cavity
Sympathetic trunk ganglia?
Primordia of tongue
HYPOTHALAMIC POOL
Mandibular
arch (I)
Hyoid
arch (II)
Pharynx

PLATE 133A

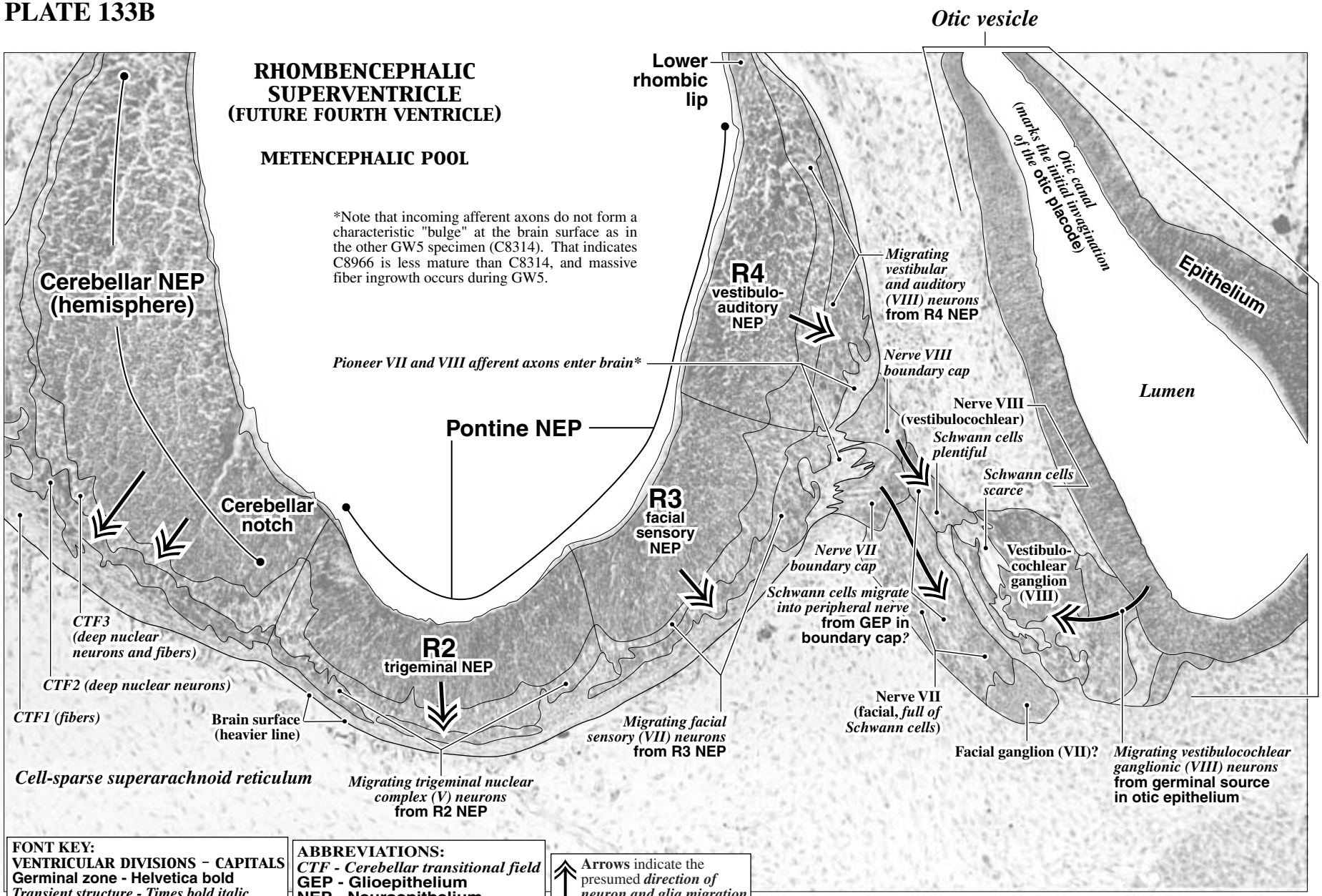
GW5 Sagittal, CR 7.1 mm, C8966
Level 4: Slide 3, Section 24

CEREBELLUM AND PONS



See Level 4 in Plates 128A and B.

PLATE 133B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
CTF - Cerebellar transitional field
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron and glia migration*** from germinal sources.

PART XI: GW4.5 CORONAL

This specimen is embryo #2300 in the Minot Collection, designated here as M2300. The crown-rump length (CR) is 6.3 mm estimated to be at gestational week (GW) 4.5. M2300's prosencephalic and anterior mesencephalic sections are cut (8 μm) in the coronal plane, but the plane shifts to predominantly horizontal in the posterior mesencephalon, pons, and medulla. We photographed 48 sections at low magnification from the frontal prominence to the posterior tips of the mesencephalon and medulla. Fourteen of these sections are illustrated in **Plates 134AB to 146AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of M2300's brain and optic vesicle (**Figure 10**), and to show each illustrated section *in situ* (*insets,* **Plates 134A to 146A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures.

The prosencephalon is considerably smaller than at GW5 (**Part IX**) with a stockbuilding neuroepithelium surrounding a small prosencephalic superventricle. Anterior sections are tentatively identified as the future telencephalon, while sections of the optic vesicle and posterior to it are more clearly identified as diencephalic. Cell migration is absent in both future telencephalic and diencephalic parts of the prosencephalon. The olfactory placode forms a thick epithelium in the anterolateral surface of the head that is much closer to the brain than at GW5. There is a thinner epithelium connecting the olfactory placode and the lens placode. The evaginated optic vesicle is just beginning to curve around the lens placode. However, a definite inner retinal neuroepithelium (thick with presumptive glial channels adjacent to the lens) and an outer pigment epithelium (thin) can be differentiated.

The mesencephalon contains a stockbuilding neuroepithelium in the pretectum and tectum; cell migration has not yet begun. The tegmental and isthmal neuroepithelia, thicker than at GW5, are stockbuilding their stem cell populations. Only a few pioneer neurons have migrated out, perhaps these are sequestered in the outer parts of the neuroepithelium itself rather than outside it. The subpial fiber band is very thin in the tegmentum, but thickens slightly in the isthmus.

The most prominent neuroepithelial structures in the rhombencephalon are the rhombomeric evaginations. In this specimen, several sections show how closely rhombomeres are associated with sensory cranial ganglia. The trigeminal ganglion (source of V sensory axons) is nearly attached to the brain surface at rhombomere 2. The vestibulocochlear ganglion (source of VIII axons) is attached to the rhombomere 4 brain surface. The otic vesicle touches the rhombomere 5 brain surface. The short nerve extending from the large vagal ganglion (source of X sensory axons) touches the rhombomere 7 brain surface. The subpial fiber band is thin throughout the rhombencephalon; even though sensory axons are touching the brain, they have yet to enter it. A very thin layer of migrating neurons lines the superficial border of some rhombomeres; for the most part, cell migration has not yet started. The small stockbuilding cerebellar neuroepithelium is only identifiable in the most posterior sections of the rhombencephalon. There are no migrating neurons outside the cerebellar neuroepithelium, only a thin cell-free fibrous layer.

M2300 Computer-aided 3-D Brain Reconstructions

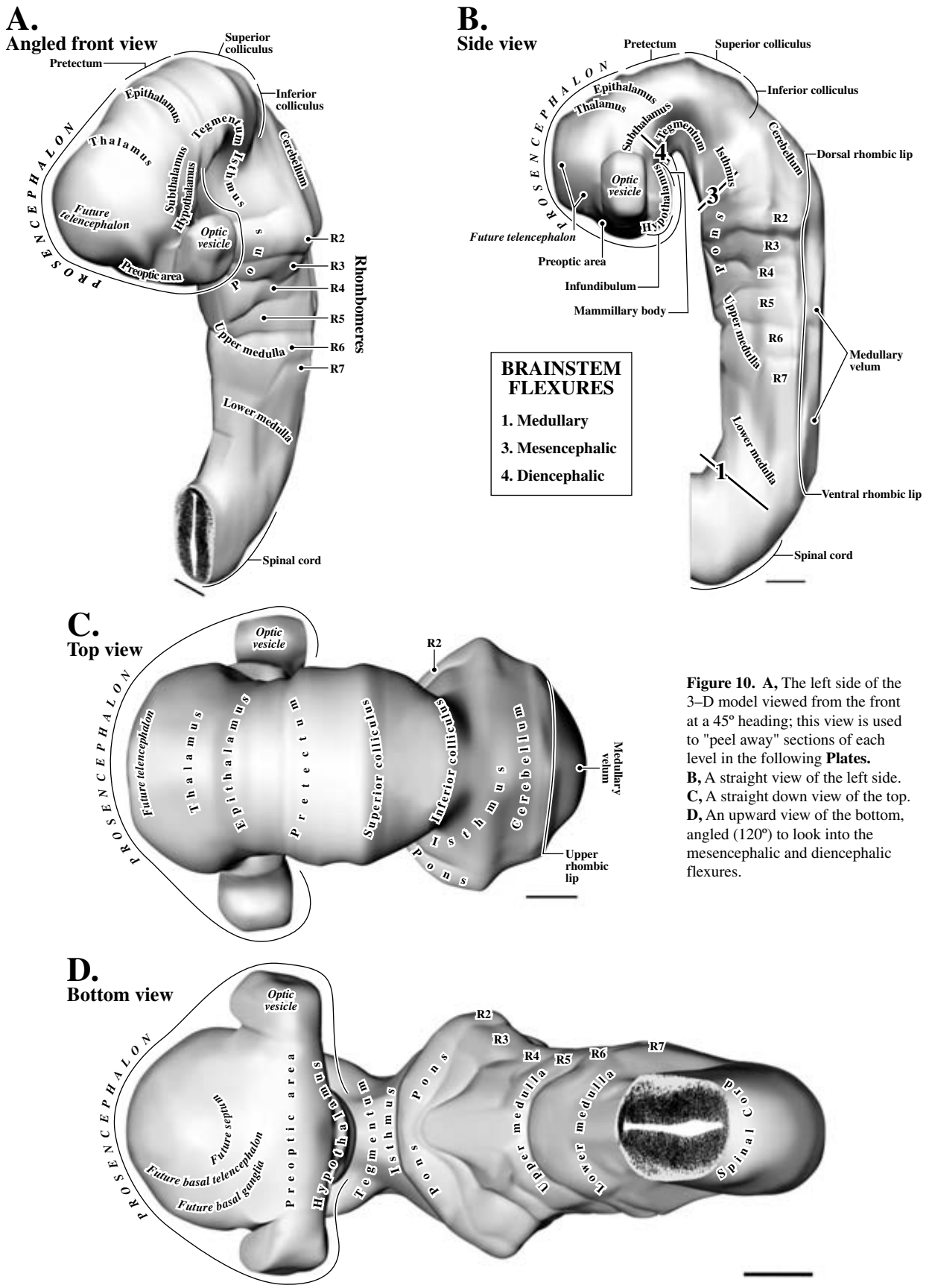


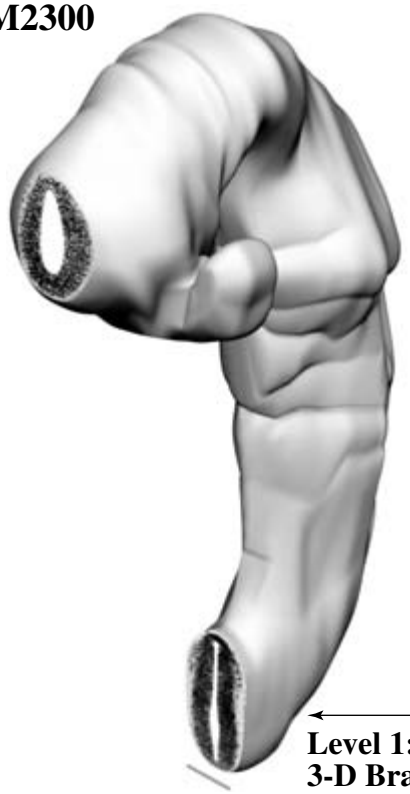
Figure 10. A, The left side of the 3–D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.** **B,** A straight view of the left side. **C,** A straight down view of the top. **D,** An upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures.

Scale bars = 0.5 mm

PLATE 134A

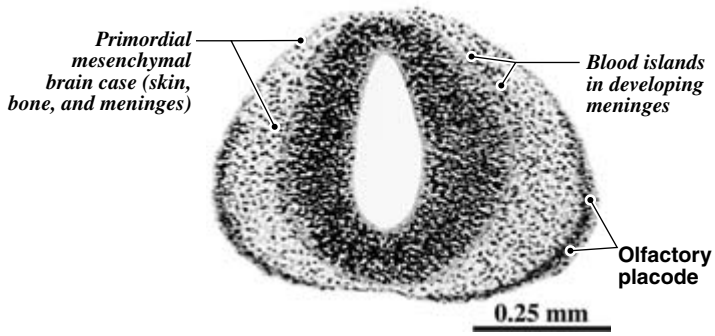
Peripheral neural and non-neural structures labeled

GW4.5 Coronal
CR 6.3 mm
M2300



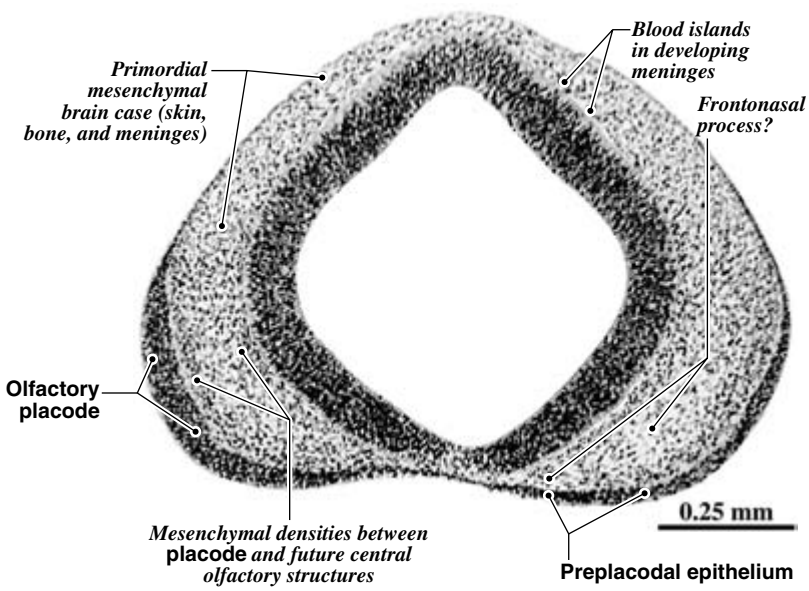
Level 1: Computer-aided 3-D Brain Reconstruction

Level 1: Section 5



Level 2: Computer-aided 3-D Brain Reconstruction

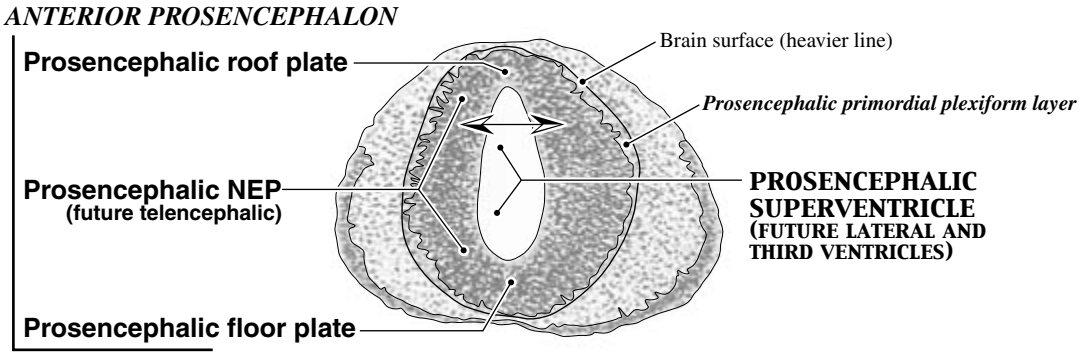
Level 2: Section 35



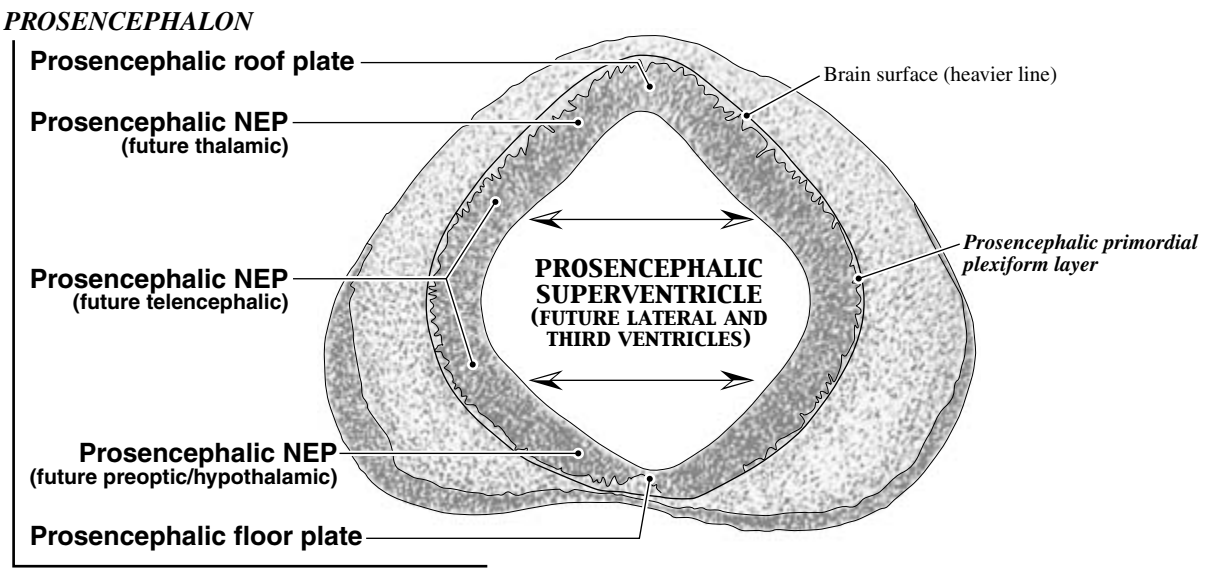
Central neural structures labeled

PLATE 134B

Level 1: Section 5



Level 2: Section 35



NEP - Neuroepithelium

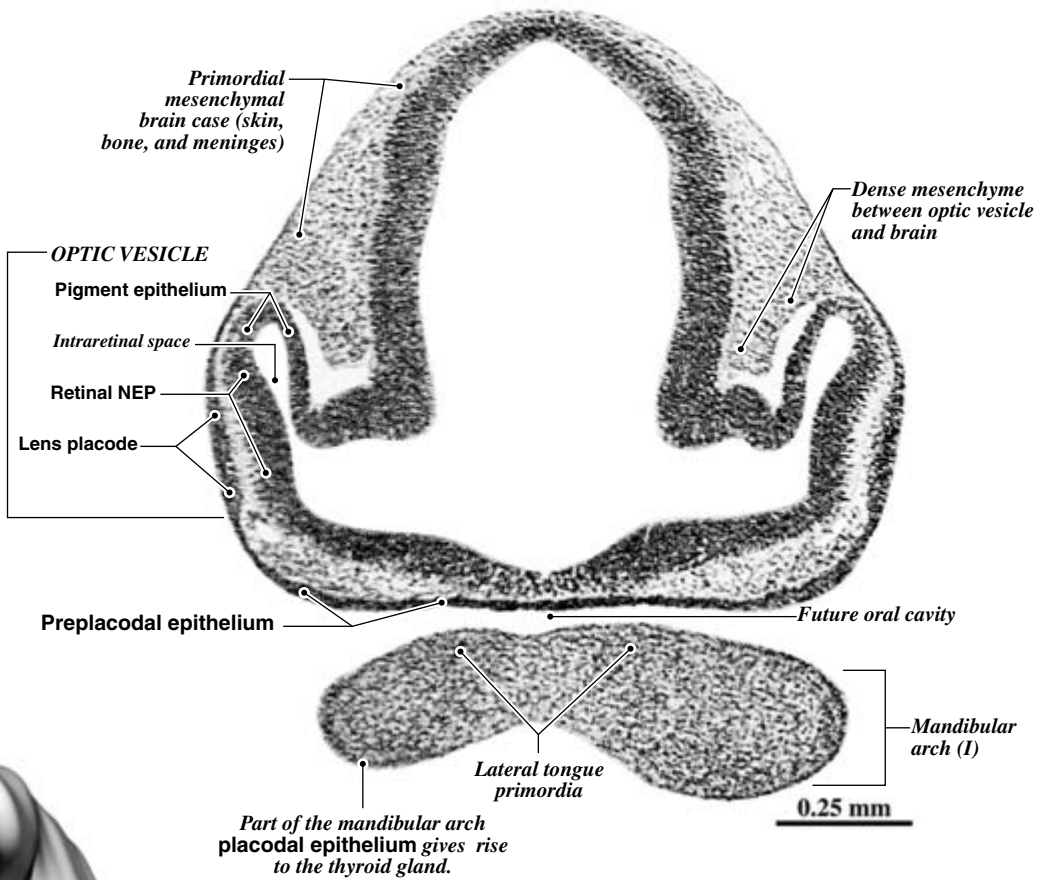
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

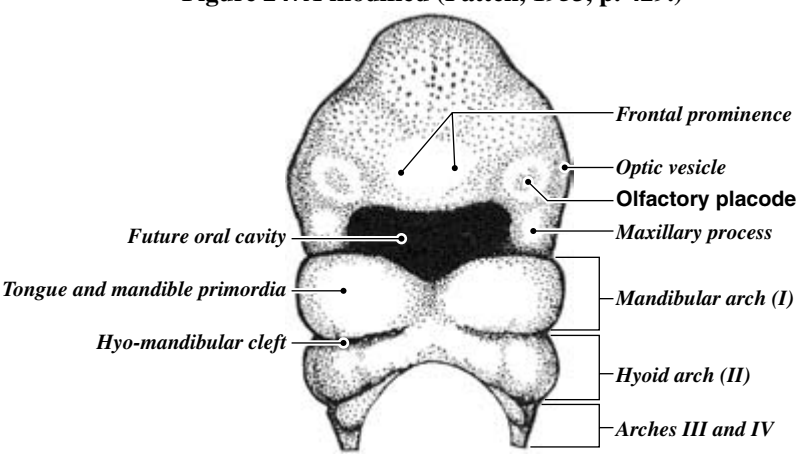
PLATE 135A

Peripheral neural and non-neural structures labeled

GW4.5 Coronal
CR 6.3 mm
M2300
Level 3: Section 65



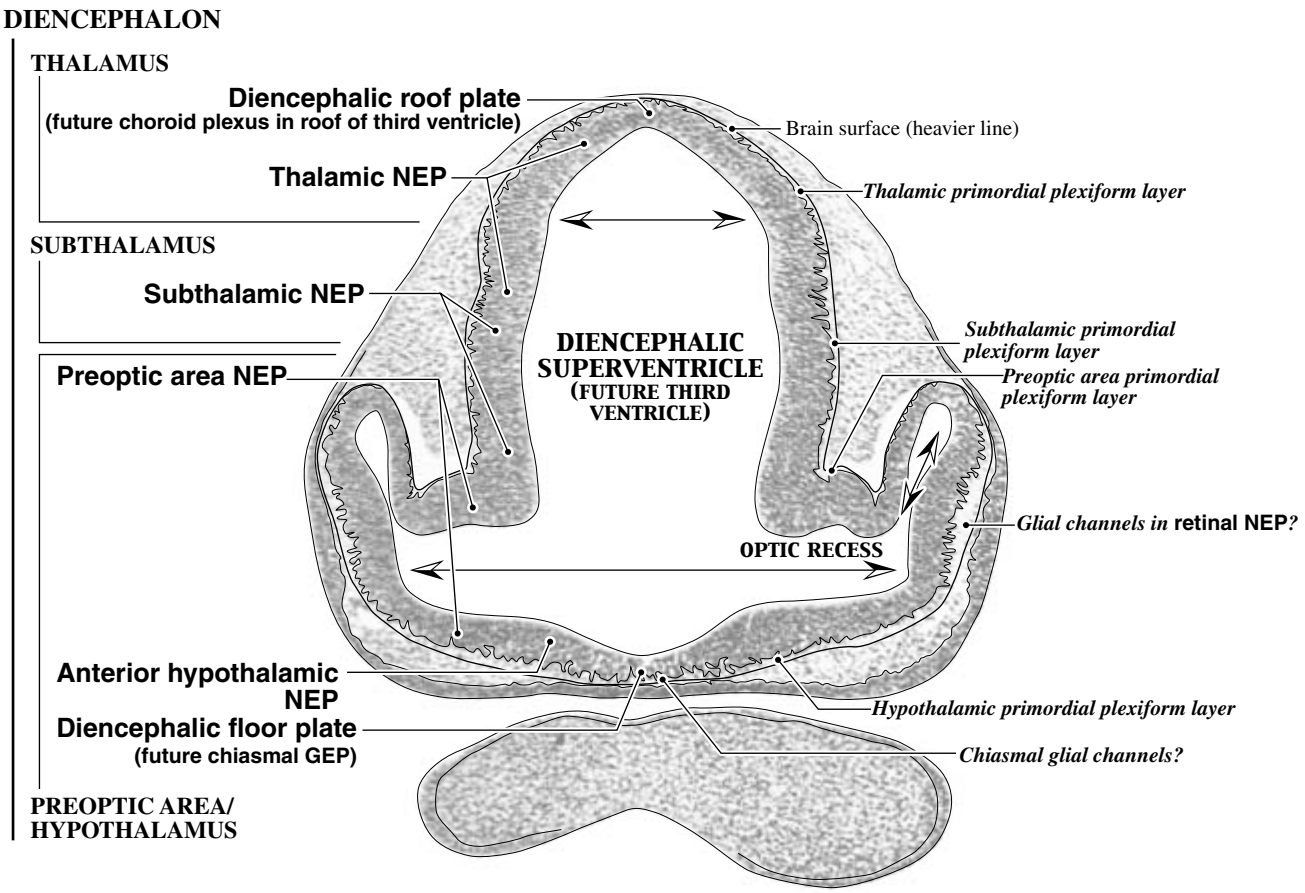
The GW4 Face and Neck
Figure 247A modified (Patten, 1953, p. 429.)



Level 3: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 135B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

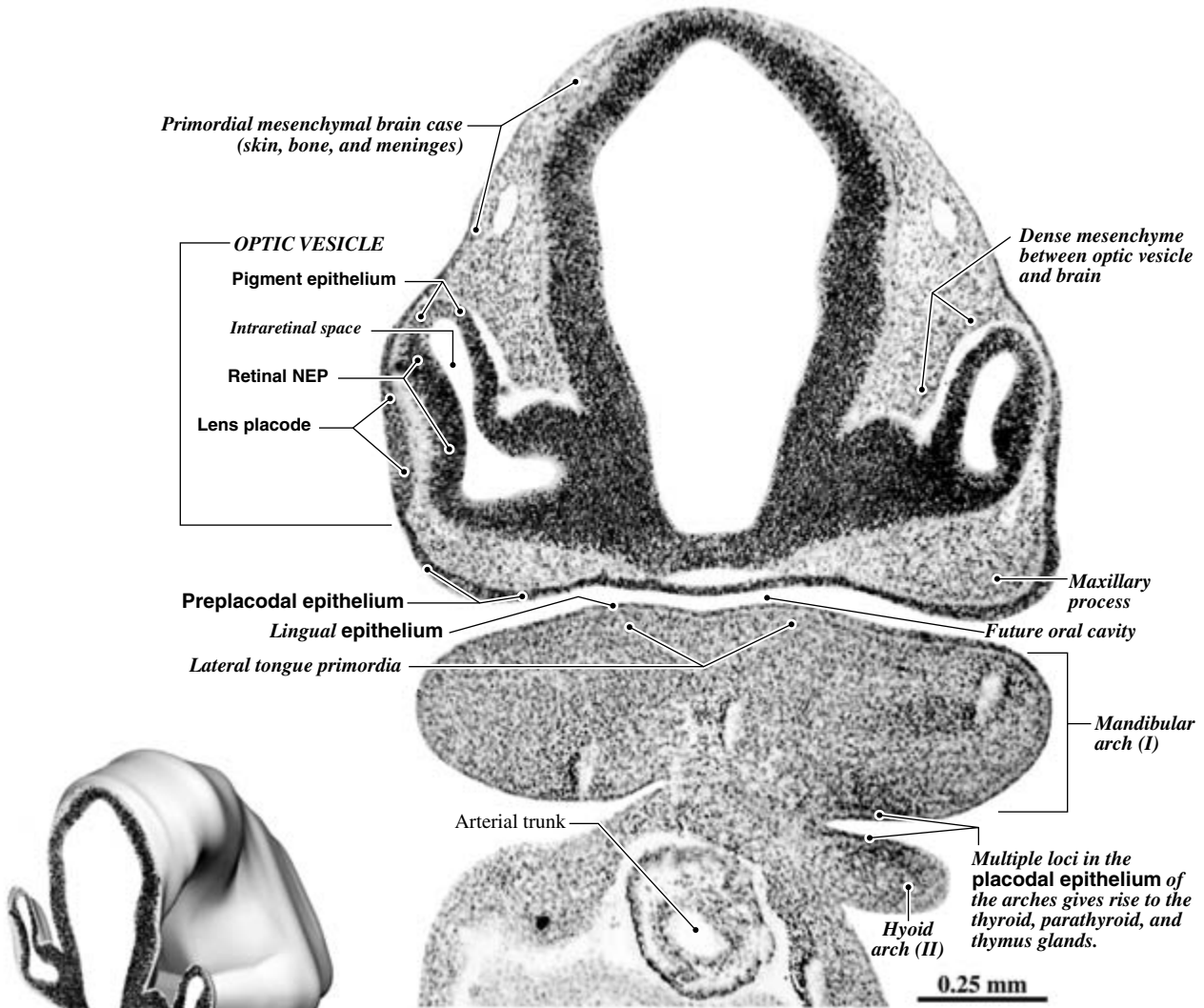
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 136A

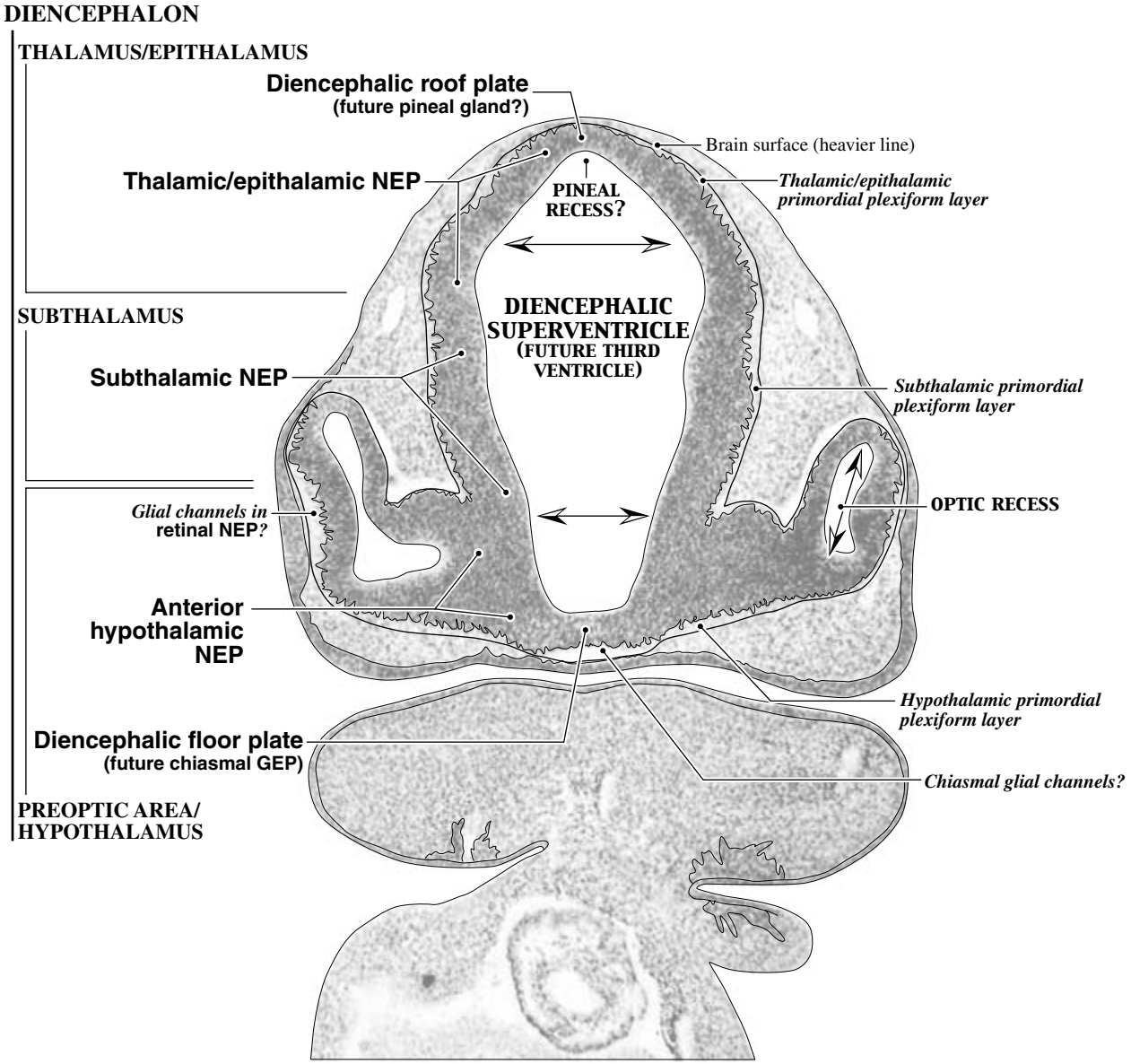
Peripheral neural and non-neural structures labeled

GW4.5 Coronal
CR 6.3 mm
M2300
Level 4: Section 75



Level 4: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled **PLATE 136B**



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

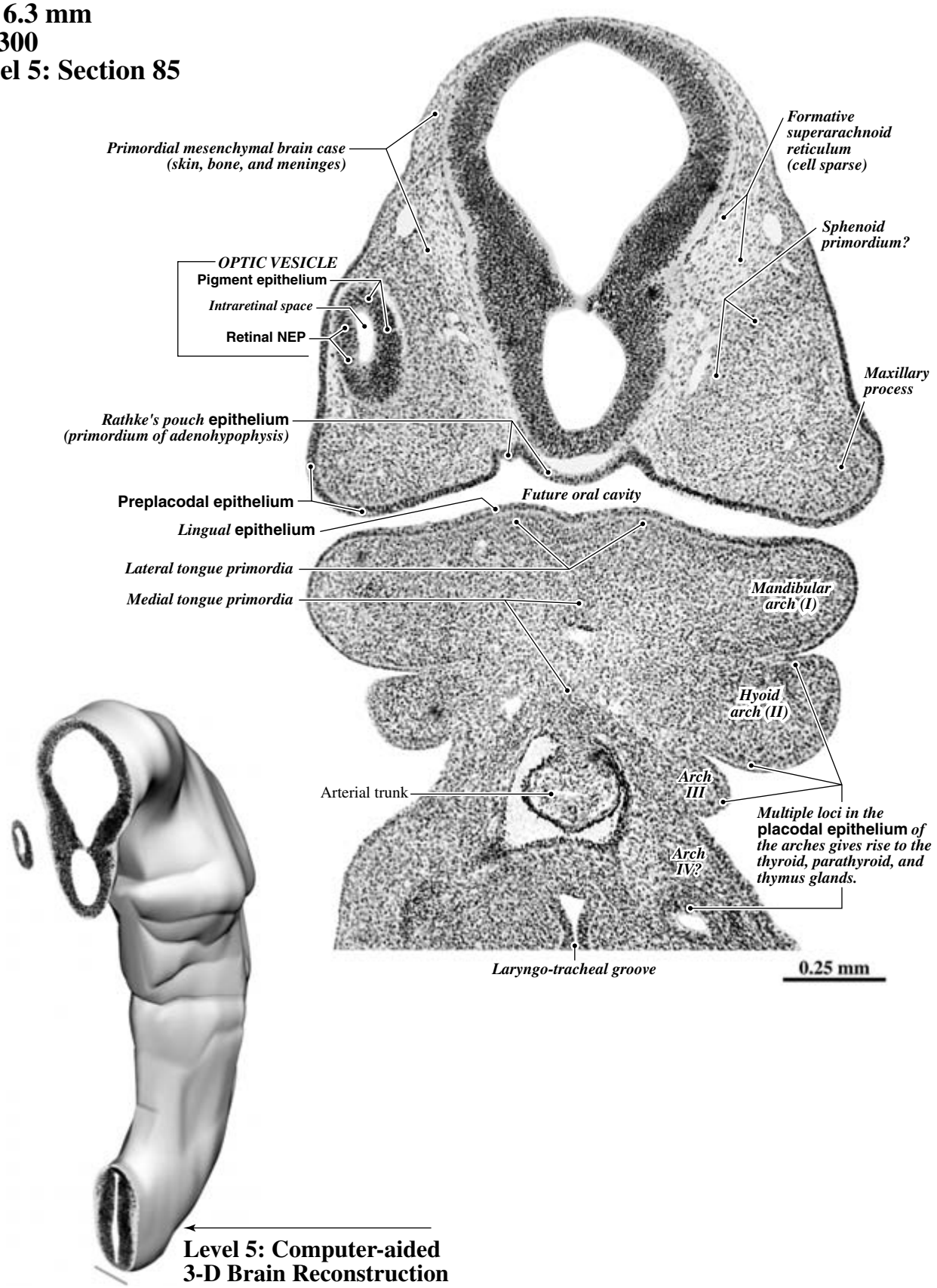
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 137A

Peripheral neural and non-neural structures labeled

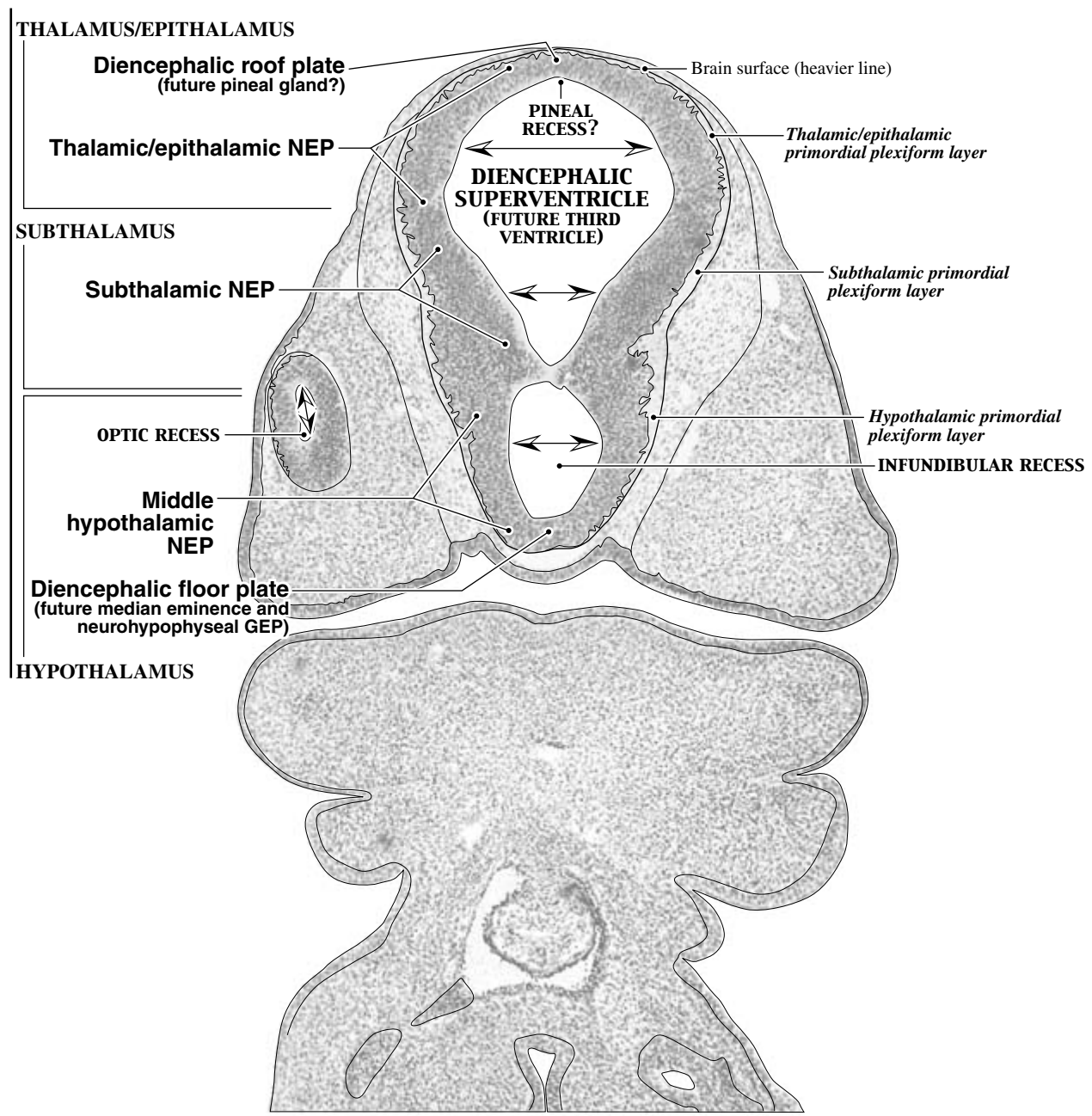
GW4.5 Coronal
CR 6.3 mm
M2300
Level 5: Section 85



Level 5: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 137B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

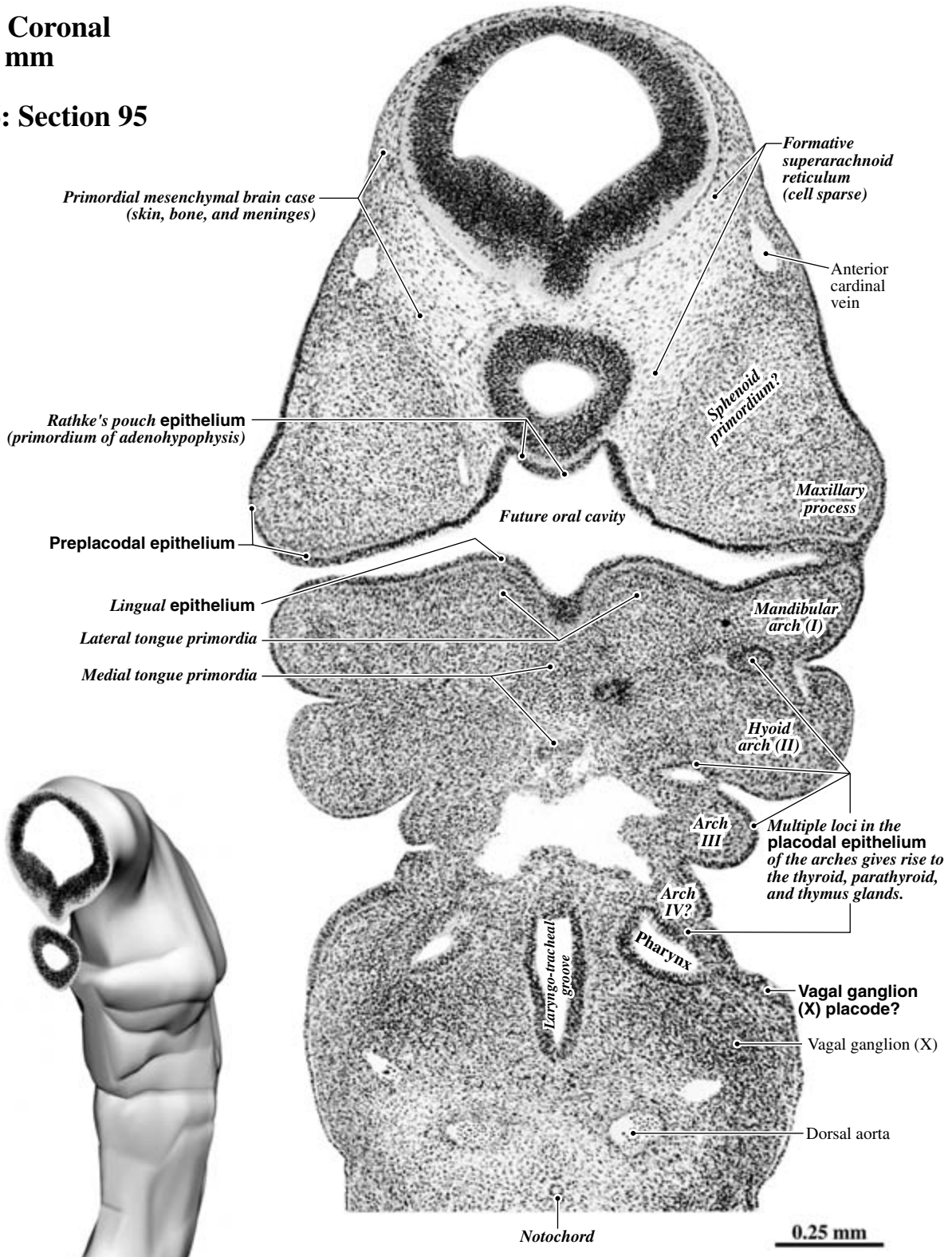
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 138A

Peripheral neural and non-neural structures labeled

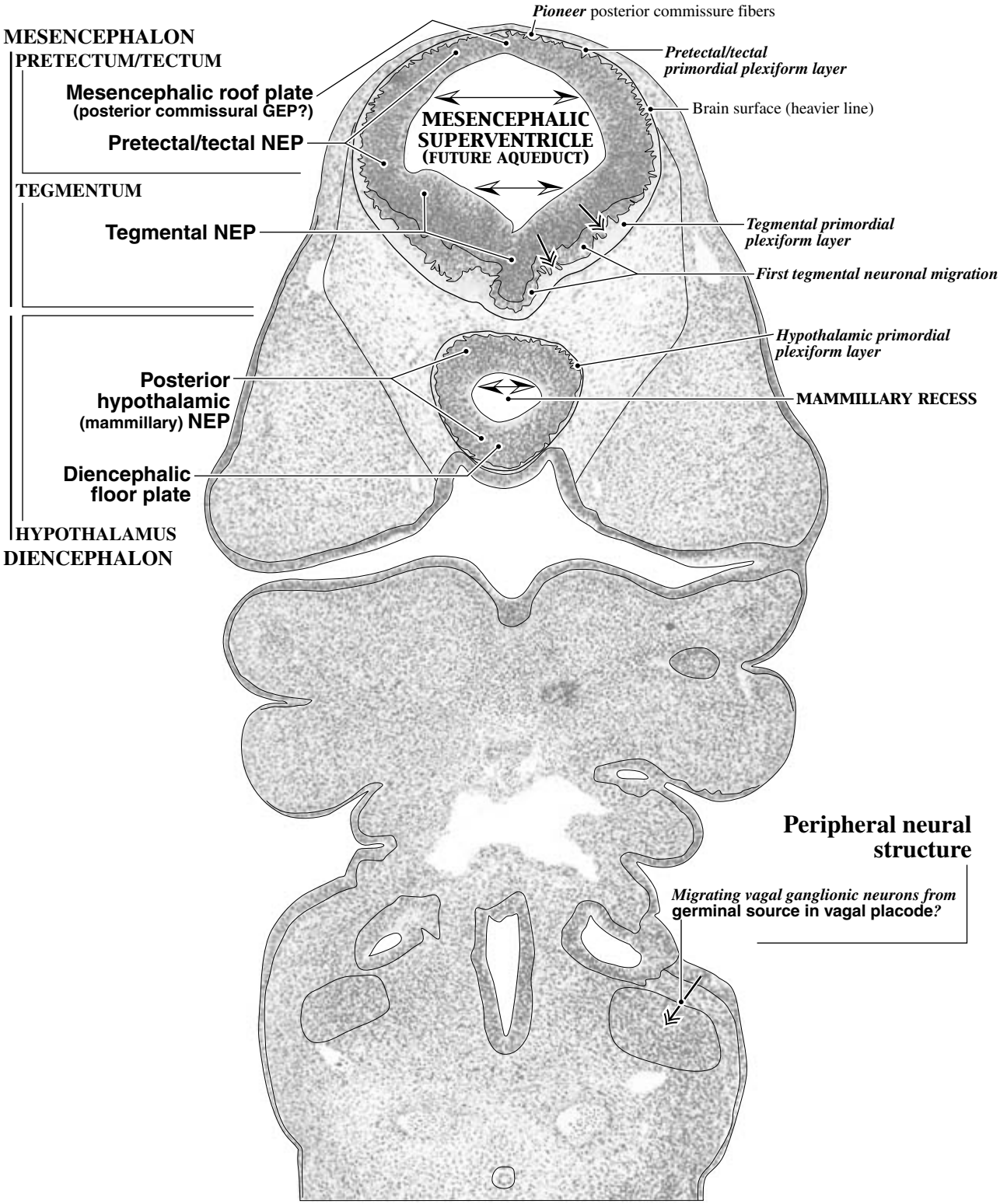
GW4.5 Coronal
CR 6.3 mm
M2300
Level 6: Section 95



Level 6: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 138B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

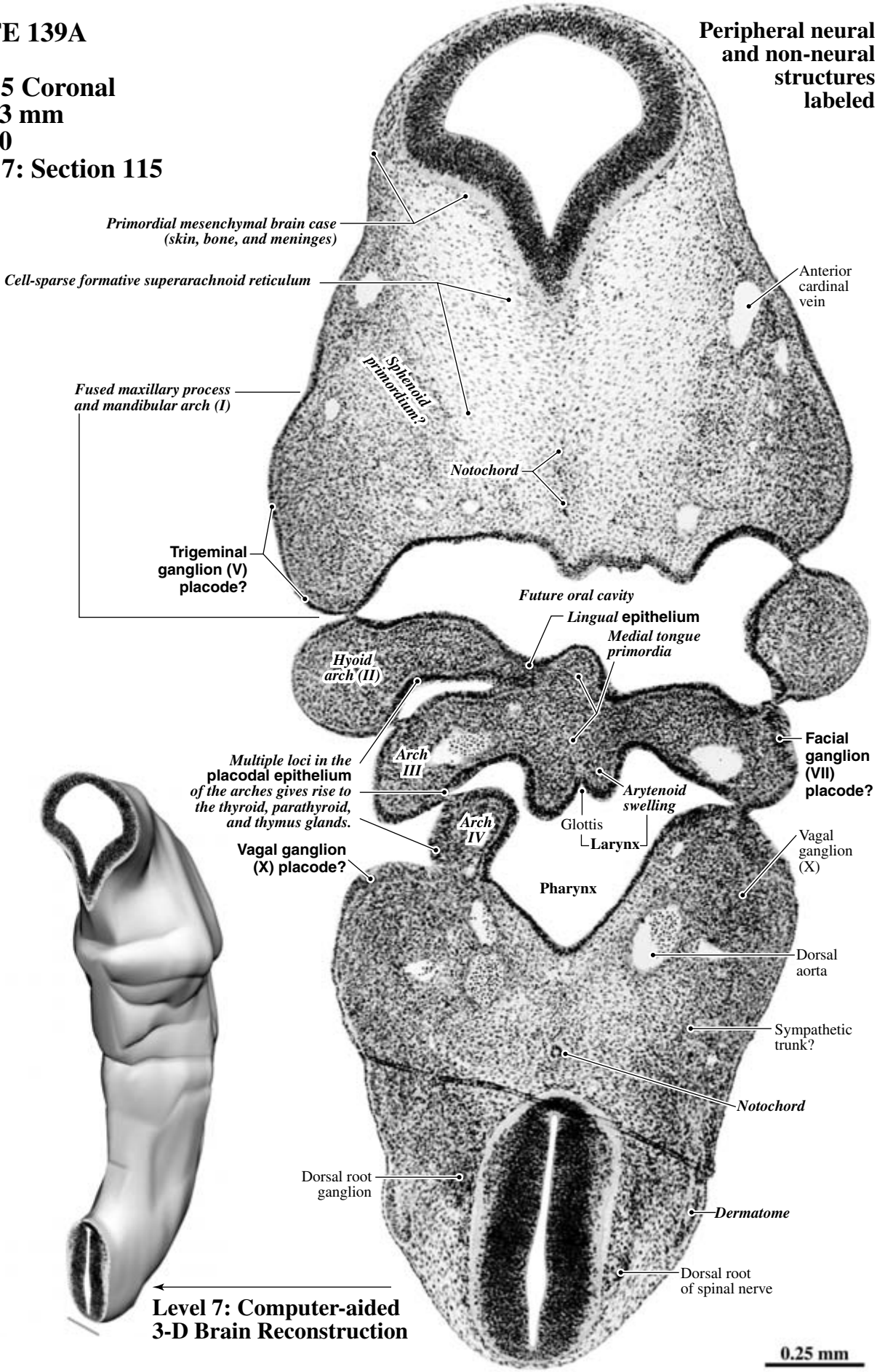
Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 139A

GW4.5 Coronal
CR 6.3 mm
M2300
Level 7: Section 115

Peripheral neural and non-neural structures labeled



Level 7: Computer-aided 3-D Brain Reconstruction

PLATE 139B

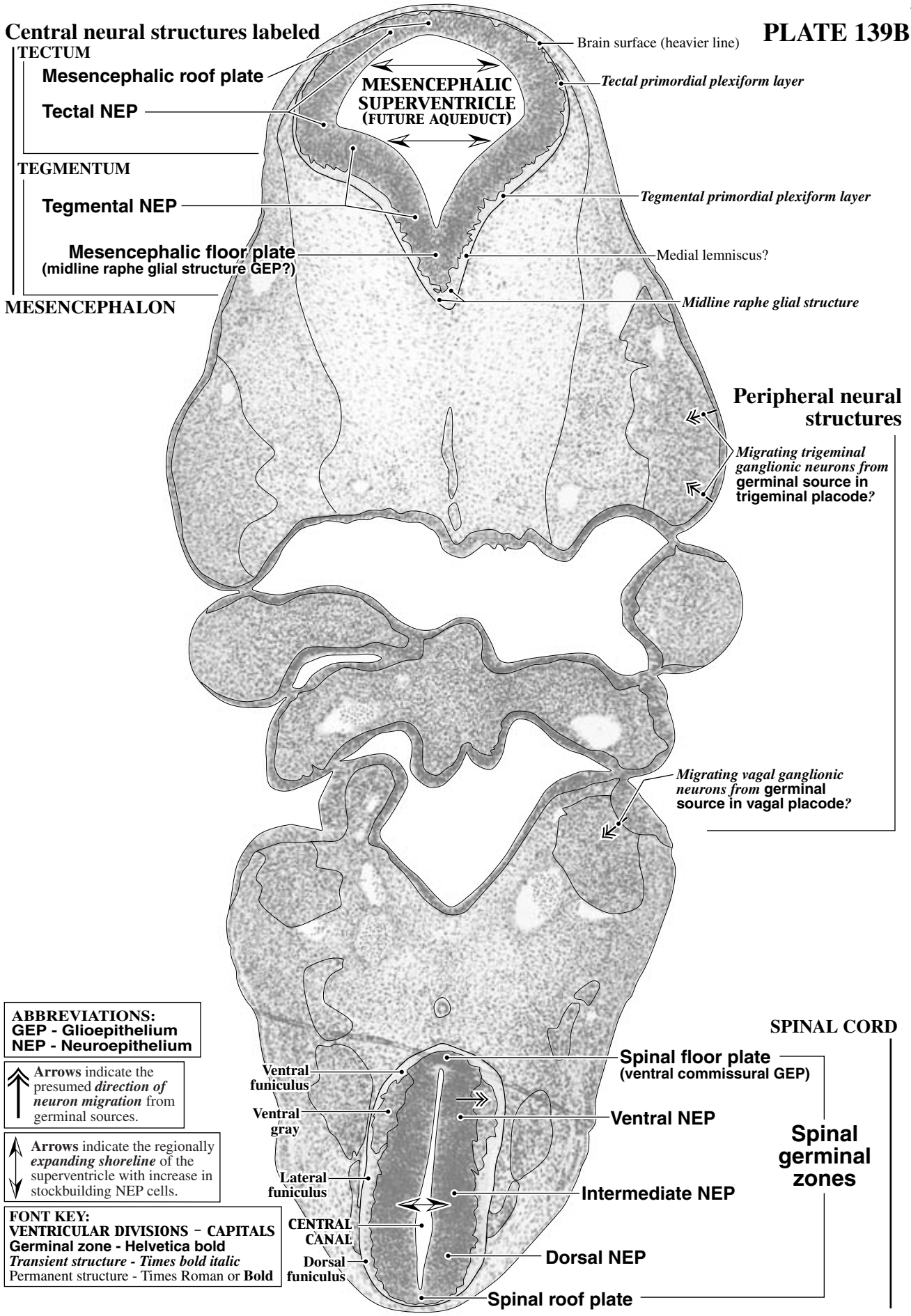
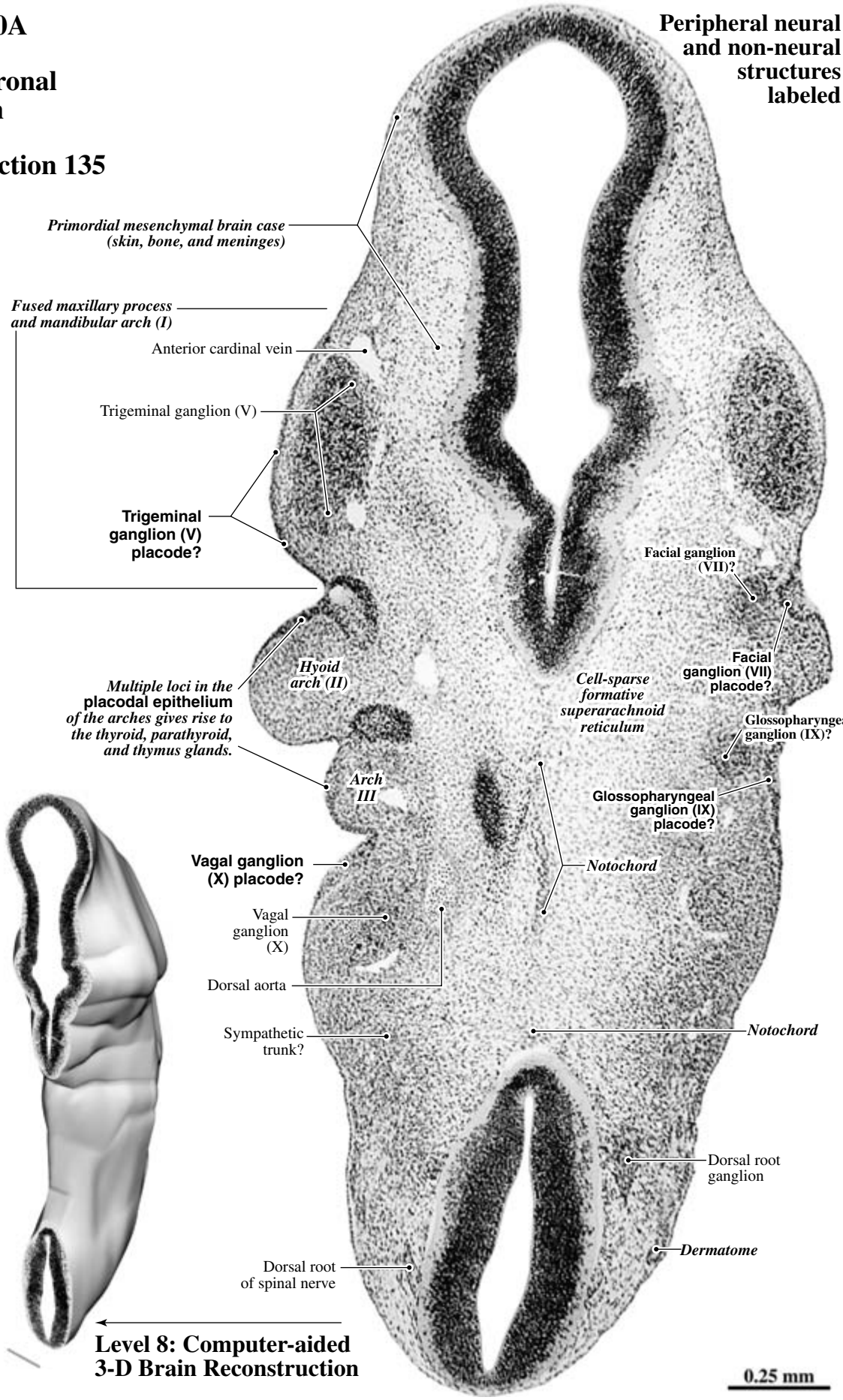

Central neural structures labeled
TECTUM
Mesencephalic roof plate
Tectal NEP
TEGMENTUM
Tegmental NEP
Mesencephalic floor plate
(midline raphe glial structure GEP?)
MESENCEPHALON
Brain surface (heavier line)
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Tectal primordial plexiform layer
Tegmental primordial plexiform layer
Medial lemniscus?
Midline raphe glial structure
Peripheral neural structures
Migrating trigeminal ganglionic neurons from germinal source in trigeminal placode?
Migrating vagal ganglionic neurons from germinal source in vagal placode?
SPINAL CORD
Spinal floor plate
(ventral commissural GEP)
Ventral funiculus
Ventral gray
Ventral NEP
Lateral funiculus
Intermediate NEP
CENTRAL CANAL
Dorsal funiculus
Dorsal NEP
Spinal roof plate
Spinal germinal zones
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
Arrows indicate the presumed direction of neuron migration from germinal sources.
Arrows indicate the regionally expanding shoreline of the superventricle with increase in stockbuilding NEP cells.
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold

PLATE 140A

GW4.5 Coronal
CR 6.3 mm
M2300
Level 8: Section 135

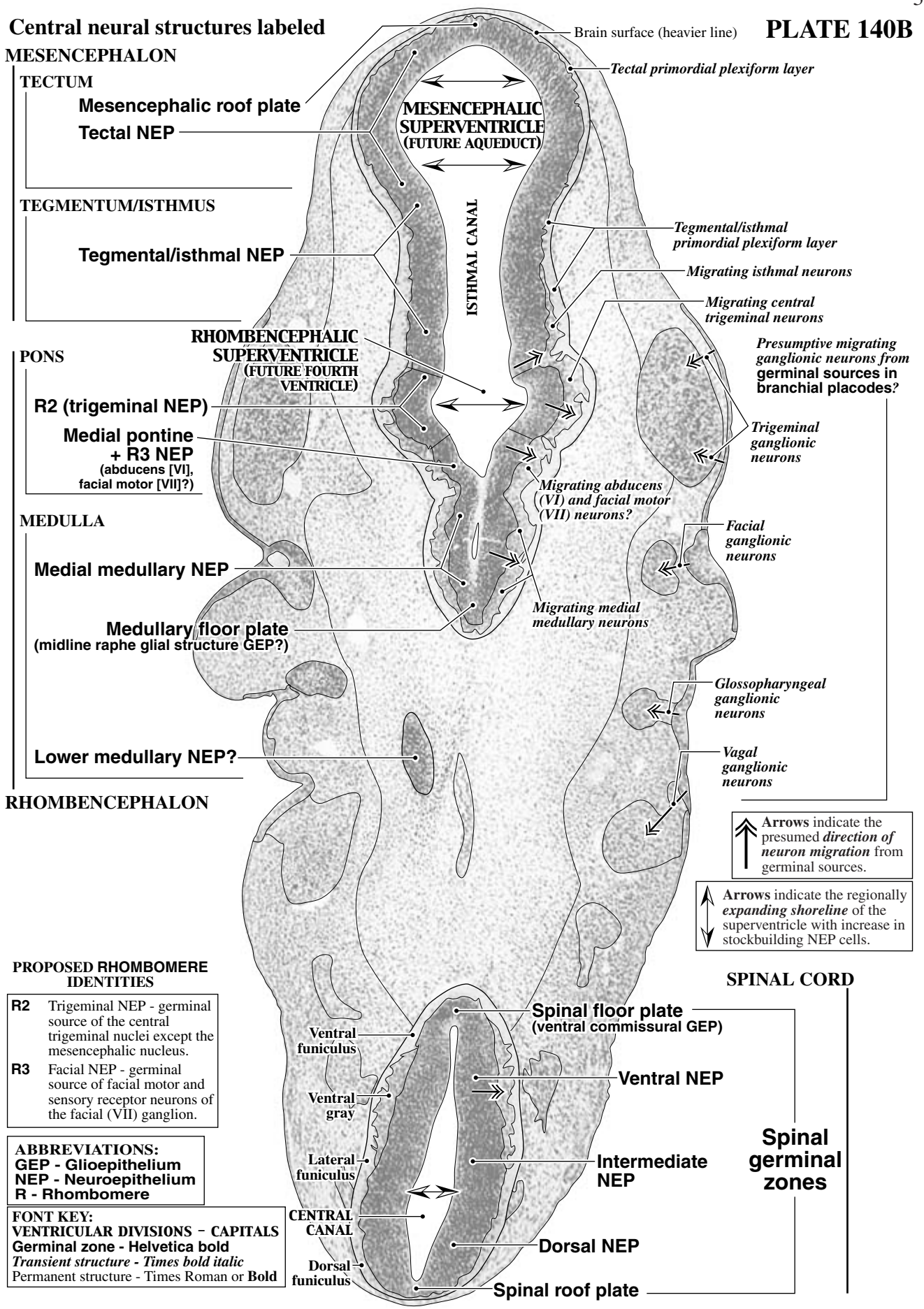
Peripheral neural and non-neural structures labeled



Level 8: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 140B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.

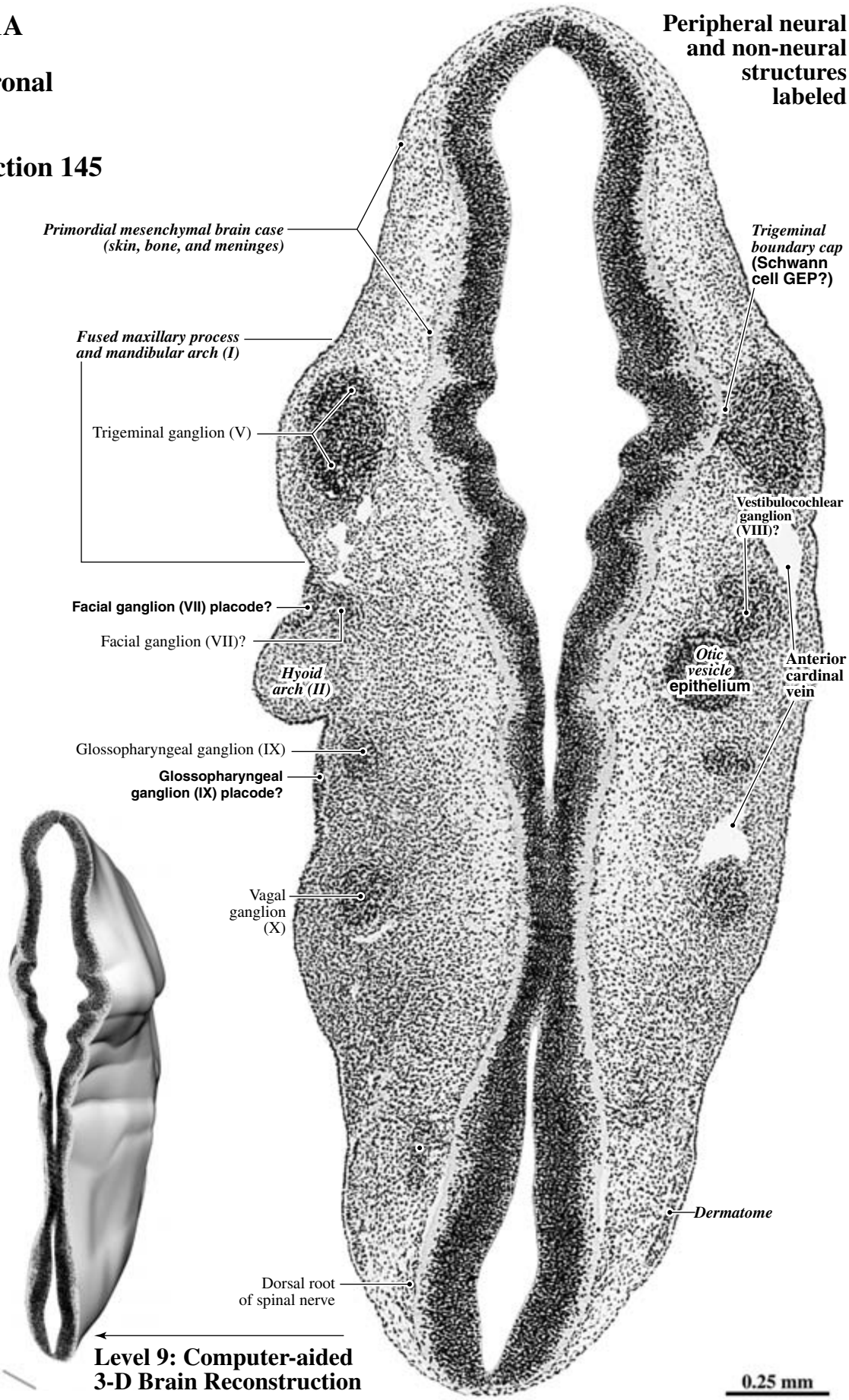
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 141A

GW4.5 Coronal
CR 6.3 mm
M2300
Level 9: Section 145

Peripheral neural and non-neural structures labeled



Level 9: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 141B

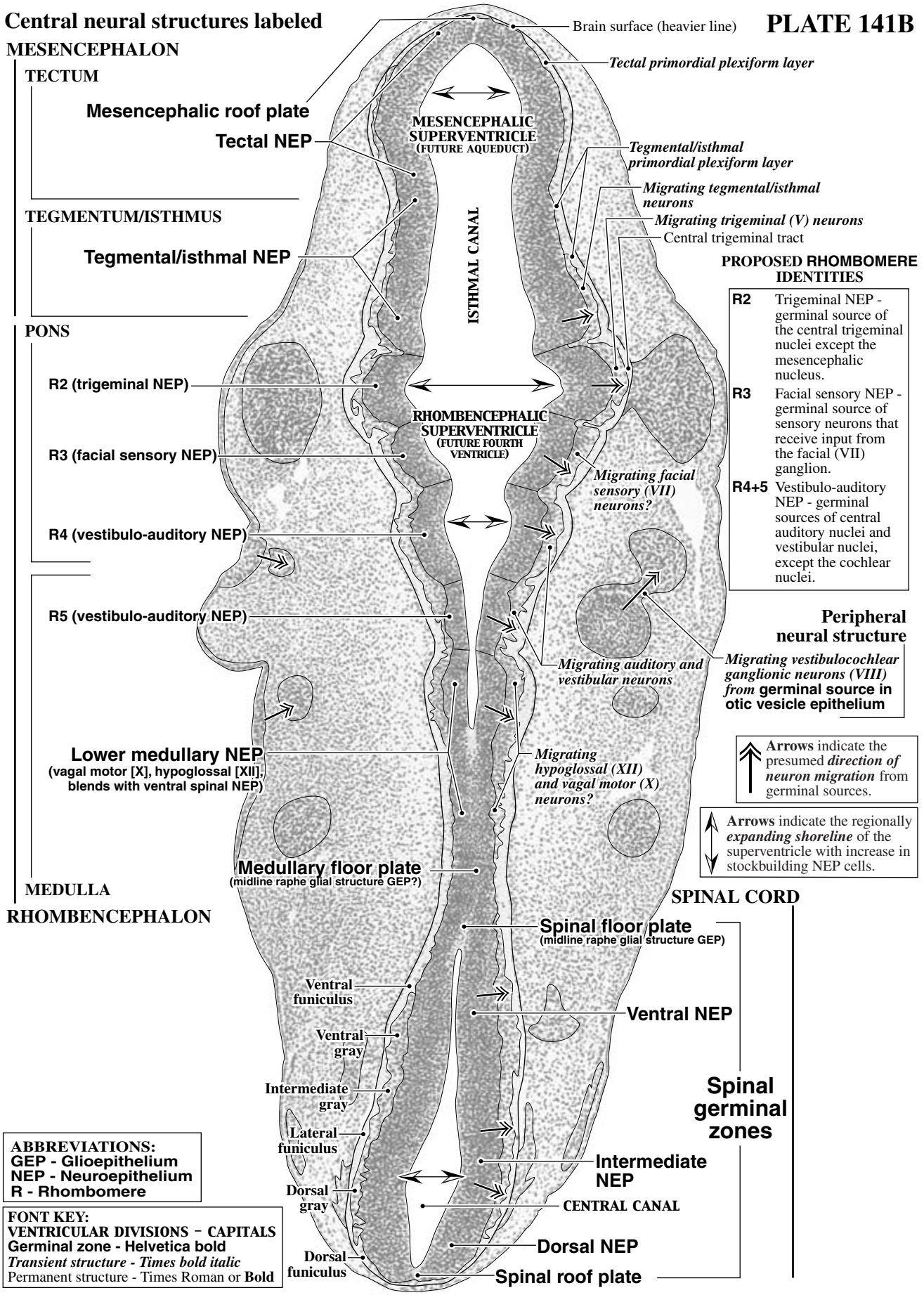
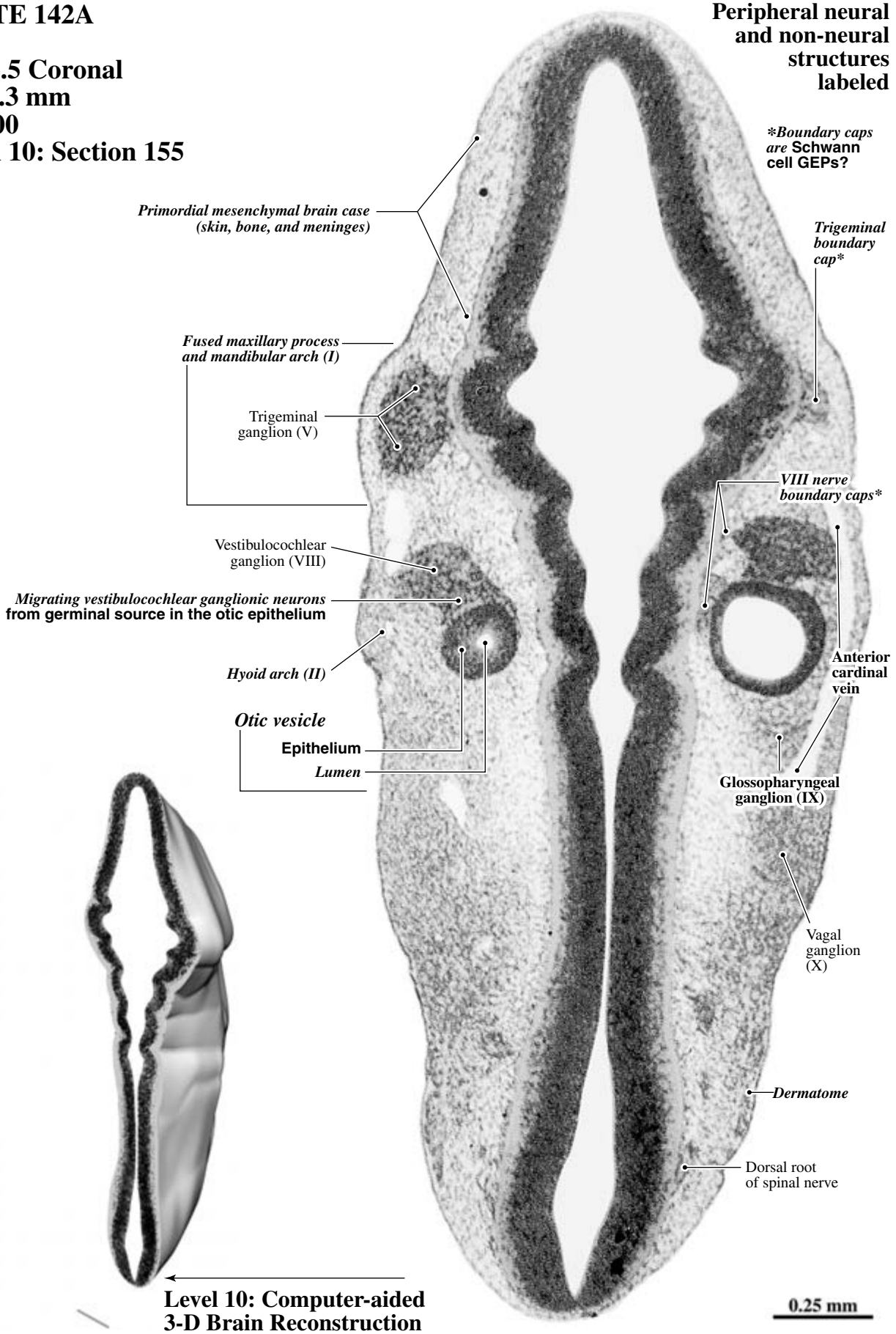


PLATE 142A

GW4.5 Coronal
CR 6.3 mm
M2300
Level 10: Section 155

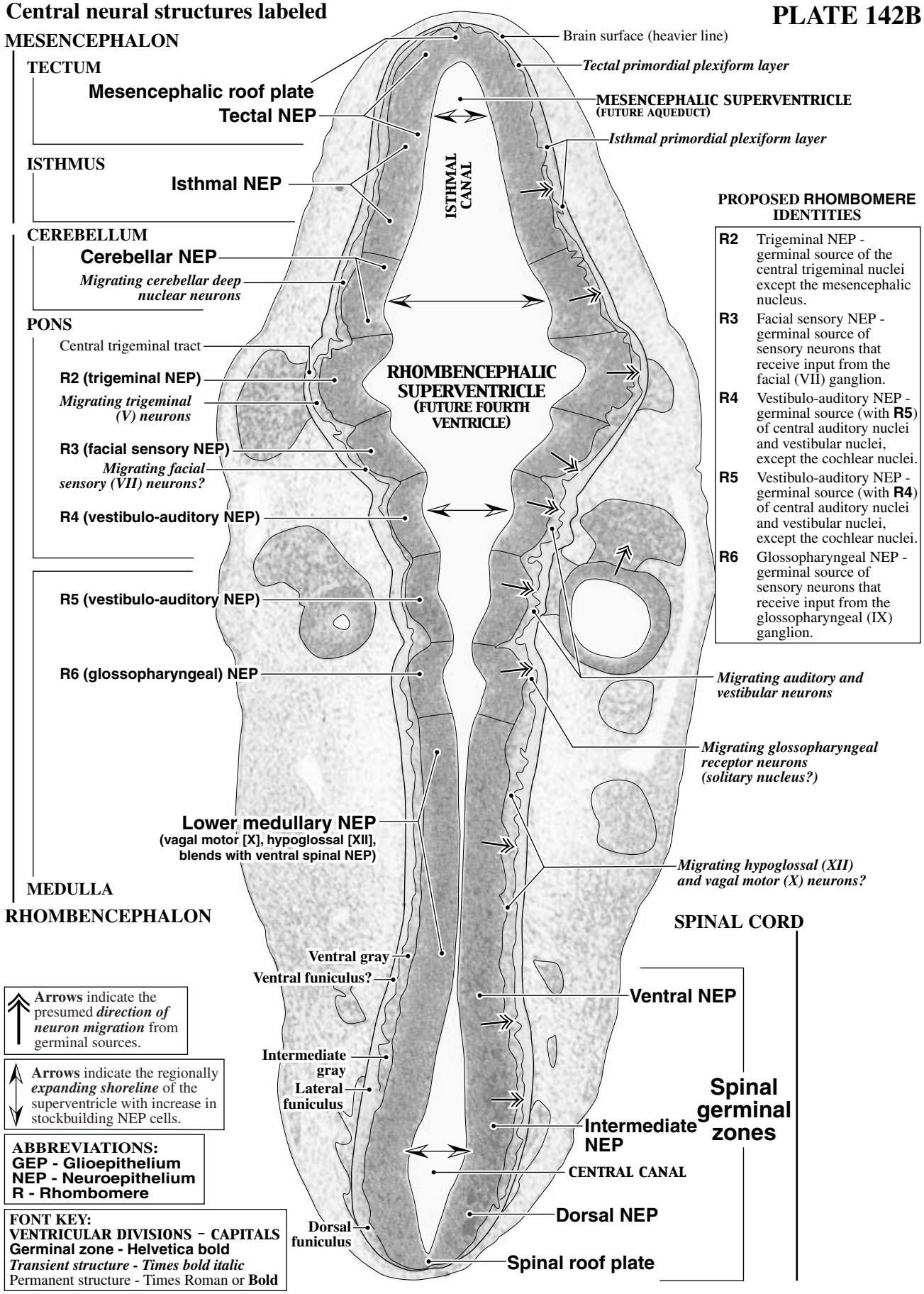
Peripheral neural and non-neural structures labeled



Level 10: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 142B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

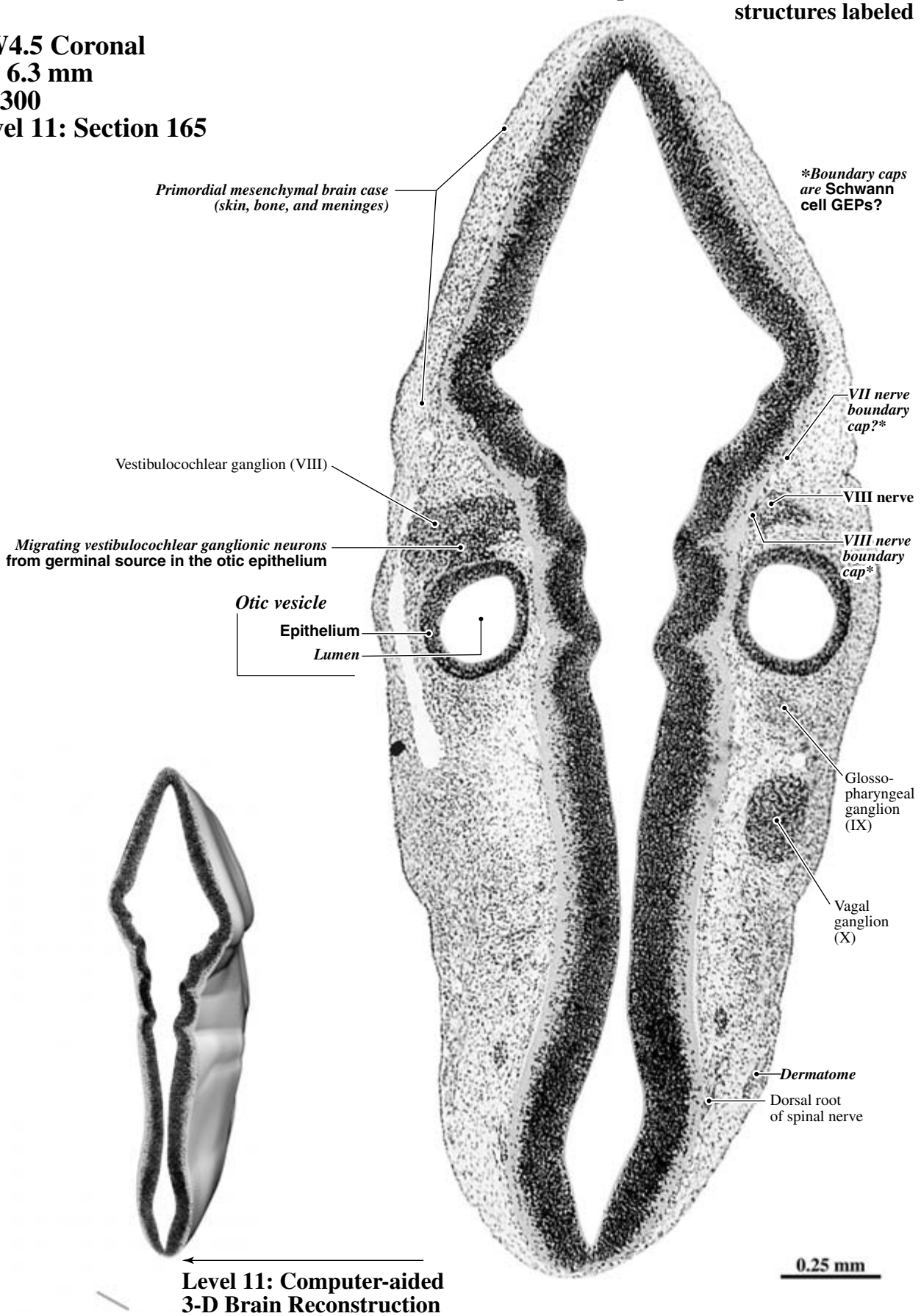
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 143A

Peripheral neural and non-neural structures labeled

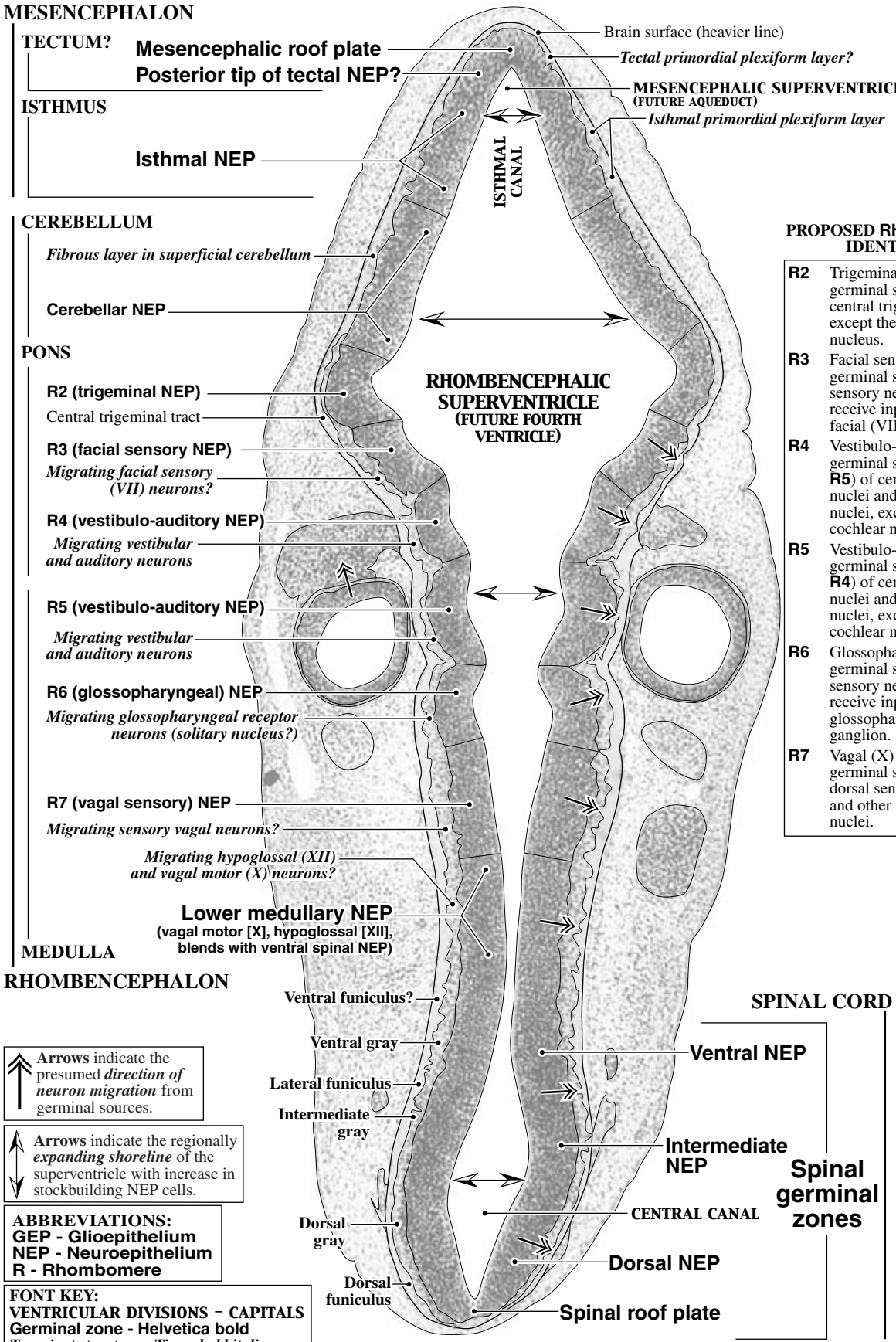
GW4.5 Coronal
CR 6.3 mm
M2300
Level 11: Section 165



Level 11: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 143B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

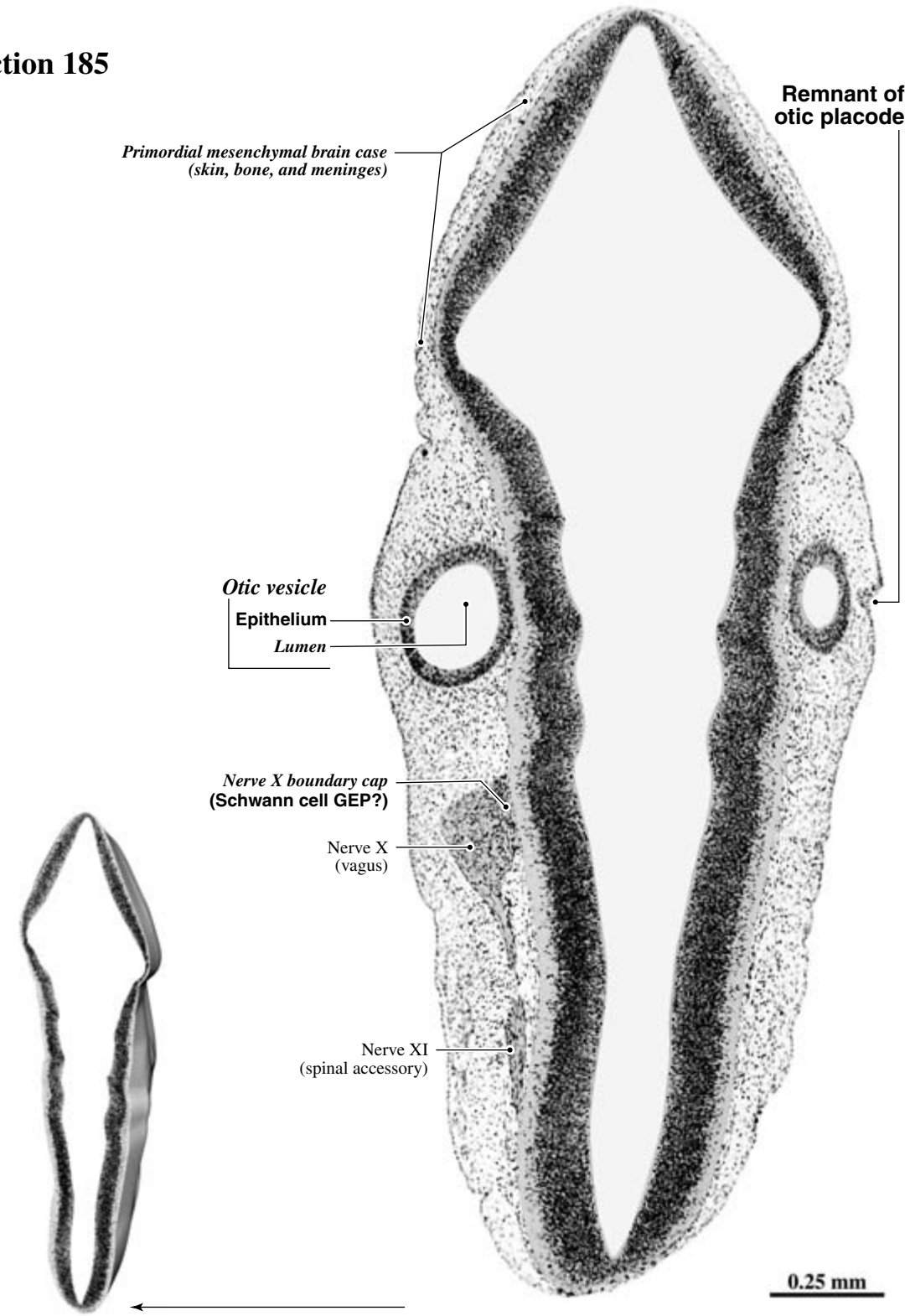
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 144A

Peripheral neural and non-neural structures labeled

GW4.5 Coronal
CR 6.3 mm
M2300
Level 12: Section 185



Level 12: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 144B

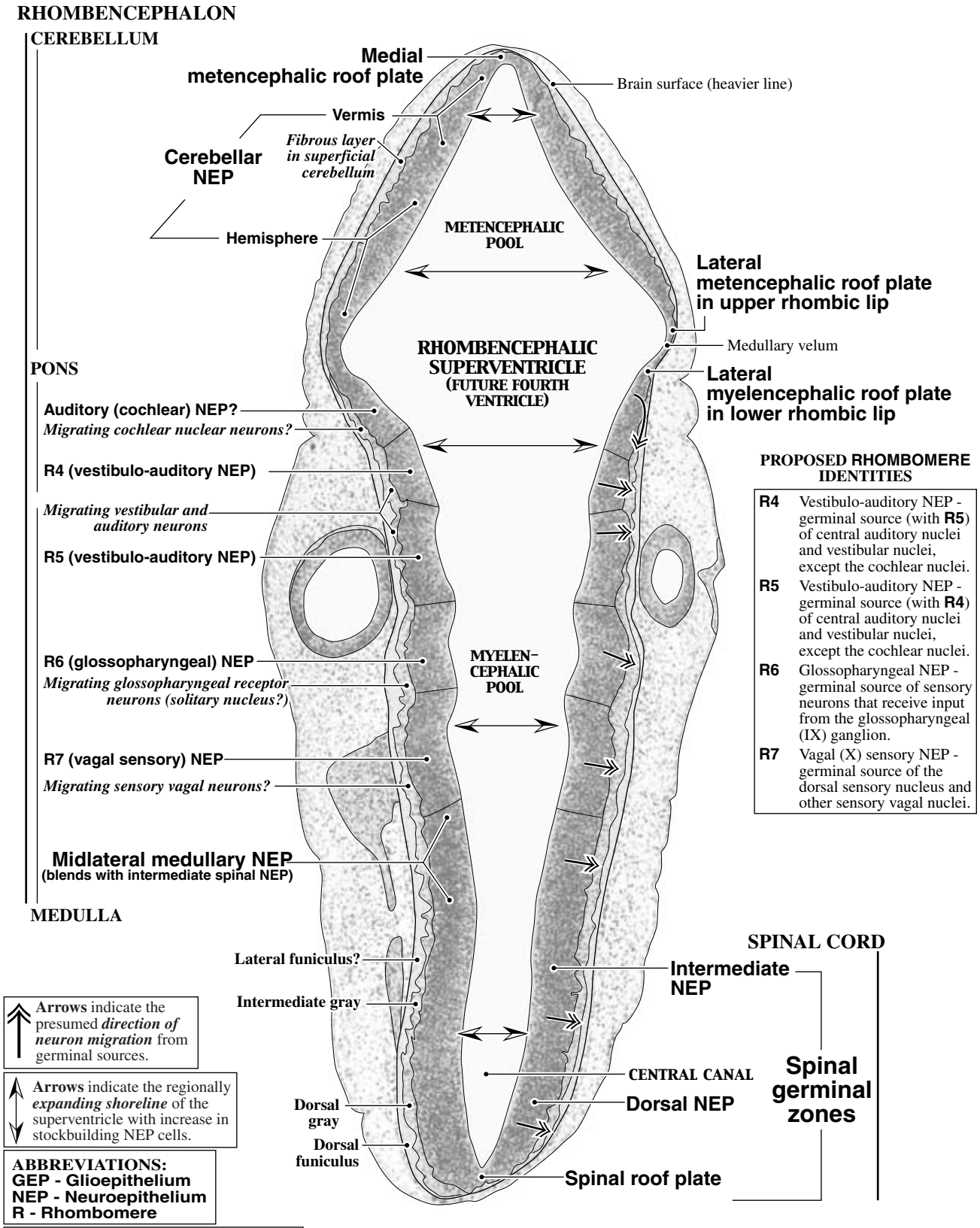
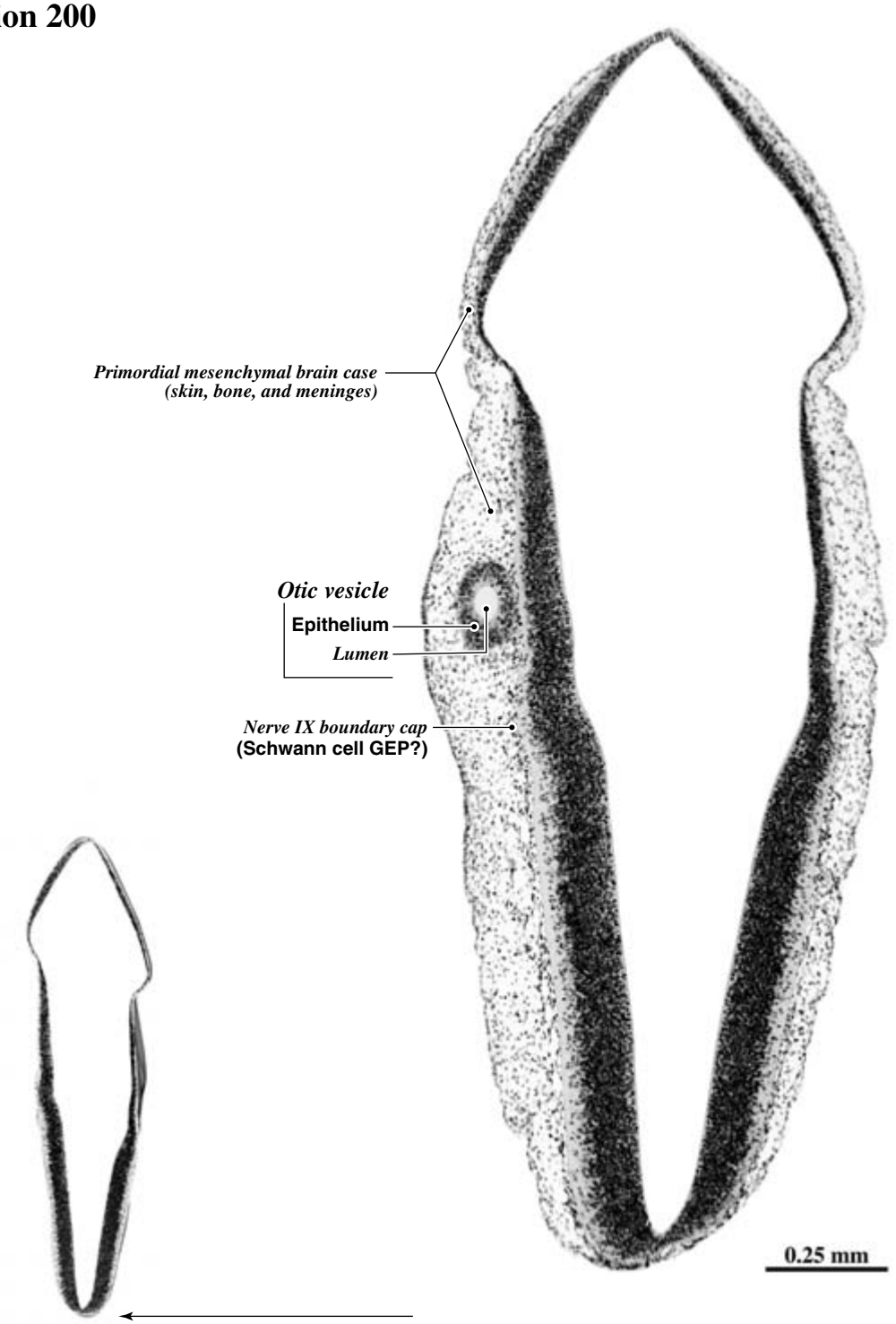


PLATE 145A

Peripheral neural and non-neural structures labeled

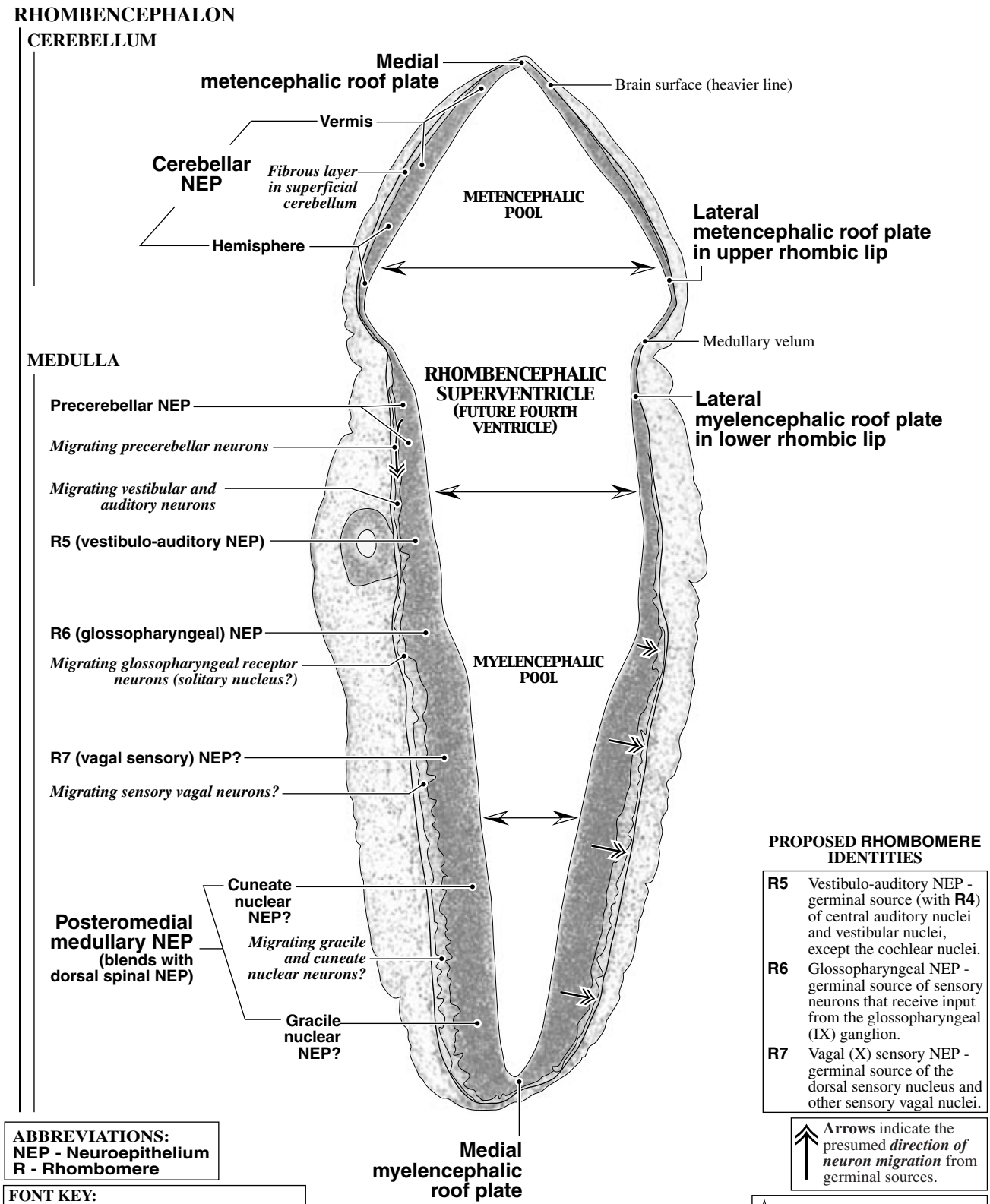
GW4.5 Coronal
CR 6.3 mm
M2300
Level 13: Section 200



Level 13: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 145B



PROPOSED RHOMBOMERE IDENTITIES

R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

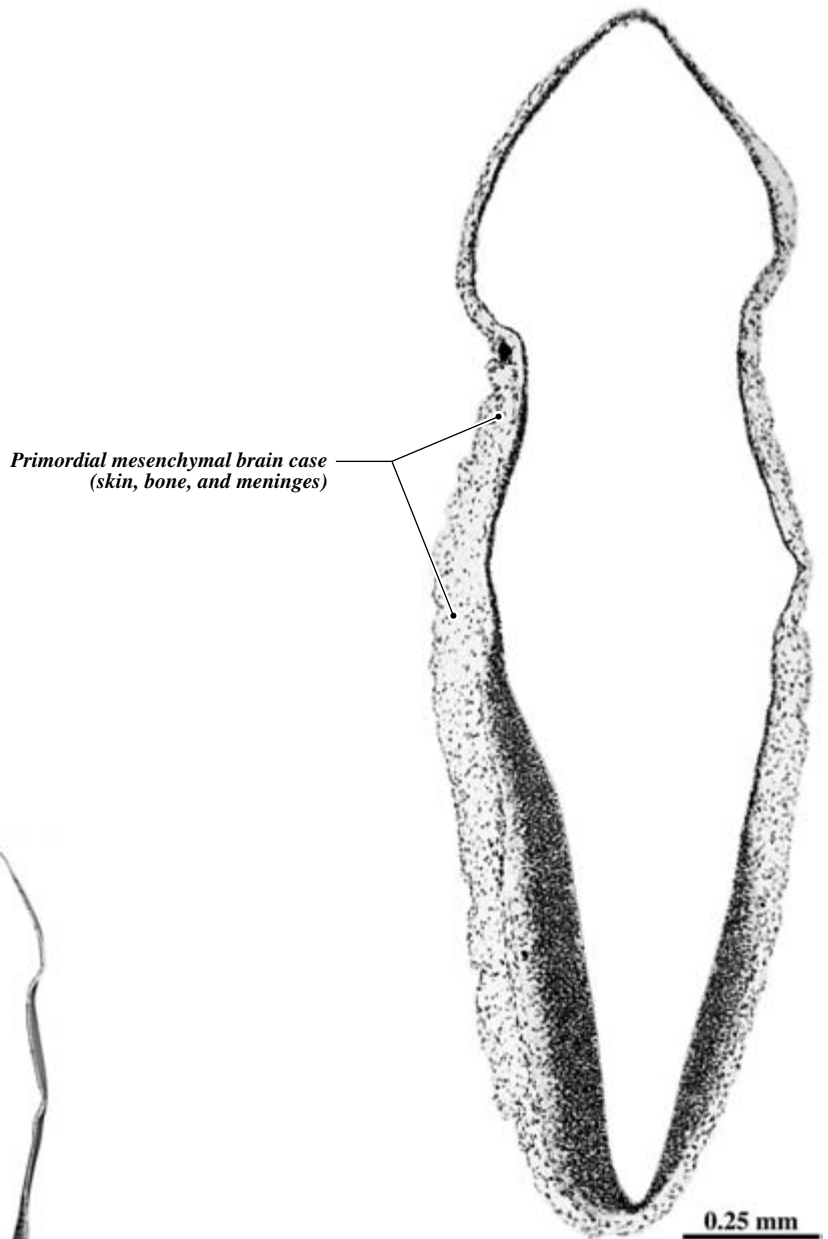
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

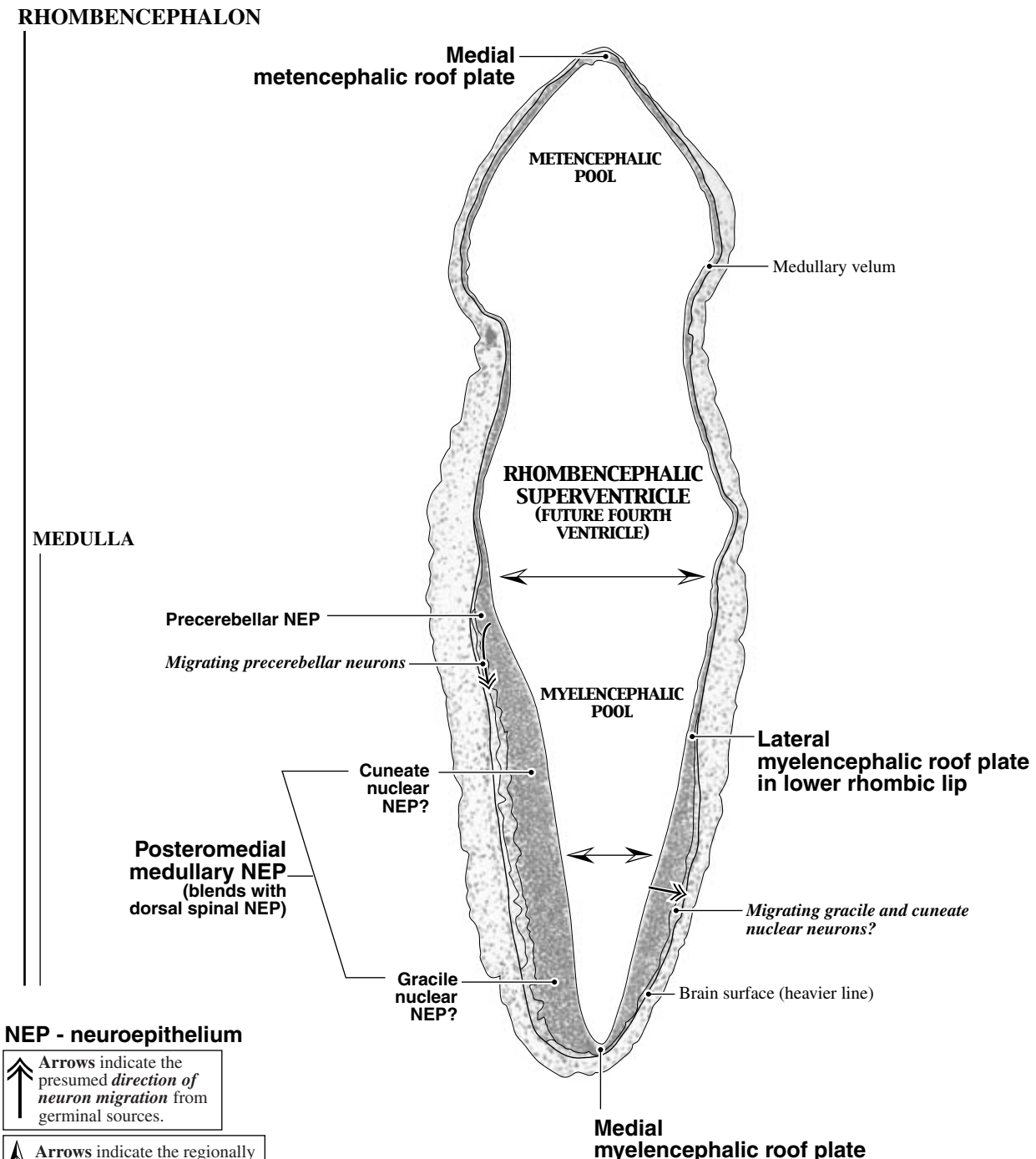
PLATE 146A **Non-neural structures labeled**

GW4.5 Coronal
CR 6.3 mm
M2300
Level 14: Section 210



Level 14: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled **PLATE 146B**



PART XII: GW4 SAGITTAL

Carnegie Collection specimen #9297 (designated here as C9297) with a 4.5-mm crown-rump length (CR) is estimated to be at gestational week (GW) 4. C9297 was embedded in a celloidin/paraffin mix and was cut in 8-µm sagittal sections that were stained with azan. Various orientations of the computer-aided 3-D reconstruction of C836's brain are used to show the gross external features of a GW4 brain (**Figure 11**). Like most sagittally cut specimens, C9297's sections are not parallel to the midline; **Figure 11** shows the approximate rotations in front (**B**) and back views (**C**). We photographed 18 sections at low magnification from the left to right sides of the brain. Nine of the sections, mainly from the left side of the brain, are illustrated in **Plates 147AB to 155AB**. Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify the approximate midline, non-neural structures, peripheral neural structures, and brain ventricular divisions; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 132AB to 133AB** show high-magnification views of the rhombencephalon.

The prosencephalon is the smallest major brain structure with little distinction between a future telencephalon and diencephalon. The entire prosencephalic neuroepithelium is rapidly stockbuilding its various populations of neuronal and glial stem cells. The lamina terminalis in the ventral prosencephalon marks the site of closure of the anterior neuropore. A cell-dense area adjacent to the olfactory placode may be supporting cells associated with growth of the olfactory nerve toward the brain.

The mesencephalon is much smaller than at GW5. The stockbuilding pretectal and tectal neuroepithelia have a relatively short anteroposterior length and blend with the presumptive cerebellar neuroepithelium in the dorsomecial rhombencephalon. The stockbuilding tegmental and isthmal neuroepithelia form a distinctive arch between the mesencephalic and diencephalic flexures. There is a very thin subpial fiber band in the tegmentum and isthmus.

The rhombencephalon is the largest brain structure. Rhombomeres 2 through 7 form well-defined swellings in the lateral neuroepithelium. Most sensory cranial ganglia and the otic vesicle are located directly lateral to the rhombomeres with which they interact. The trigeminal ganglion (V afferents) appears in sections lateral to the last section that contains rhombomere 2. The vestibulocochlear ganglion (VIII afferents) is lateral to the last section that contains rhombomere 4; the otic vesicle is lateral to the last section that contains rhombomere 5. The presumptive superior glossopharyngeal ganglion (IX afferents) is lateral to the last section with rhombomere 6, and the large superior vagal ganglion (X afferents) is lateral to the last section with rhombomere 7. The association of rhombomere 3 with the sensory part of nerve VII is less clear, but the facial ganglion (VII afferents) is near its presumptive placodal source in lateral sections. Each rhombomere has a thin layer of pioneer migrating neurons that are only visible in most lateral sections, where the outer edges of the rhombomeric neuroepithelium are cut tangentially. Virtually no fibers have yet entered the brain from these ganglia. Sections near the midline show a smooth neuroepithelium. Some migrating cells are outside the lower medullary neuroepithelium, and the subpial fiber band is thicker as the brain blends with the spinal cord. The cerebellum stands out as the most immature and smallest rhombencephalic structure. The most lateral sections show a very thin layer of migrating neurons outside the cerebellar neuroepithelium.

EXTERNAL FEATURES OF THE GW4 BRAIN

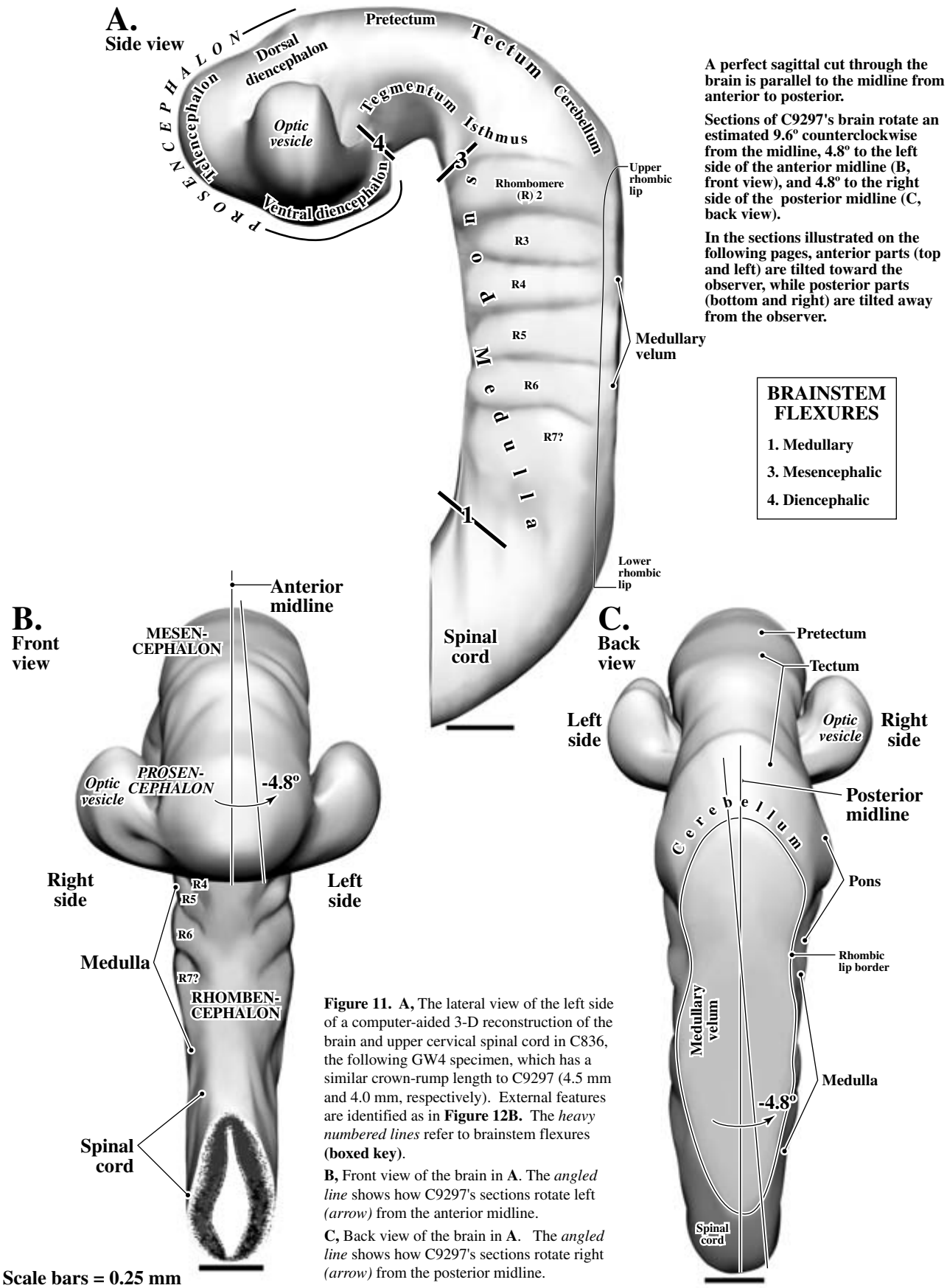


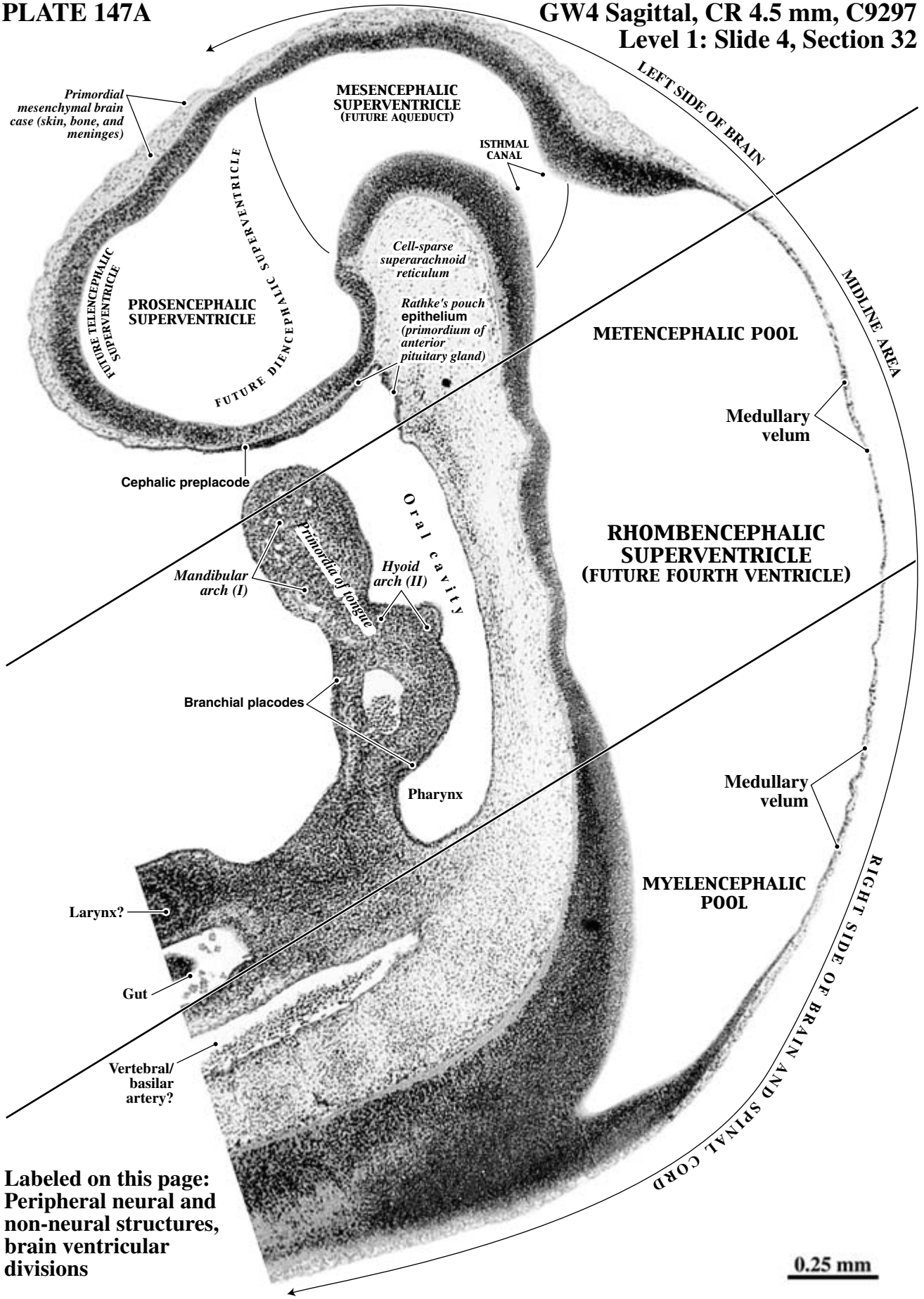
Figure 11. A, The lateral view of the left side of a computer-aided 3-D reconstruction of the brain and upper cervical spinal cord in C836, the following GW4 specimen, which has a similar crown-rump length to C9297 (4.5 mm and 4.0 mm, respectively). External features are identified as in **Figure 12B.** The *heavy numbered lines* refer to brainstem flexures **(boxed key)**.

B, Front view of the brain in **A**. The *angled line* shows how C9297's sections rotate left *(arrow)* from the anterior midline.

C, Back view of the brain in **A**. The *angled line* shows how C9297's sections rotate right *(arrow)* from the posterior midline.

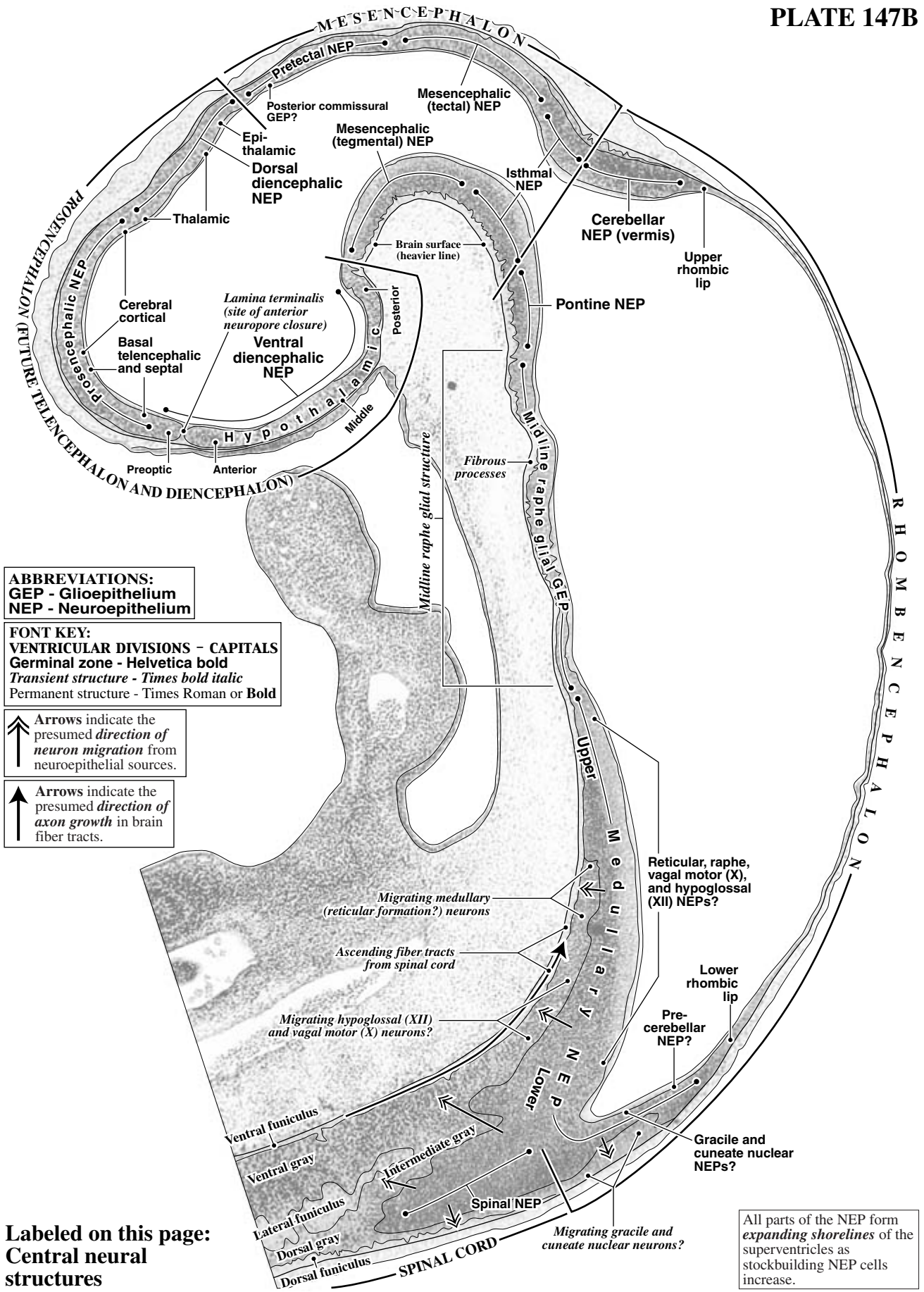
PLATE 147A

GW4 Sagittal, CR 4.5 mm, C9297
Level 1: Slide 4, Section 32



Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 147B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

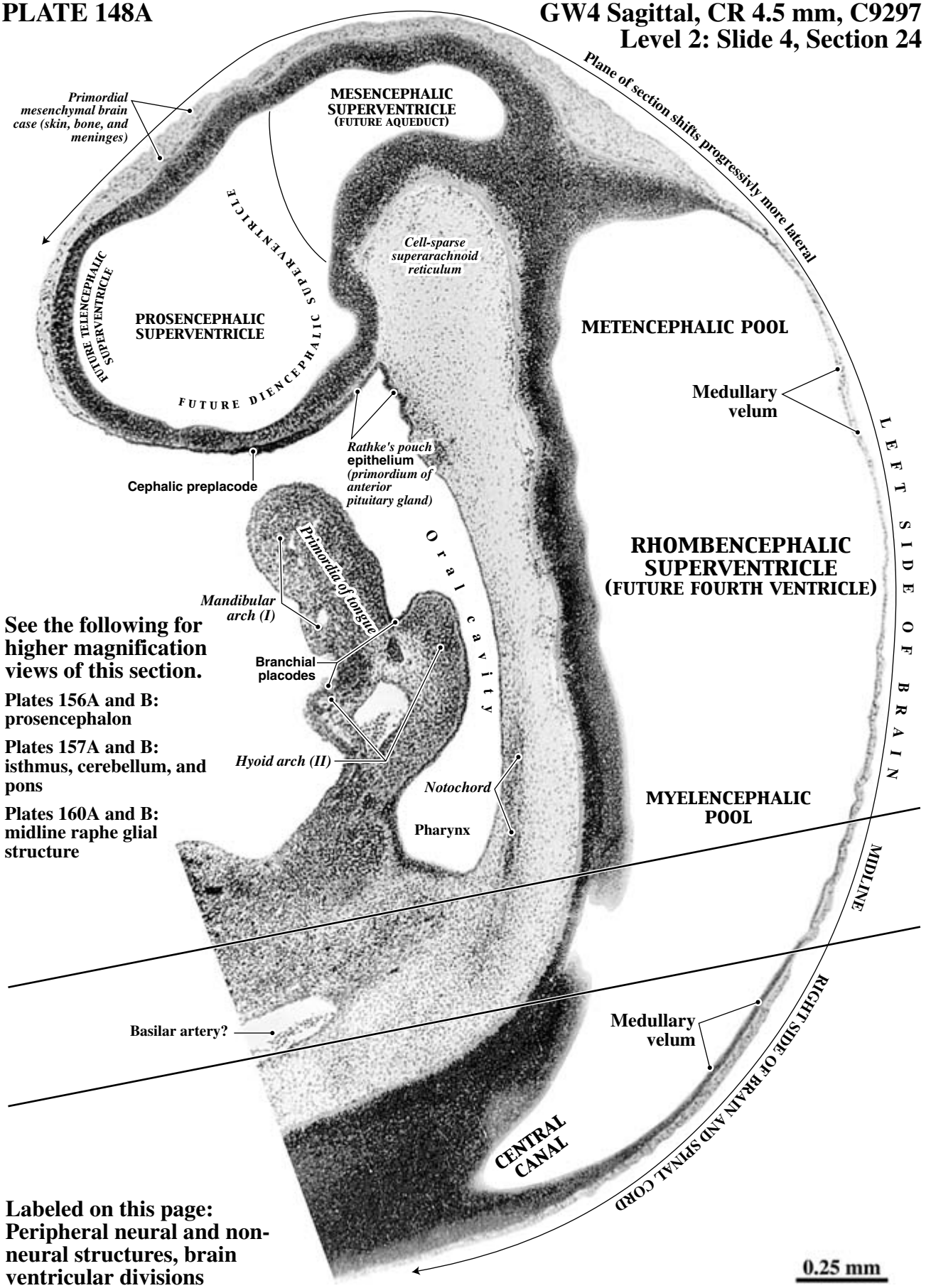
Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Labeled on this page:
Central neural structures

All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

PLATE 148A

GW4 Sagittal, CR 4.5 mm, C9297
Level 2: Slide 4, Section 24



See the following for higher magnification views of this section.

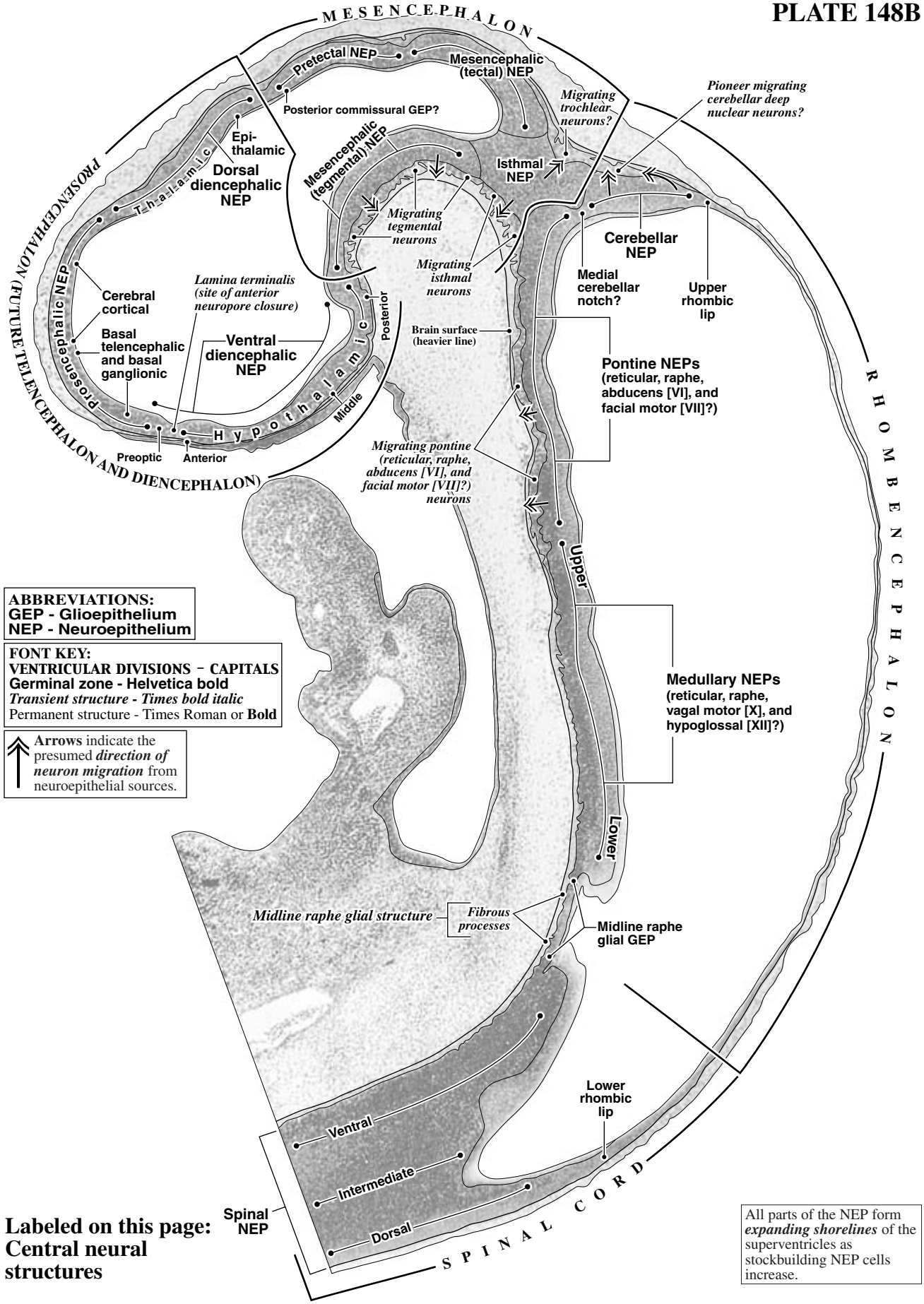
Plates 156A and B: prosencephalon

Plates 157A and B: isthmus, cerebellum, and pons

Plates 160A and B: midline raphe glial structure

Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 148B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

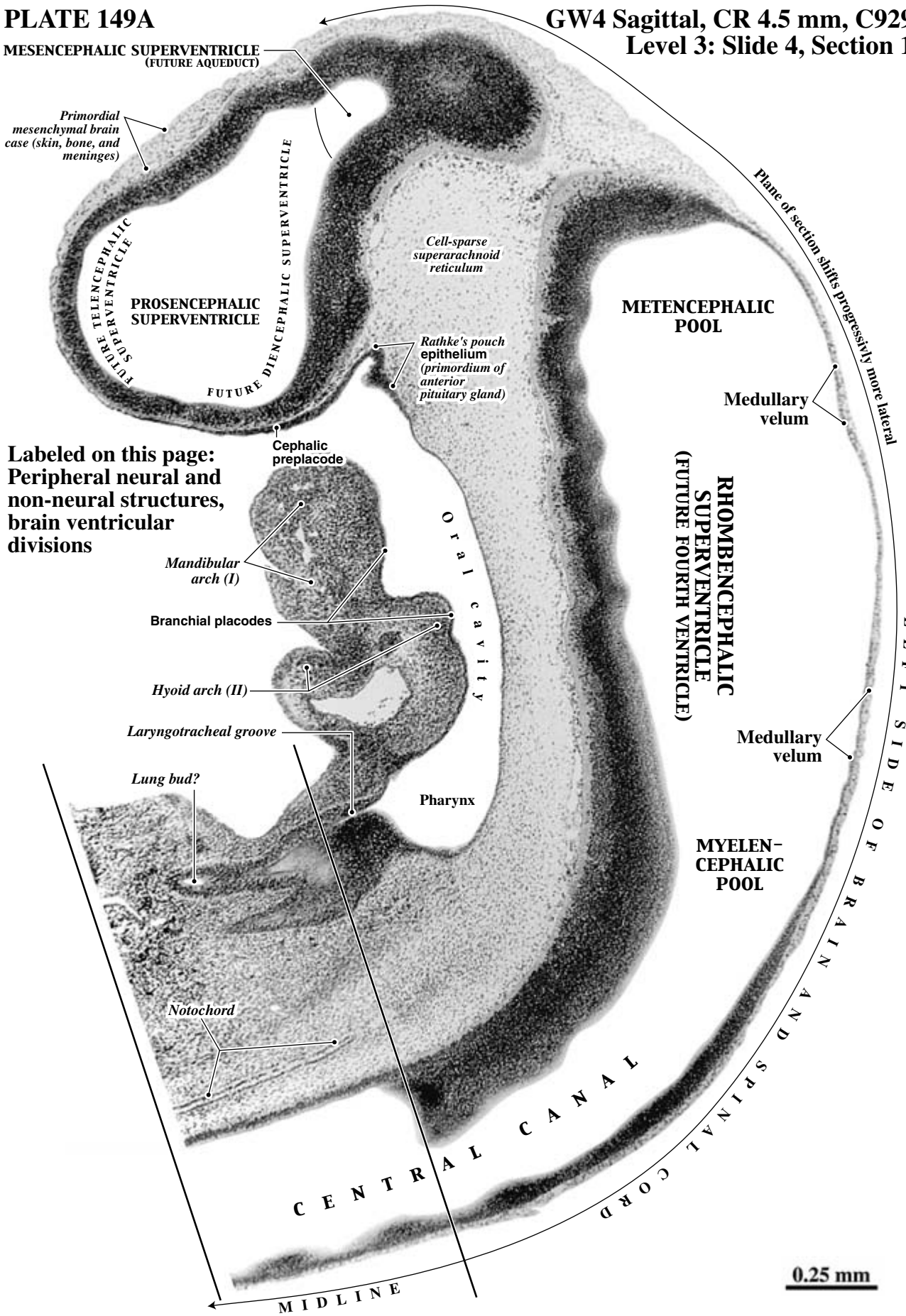
Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Labeled on this page:
Central neural structures

All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

PLATE 149A

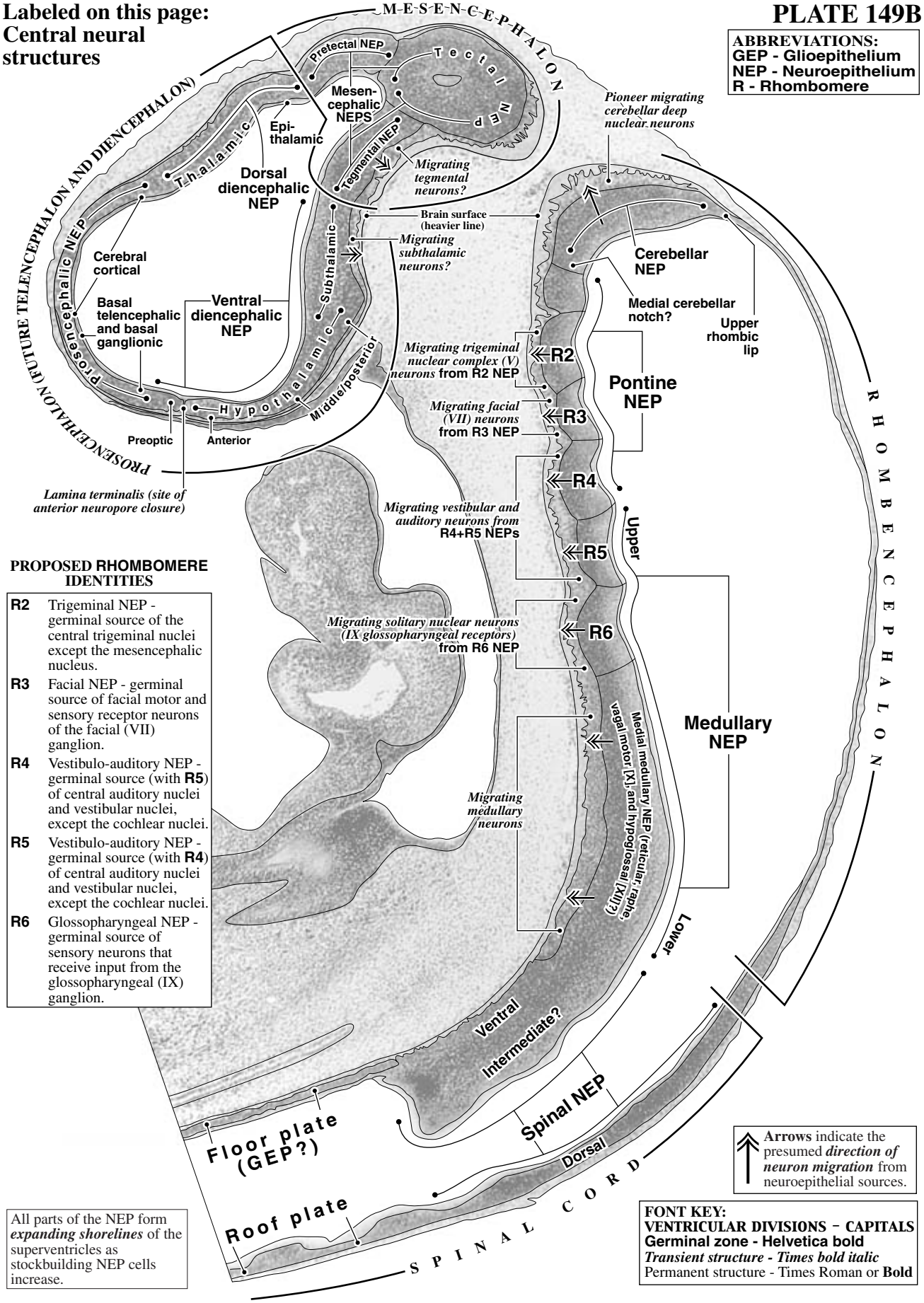
GW4 Sagittal, CR 4.5 mm, C9297
Level 3: Slide 4, Section 16



Labeled on this page:
Central neural structures

PLATE 149B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

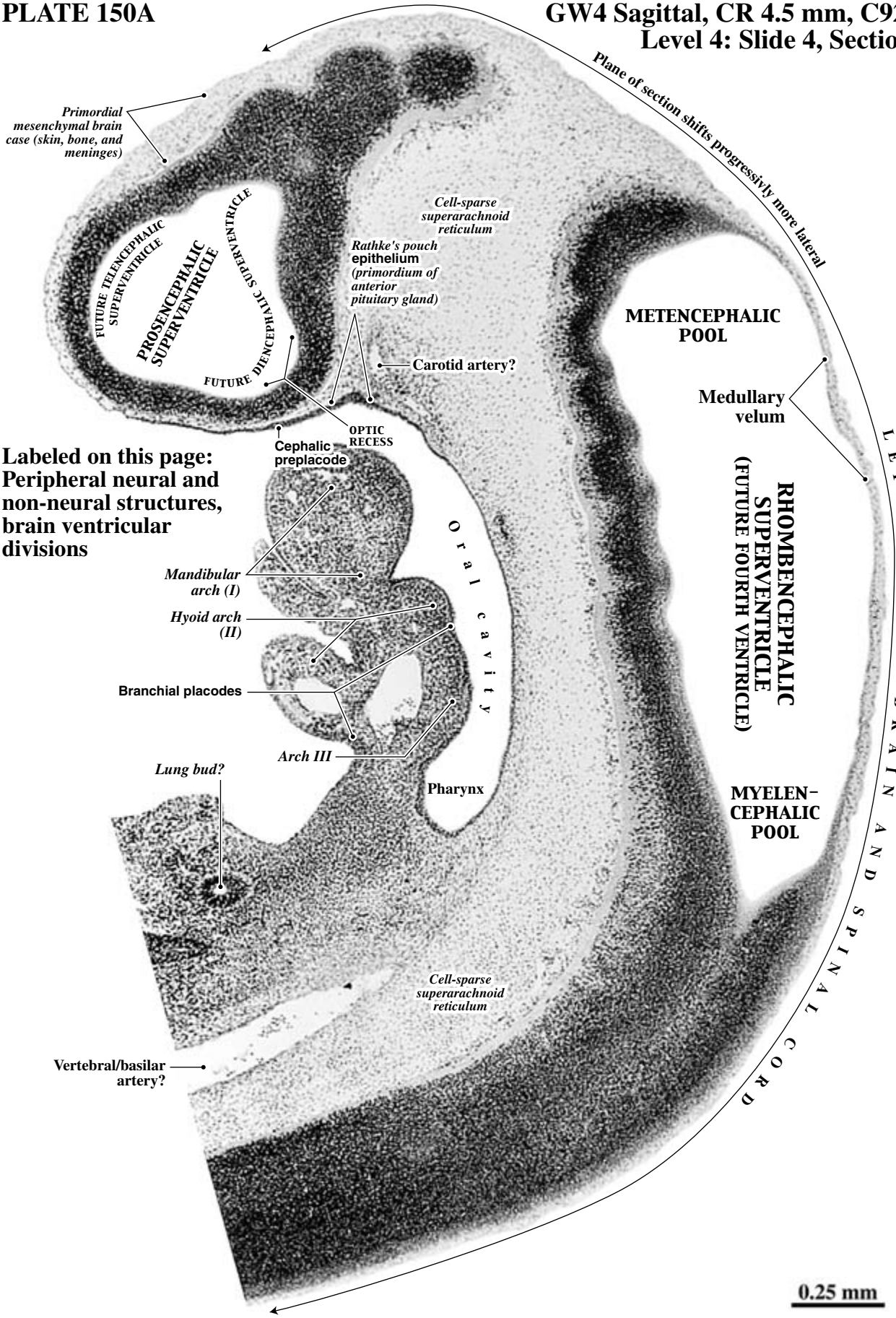
All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 150A

GW4 Sagittal, CR 4.5 mm, C9297
Level 4: Slide 4, Section 8

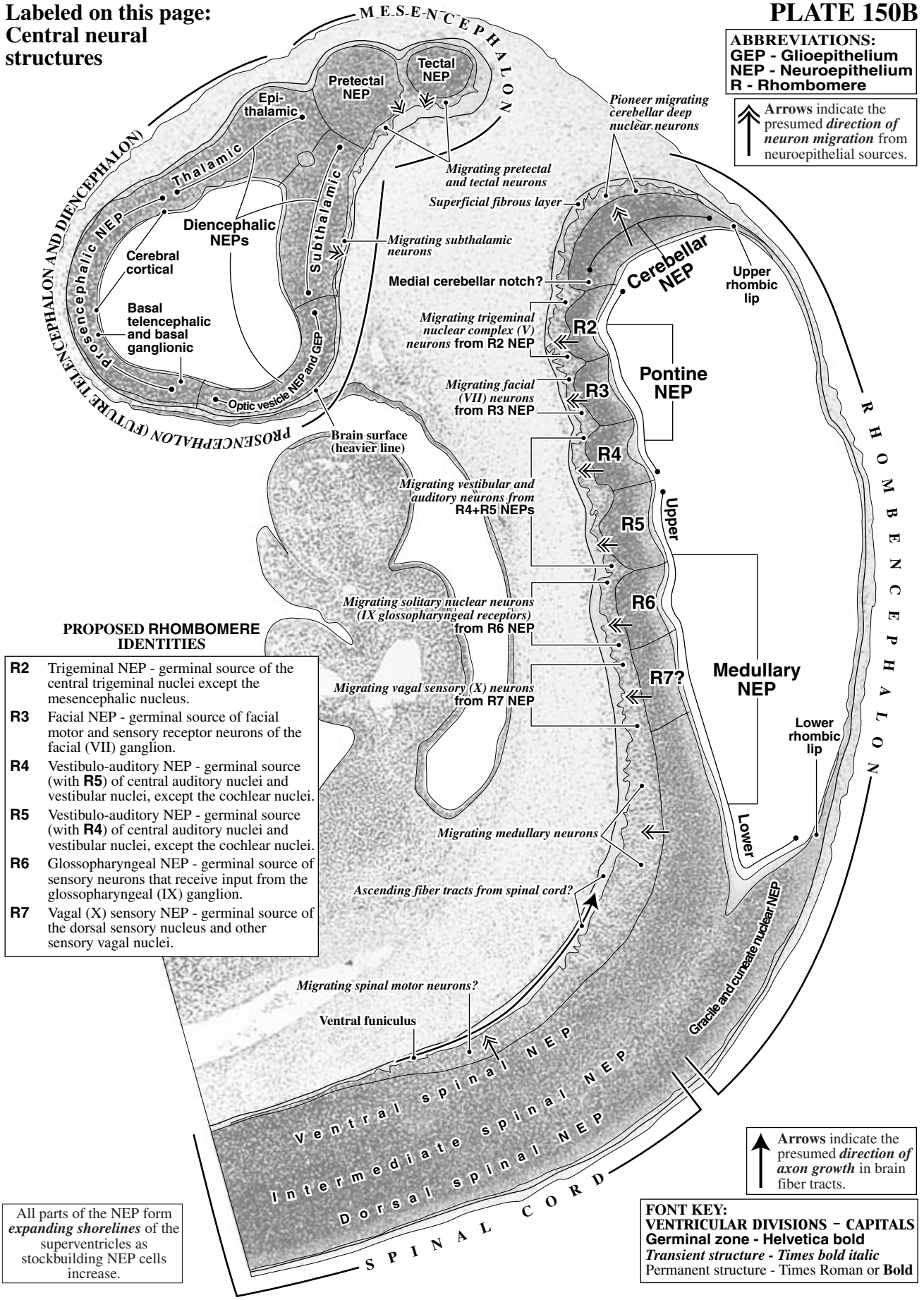


Labeled on this page:
Central neural structures

PLATE 150B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

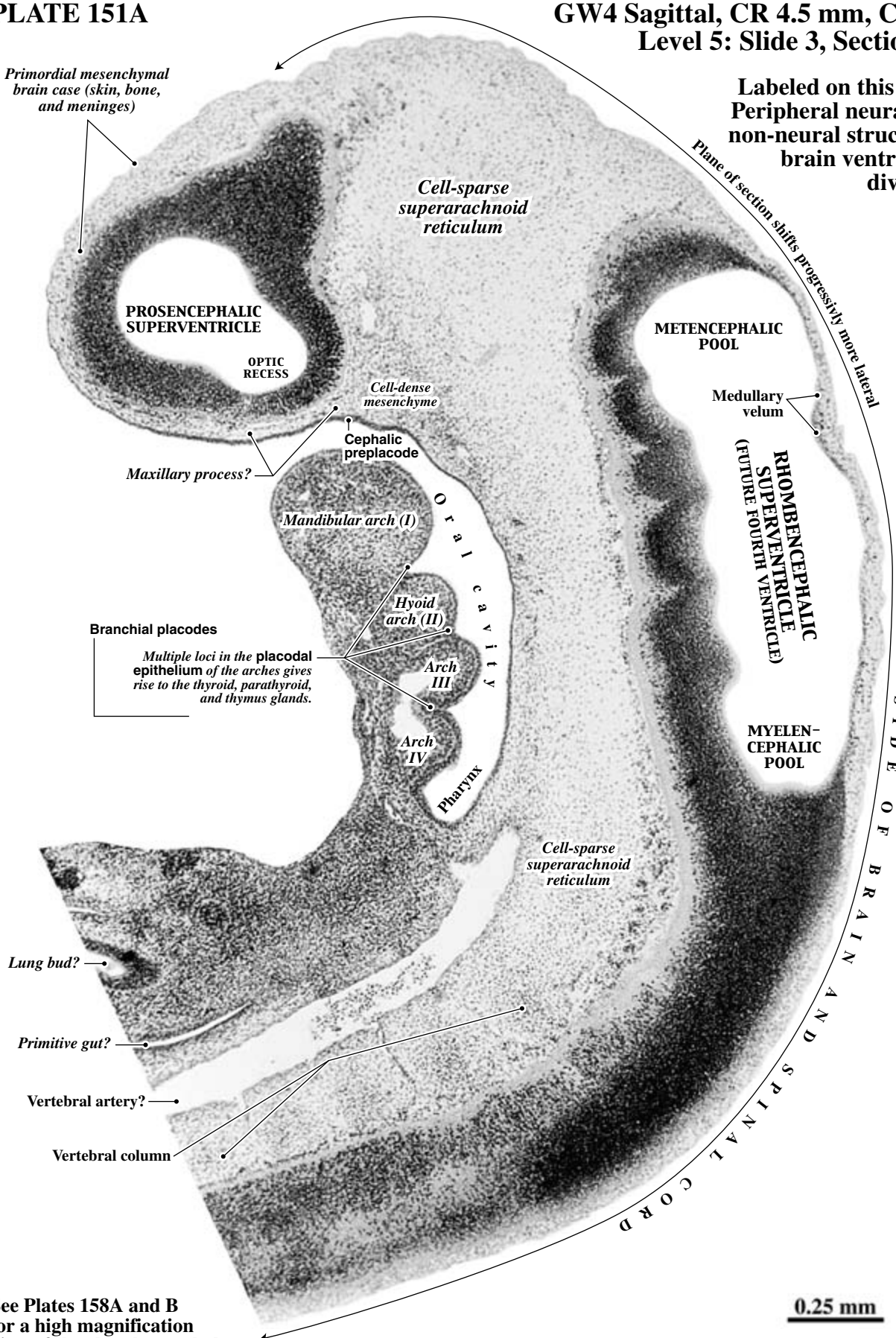
Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 151A

GW4 Sagittal, CR 4.5 mm, C9297
Level 5: Slide 3, Section 40

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



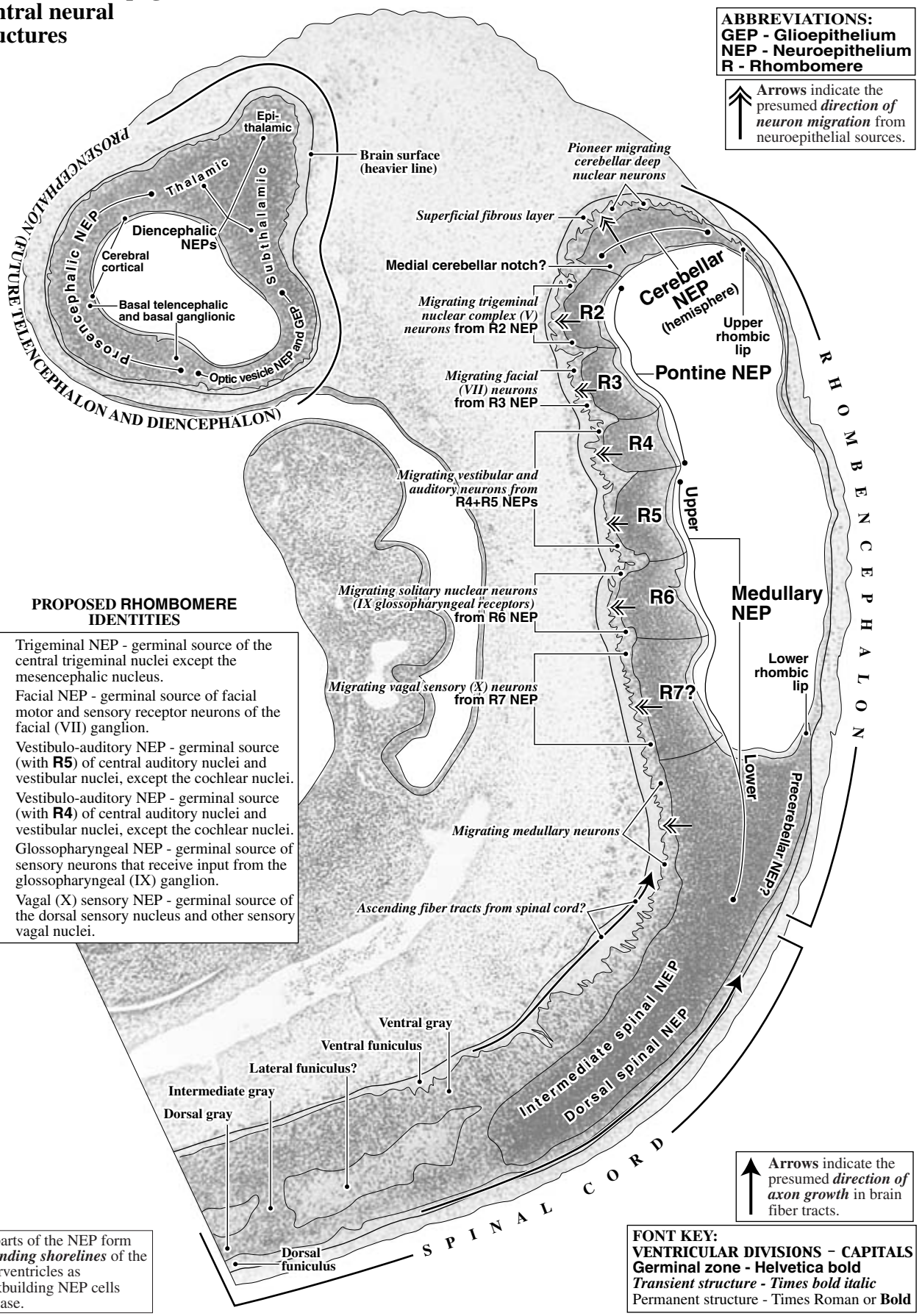
See Plates 158A and B for a high magnification view of the rhombencephalon.

Labeled on this page:
Central neural structures

PLATE 151B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

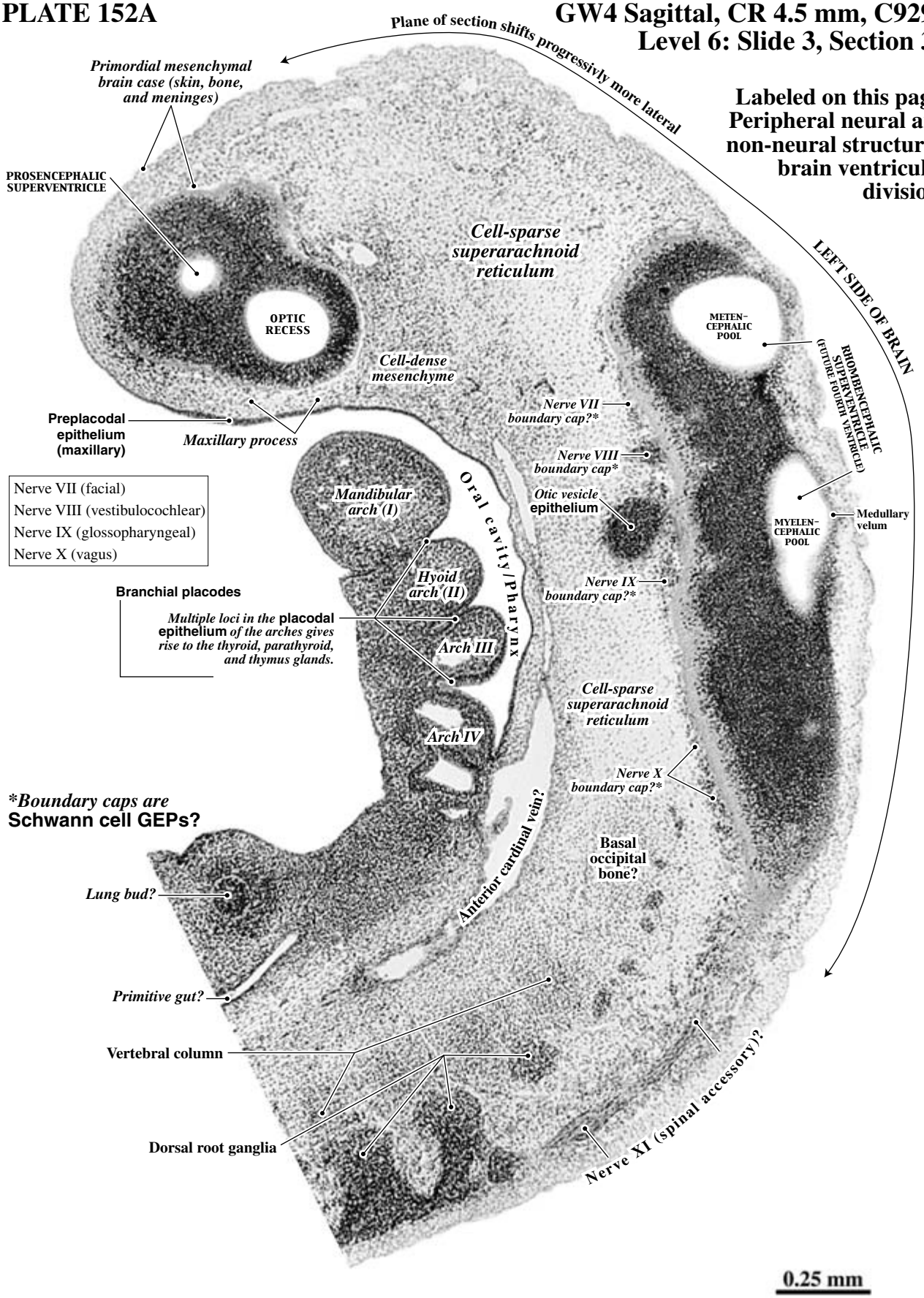
Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 152A

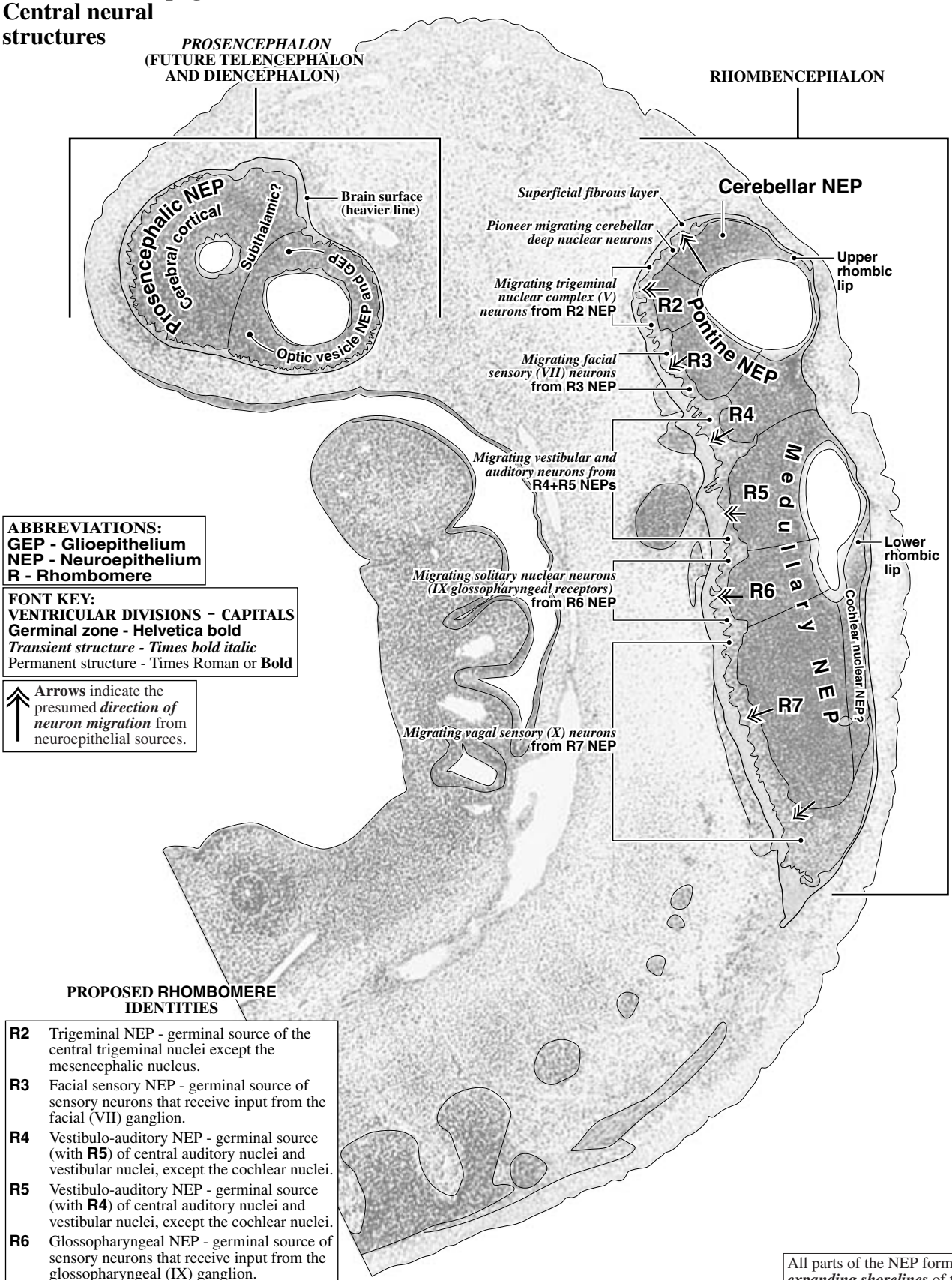
GW4 Sagittal, CR 4.5 mm, C9297
Level 6: Slide 3, Section 32

Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions



Labeled on this page:
Central neural structures

PLATE 152B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PROPOSED RHOMBOMERE IDENTITIES

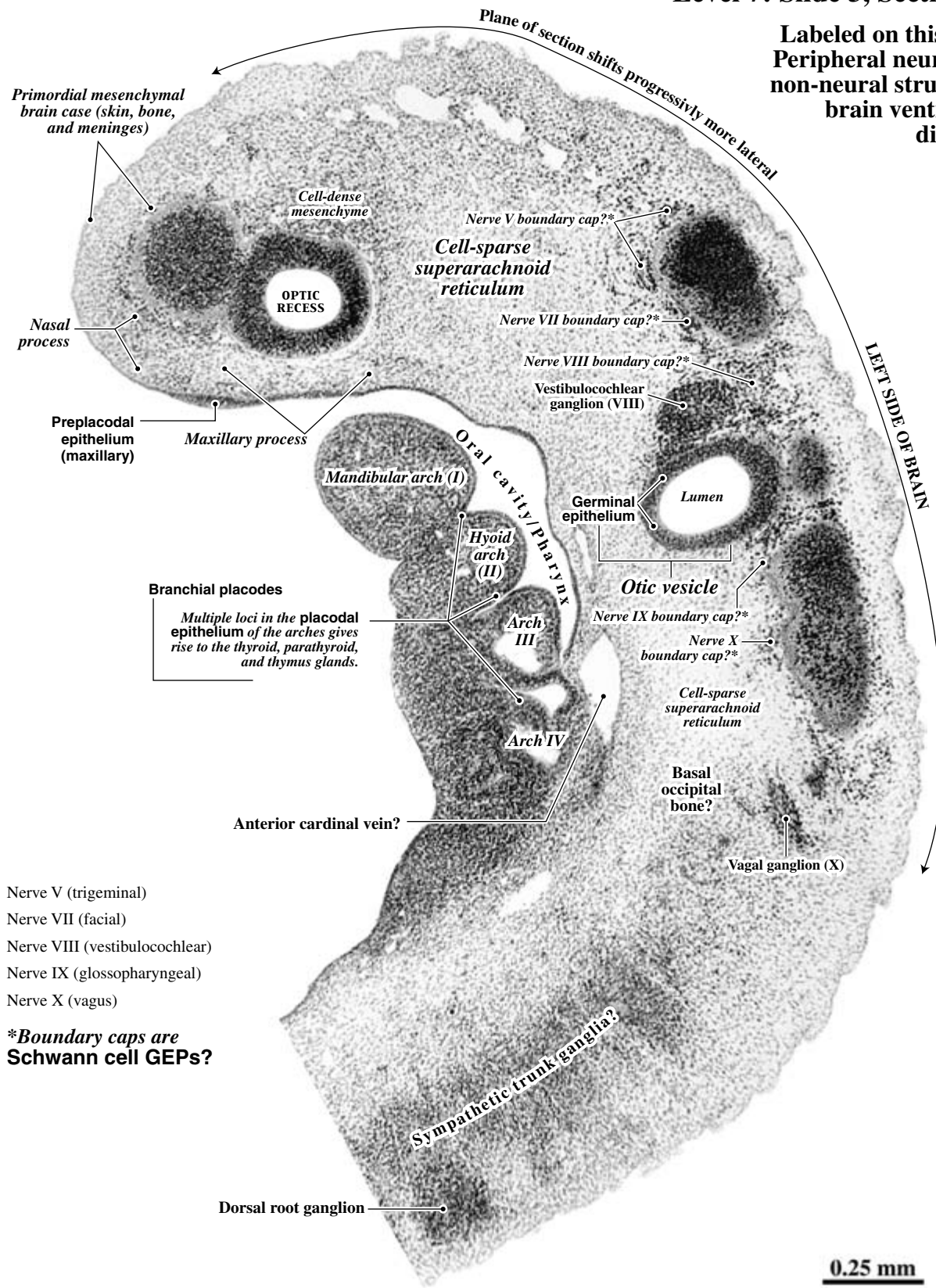
R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

PLATE 153A

GW4 Sagittal, CR 4.5 mm, C9297
Level 7: Slide 3, Section 24

Labeled on this page: Peripheral neural and non-neural structures, brain ventricular divisions



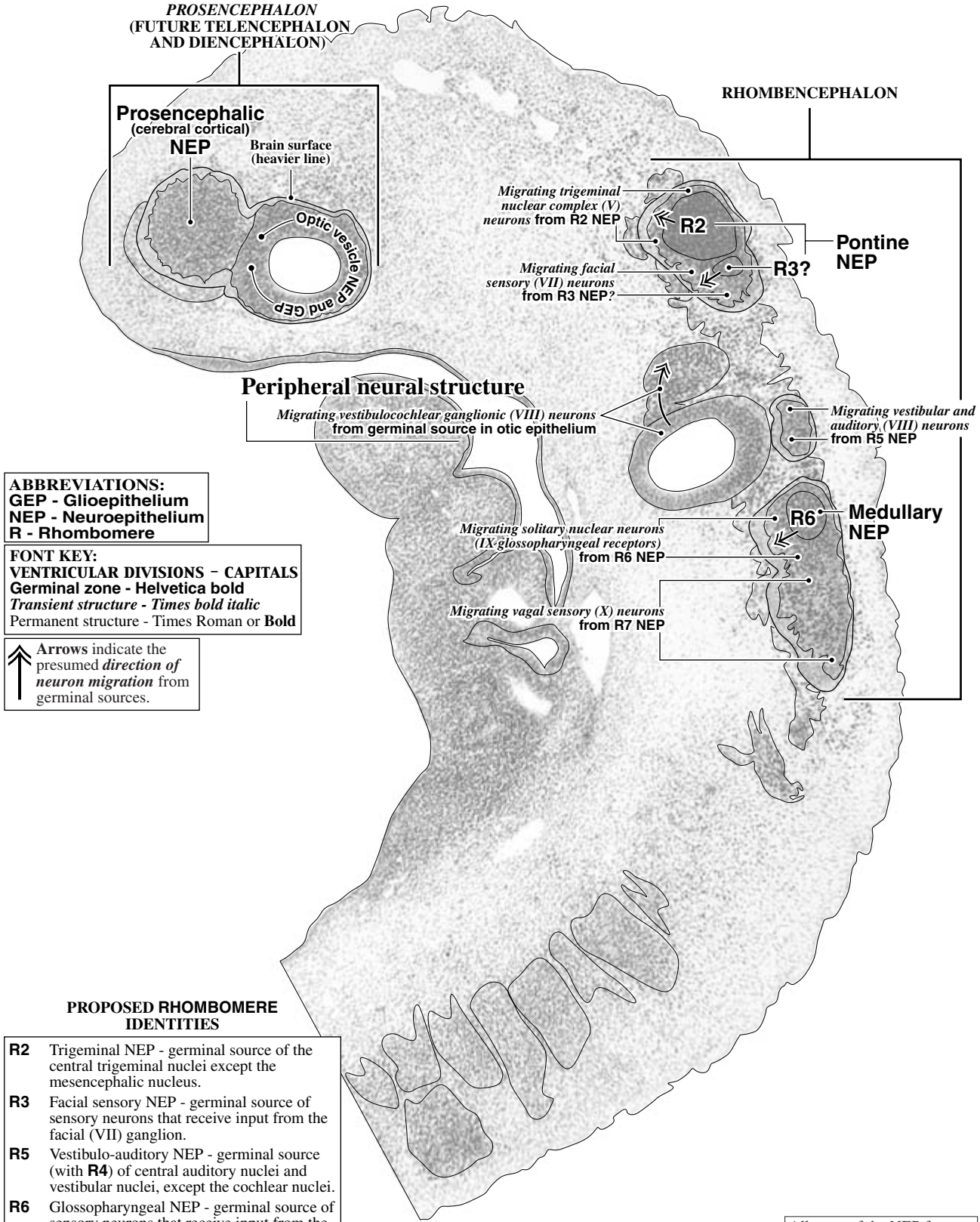
Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Nerve X (vagus)

***Boundary caps are Schwann cell GEPs?**

See a higher magnification view of the rhombencephalon in Plates 159A and B.

Labeled on this page:
Central neural structures

PLATE 153B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PROPOSED RHOMBOMERE IDENTITIES

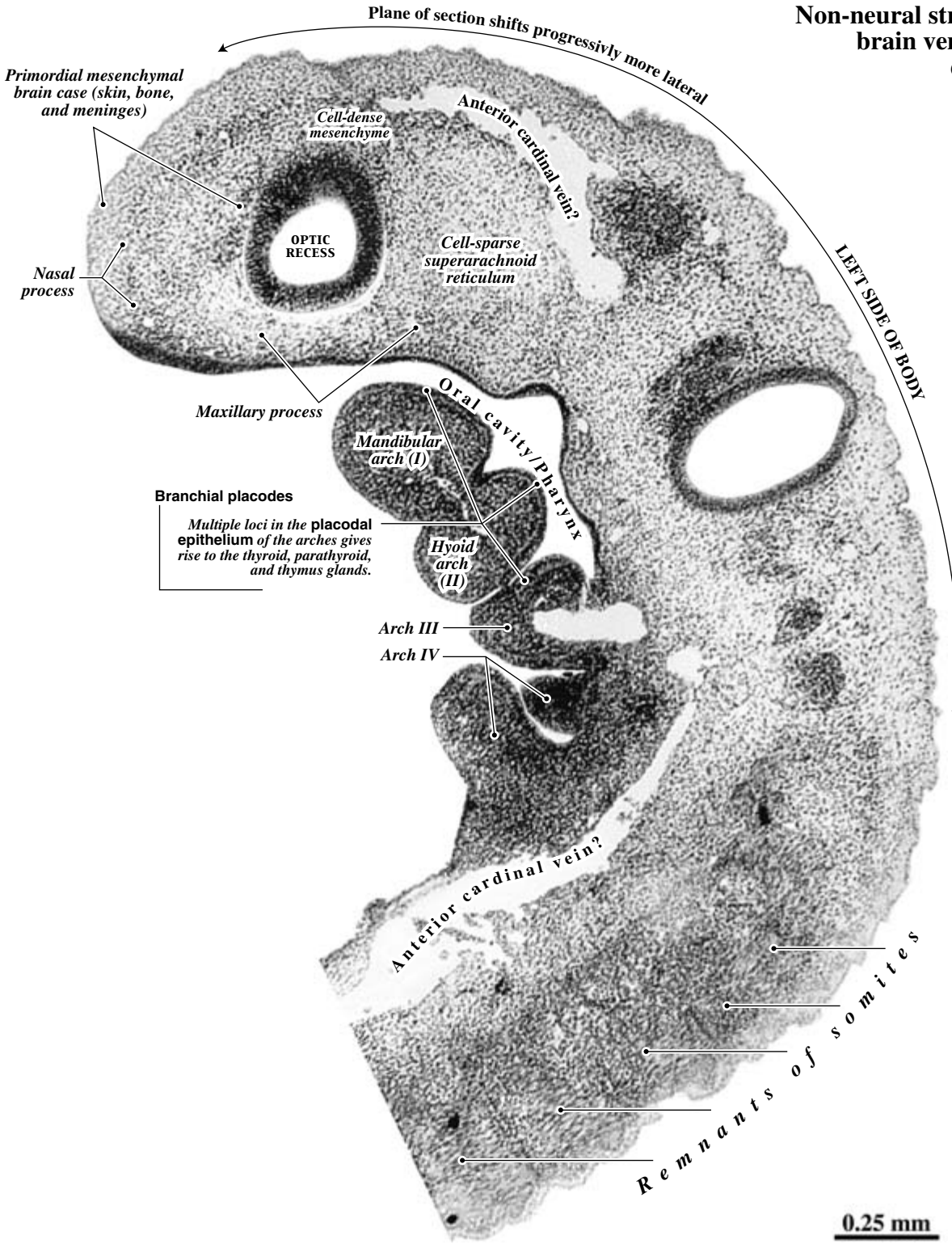
R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

All parts of the NEP form ***expanding shorelines*** of the superventricles as stockbuilding NEP cells increase.

PLATE 154A

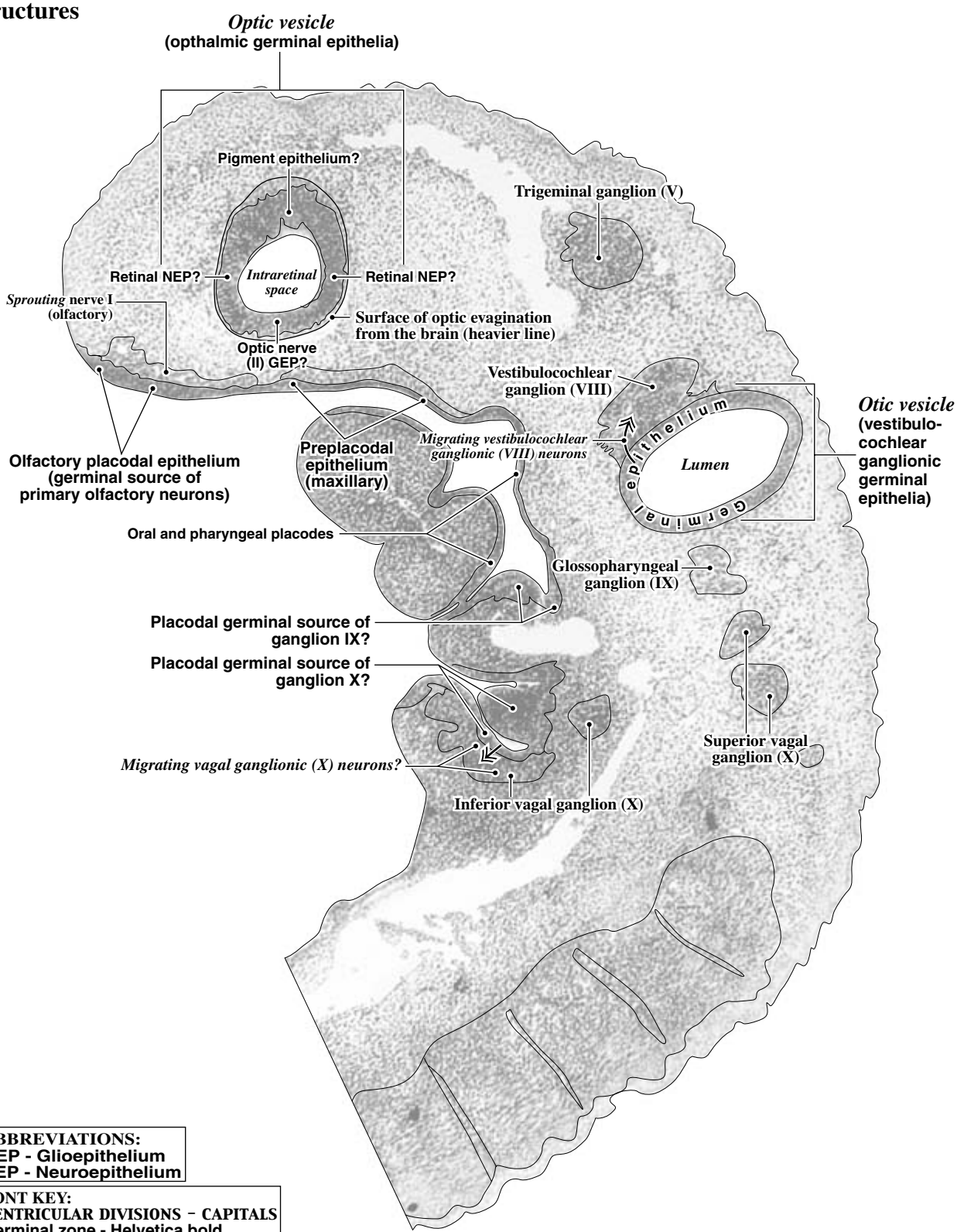
GW4 Sagittal, CR 4.5 mm, C9297
Level 8: Slide 3, Section 16

Labeled on this page:
Non-neural structures, brain ventricular divisions



Labeled on this page:
Peripheral neural structures

PLATE 154B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

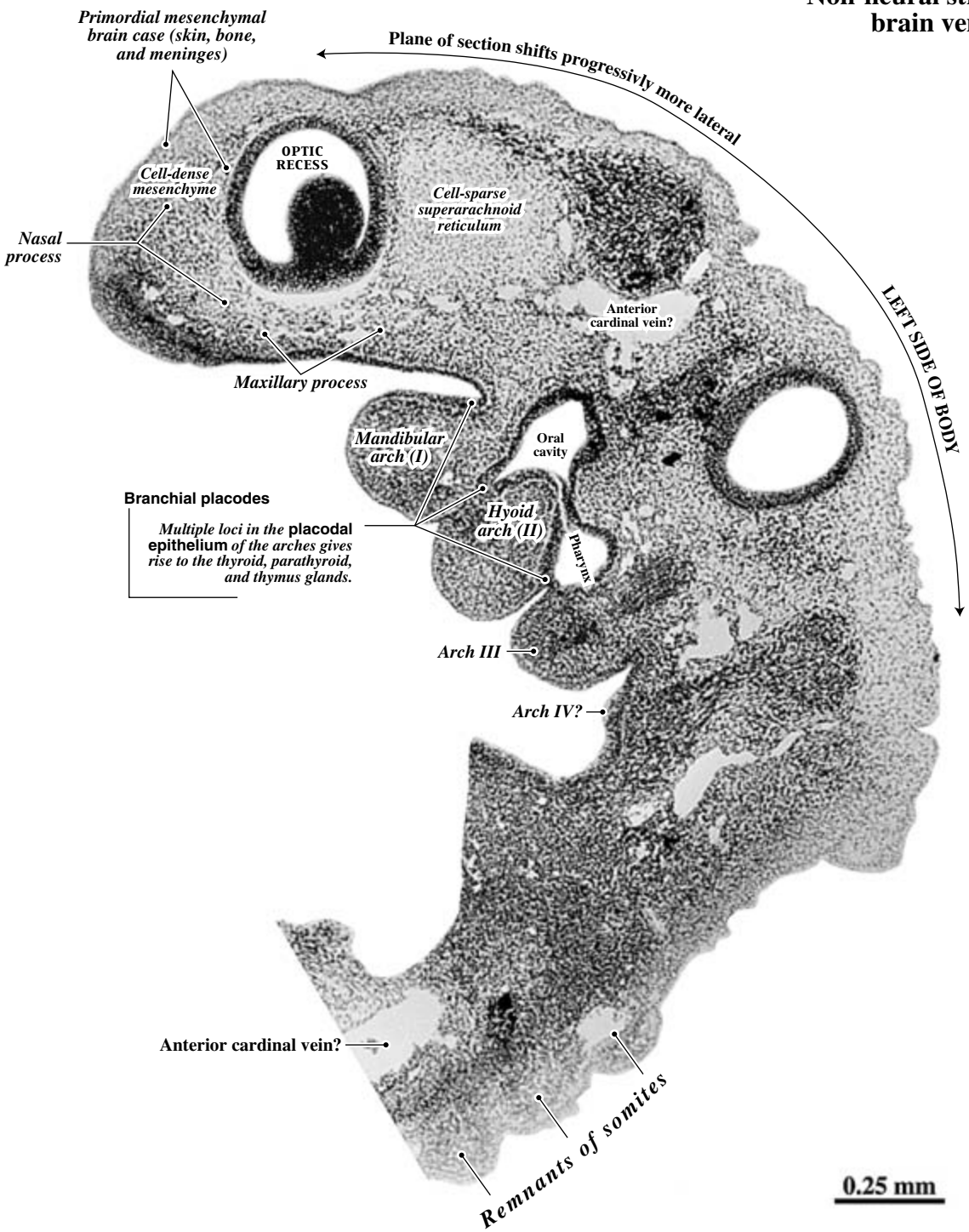
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PLATE 155A

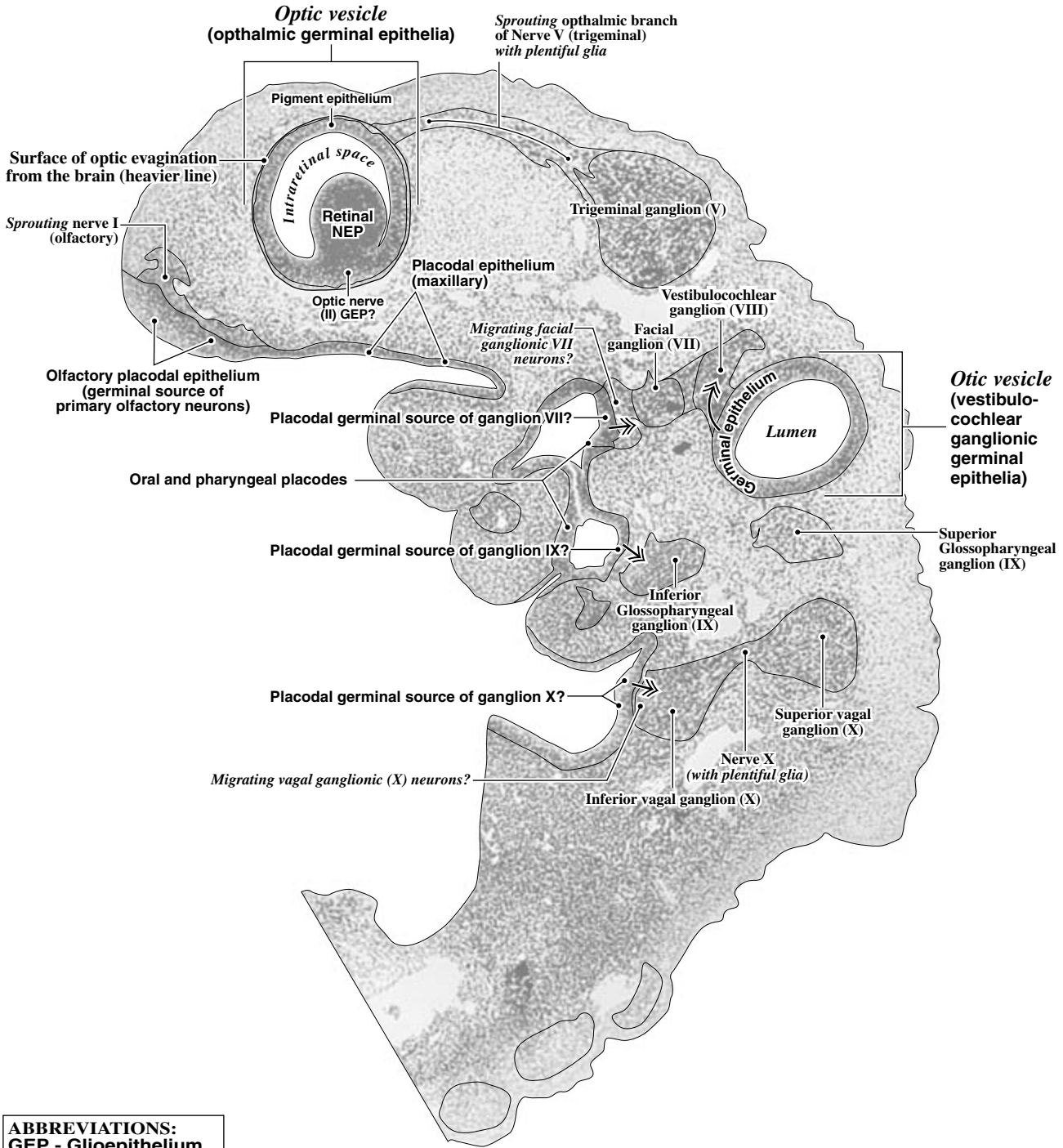
GW4 Sagittal, CR 4.5 mm, C9297
Level 9: Slide 3, Section 8

Labeled on this page:
Non-neural structures, brain ventricular divisions



Labeled on this page:
Peripheral neural structures

PLATE 155B



ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

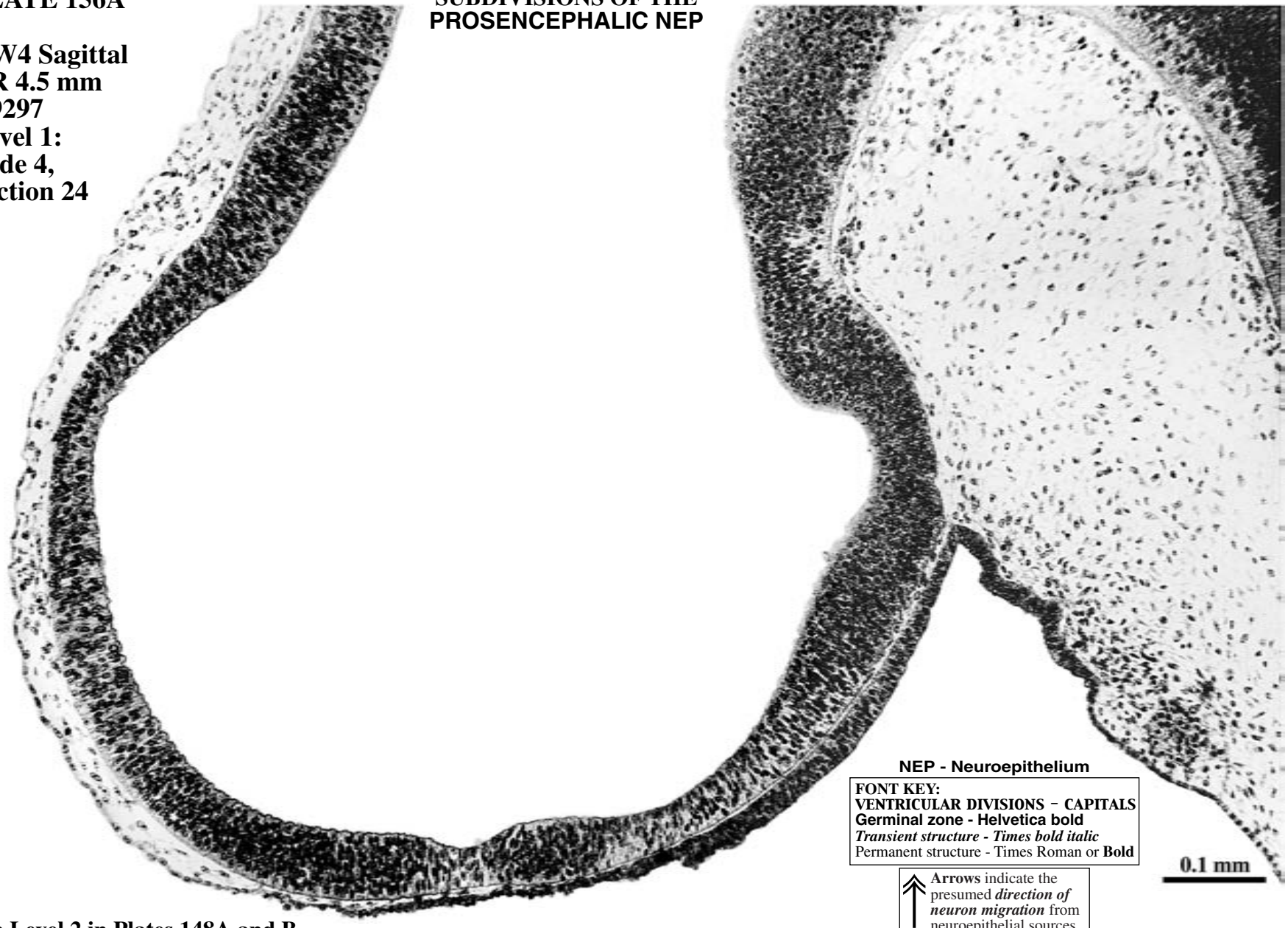
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

PLATE 156A

GW4 Sagittal
CR 4.5 mm
C9297
Level 1:
Slide 4,
Section 24

SUBDIVISIONS OF THE PROSENCEPHALIC NEP



See Level 2 in Plates 148A and B.

PLATE 156B

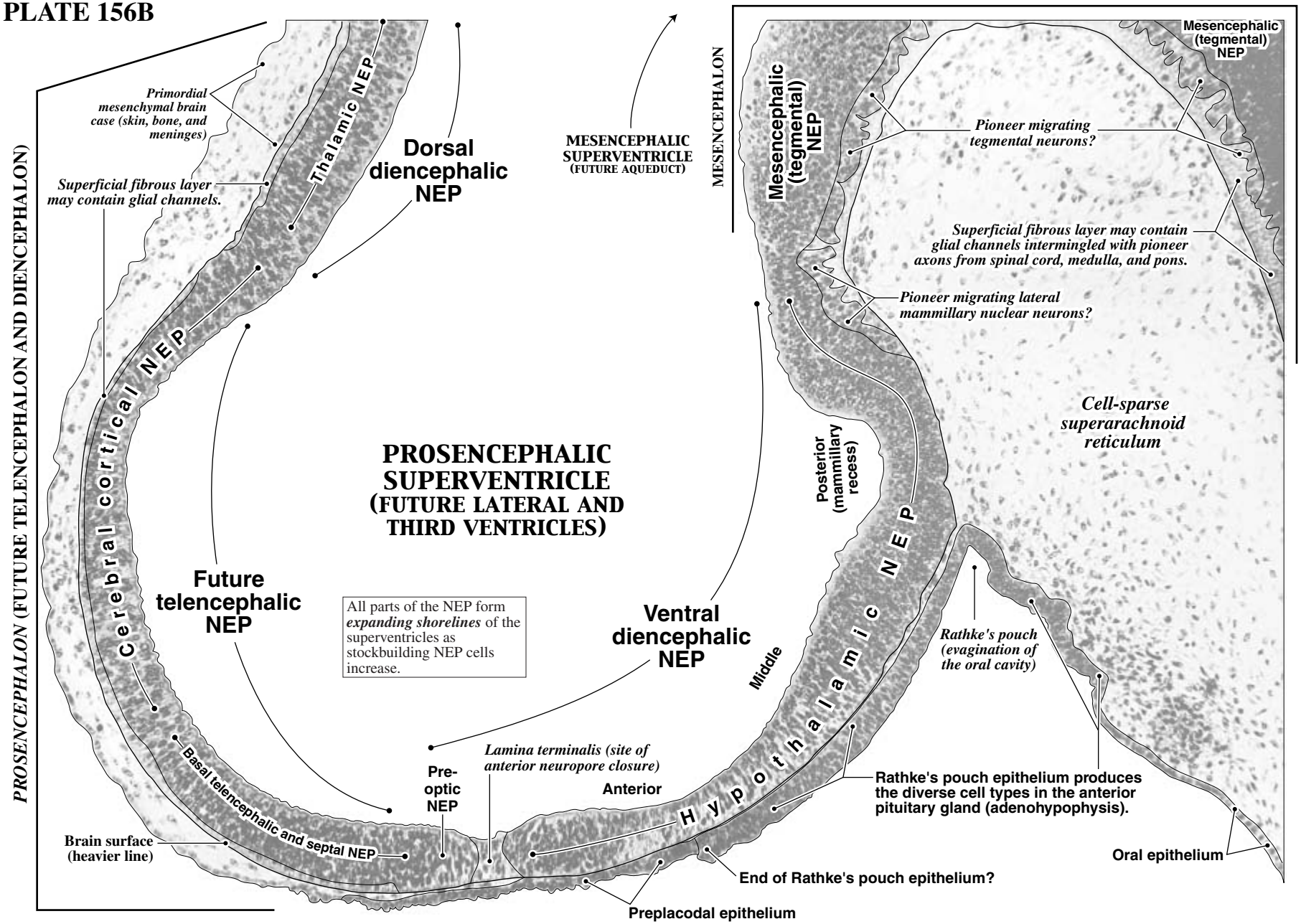
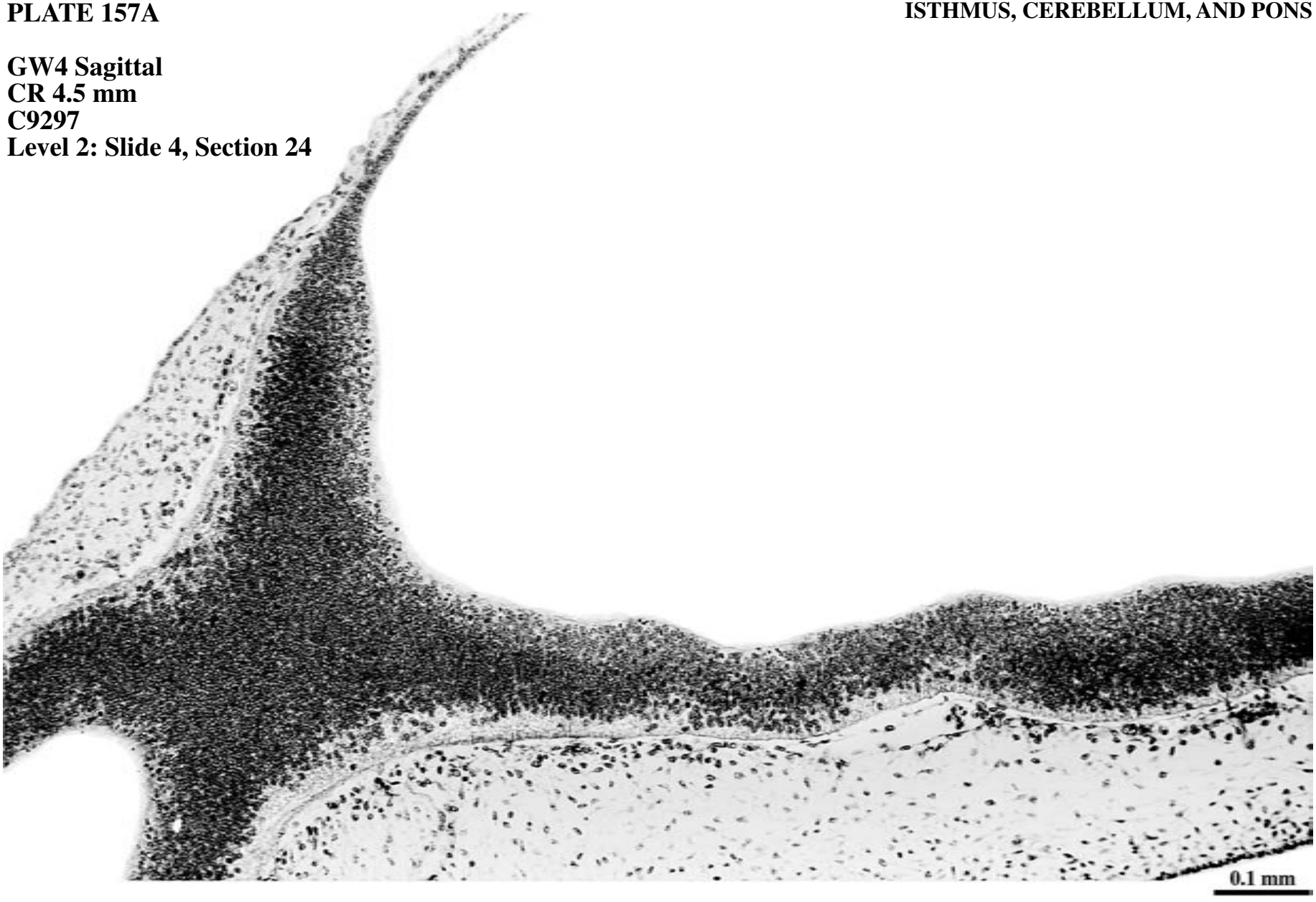

PROSENCEPHALON (FUTURE TELENCEPHALON AND DIENCEPHALON)
MESENCEPHALON
Primordial mesenchymal brain case (skin, bone, and meninges)
Superficial fibrous layer may contain glial channels.
Thalamic NEP
Dorsal diencephalic NEP
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Mesencephalic (tegmental) NEP
Pioneer migrating tegmental neurons?
Superficial fibrous layer may contain glial channels intermingled with pioneer axons from spinal cord, medulla, and pons.
Pioneer migrating lateral mammillary nuclear neurons?
Cell-sparse superarachnoid reticulum
Cerebral cortical NEP
PROSENCEPHALIC SUPERVENTRICLE (FUTURE LATERAL AND THIRD VENTRICLES)
Posterior (mammillary recess)
Hypothalamic NEP
Future telencephalic NEP
All parts of the NEP form expanding shorelines of the superventricles as stockbuilding NEP cells increase.
Ventral diencephalic NEP
Middle
Rathke's pouch (evagination of the oral cavity)
Lamina terminalis (site of anterior neuropore closure)
Pre-optic NEP
Anterior
Basal telencephalic and septal NEP
Rathke's pouch epithelium produces the diverse cell types in the anterior pituitary gland (adenohypophysis).
Brain surface (heavier line)
Oral epithelium
End of Rathke's pouch epithelium?
Preplacodal epithelium

PLATE 157A

GW4 Sagittal
CR 4.5 mm
C9297
Level 2: Slide 4, Section 24



See Level 2 in Plates 148A and B.

PLATE 157B

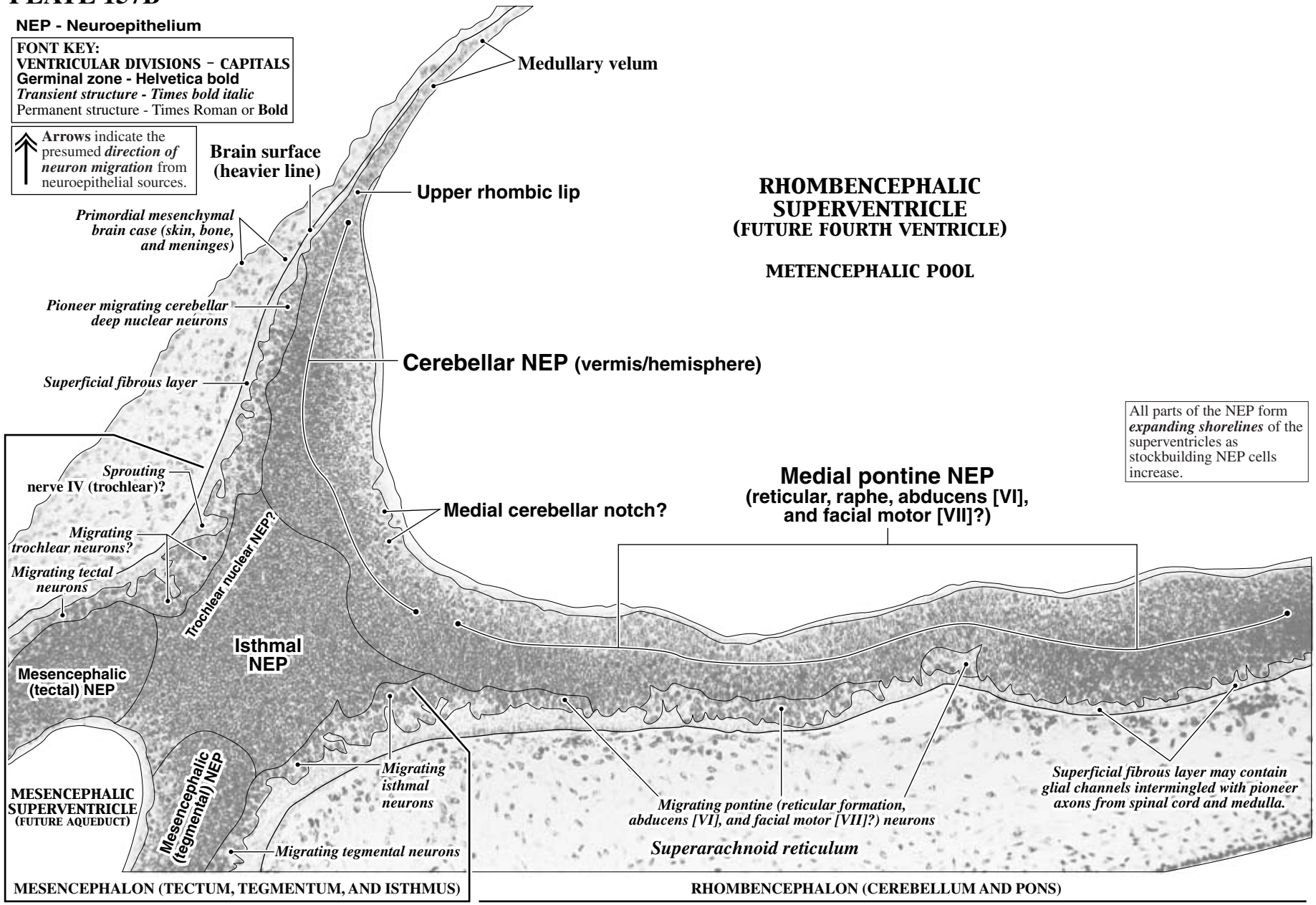
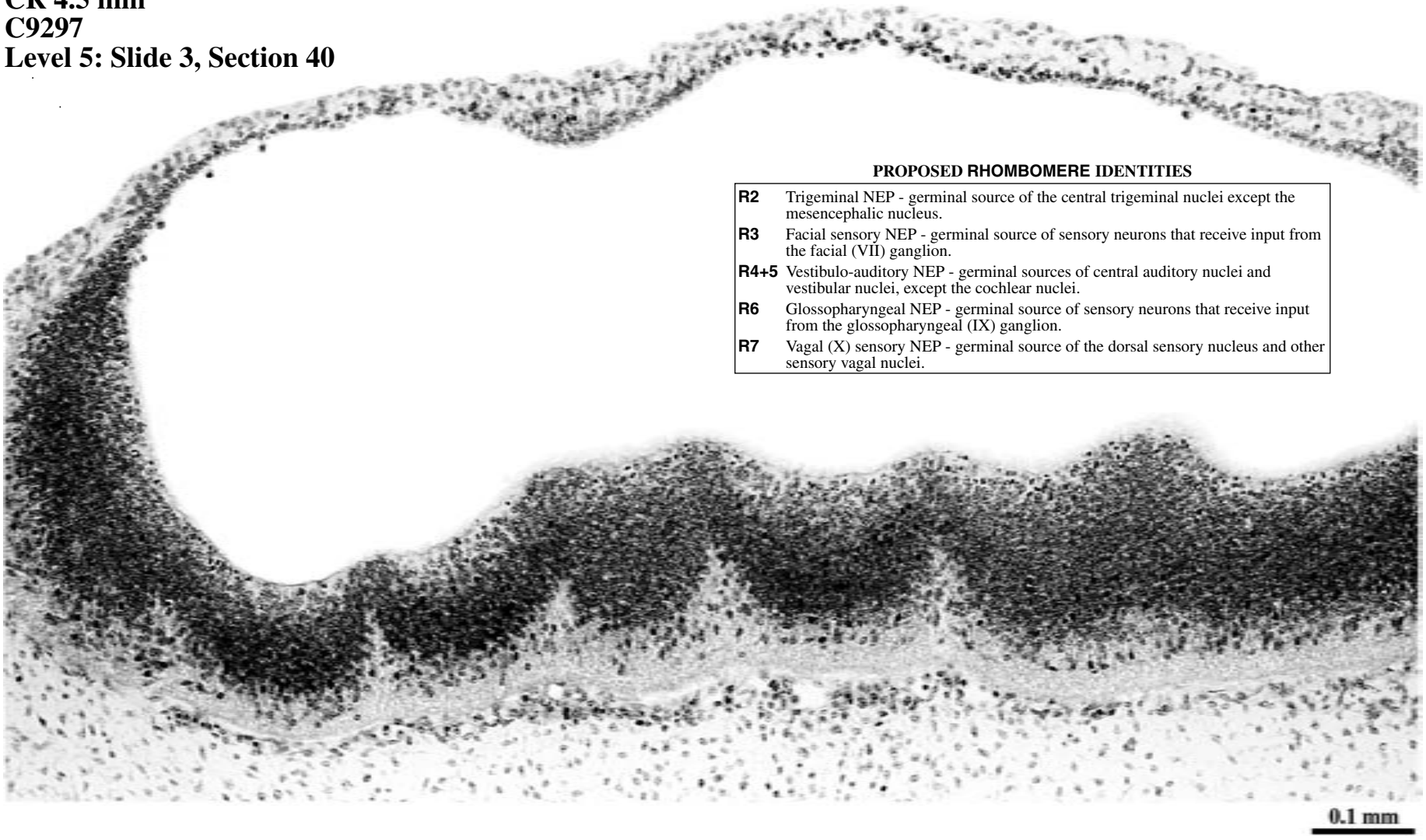

NEP - Neuroepithelium
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Medullary velum
Brain surface (heavier line)
Upper rhombic lip
RHOMBENCEPHALIC SUPERVENTRICLE (FUTURE FOURTH VENTRICLE)
METENCEPHALIC POOL
Primordial mesenchymal brain case (skin, bone, and meninges)
Pioneer migrating cerebellar deep nuclear neurons
Cerebellar NEP (vermis/hemisphere)
Superficial fibrous layer
All parts of the NEP form expanding shorelines of the superventricles as stockbuilding NEP cells increase.
Sprouting nerve IV (trochlear)?
Medial pontine NEP (reticular, raphe, abducens [VI], and facial motor [VII]?)
Medial cerebellar notch?
Migrating trochlear neurons?
Migrating tectal neurons
Trochlear nuclear NEP?
Isthmal NEP
Mesencephalic (tectal) NEP
Mesencephalic (tegmental) NEP
MESENCEPHALIC SUPERVENTRICLE (FUTURE AQUEDUCT)
Migrating isthmal neurons
Migrating tegmental neurons
Migrating pontine (reticular formation, abducens [VI], and facial motor [VII]?) neurons
Superficial fibrous layer may contain glial channels intermingled with pioneer axons from spinal cord and medulla.
Superarachnoid reticulum
MESENCEPHALON (TECTUM, TEGMENTUM, AND ISTHMUS)
RHOMBENCEPHALON (CEREBELLUM AND PONS)

PLATE 158A

RHOMBOMERES IN PONS AND MEDULLA

GW4 Sagittal
CR 4.5 mm
C9297
Level 5: Slide 3, Section 40



See Level 5 in Plates 151A and B.

PLATE 158B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

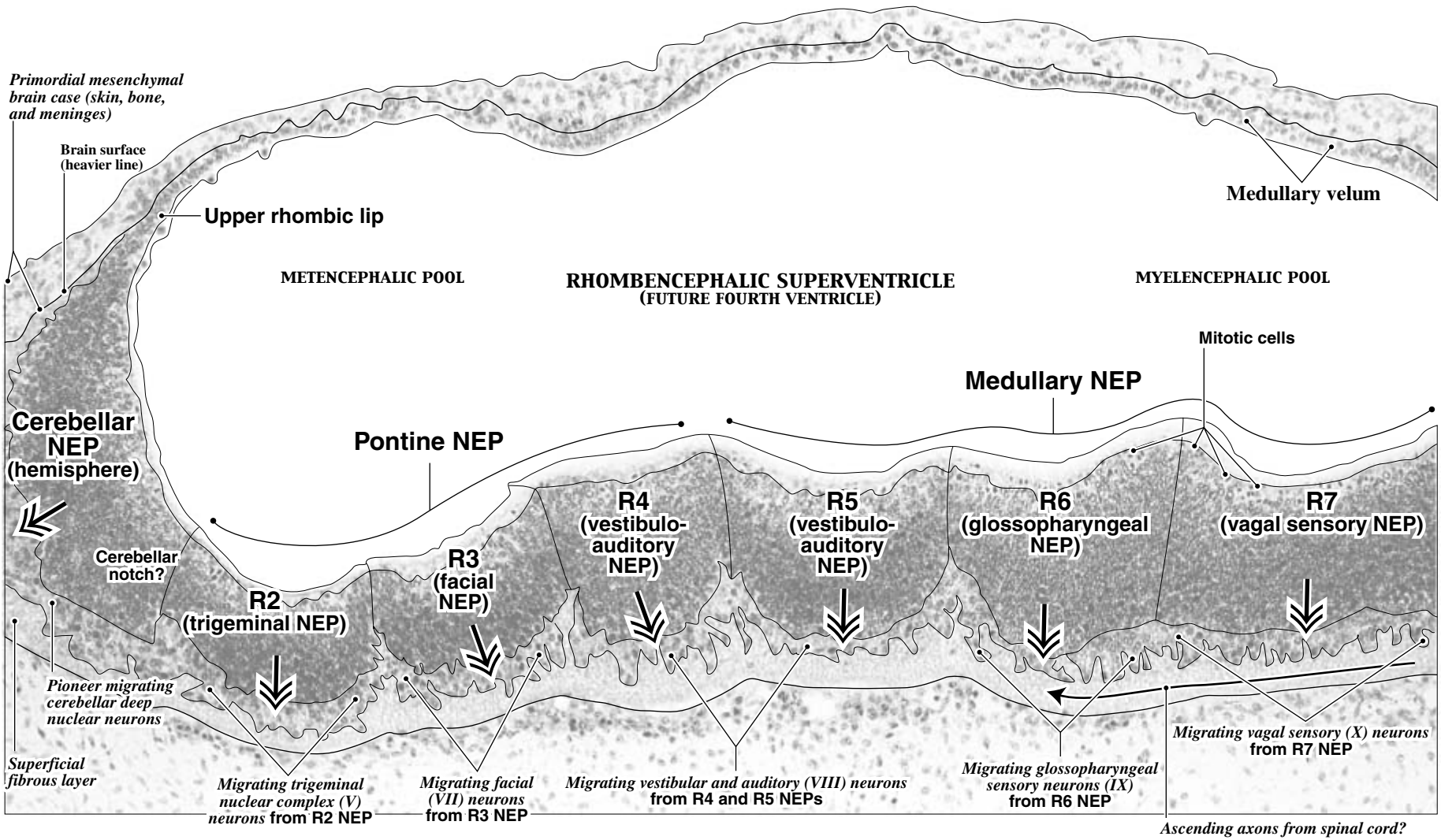
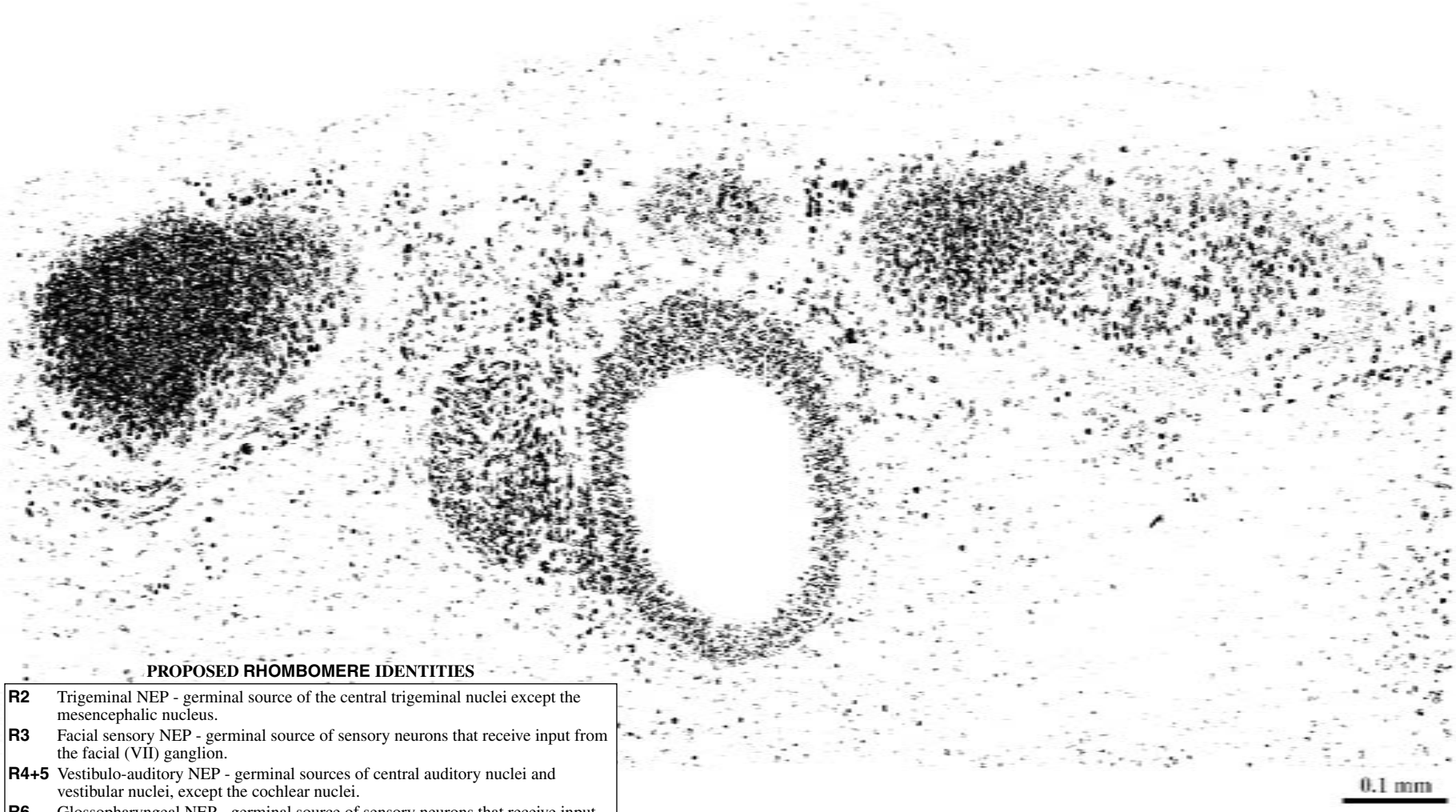


PLATE 159A

GW4 Sagittal, CR 4.5 mm, C9297
Level 7: Slide 3, Section 24

See Level 7 in Plates 153A and B.



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial sensory NEP - germinal source of sensory neurons that receive input from the facial (VII) ganglion.
R4+5	Vestibulo-auditory NEP - germinal sources of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

PLATE 159B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

Note that R4, R5, and R7 NEPs are not in the plane of this section.

Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Nerve X (vagus)

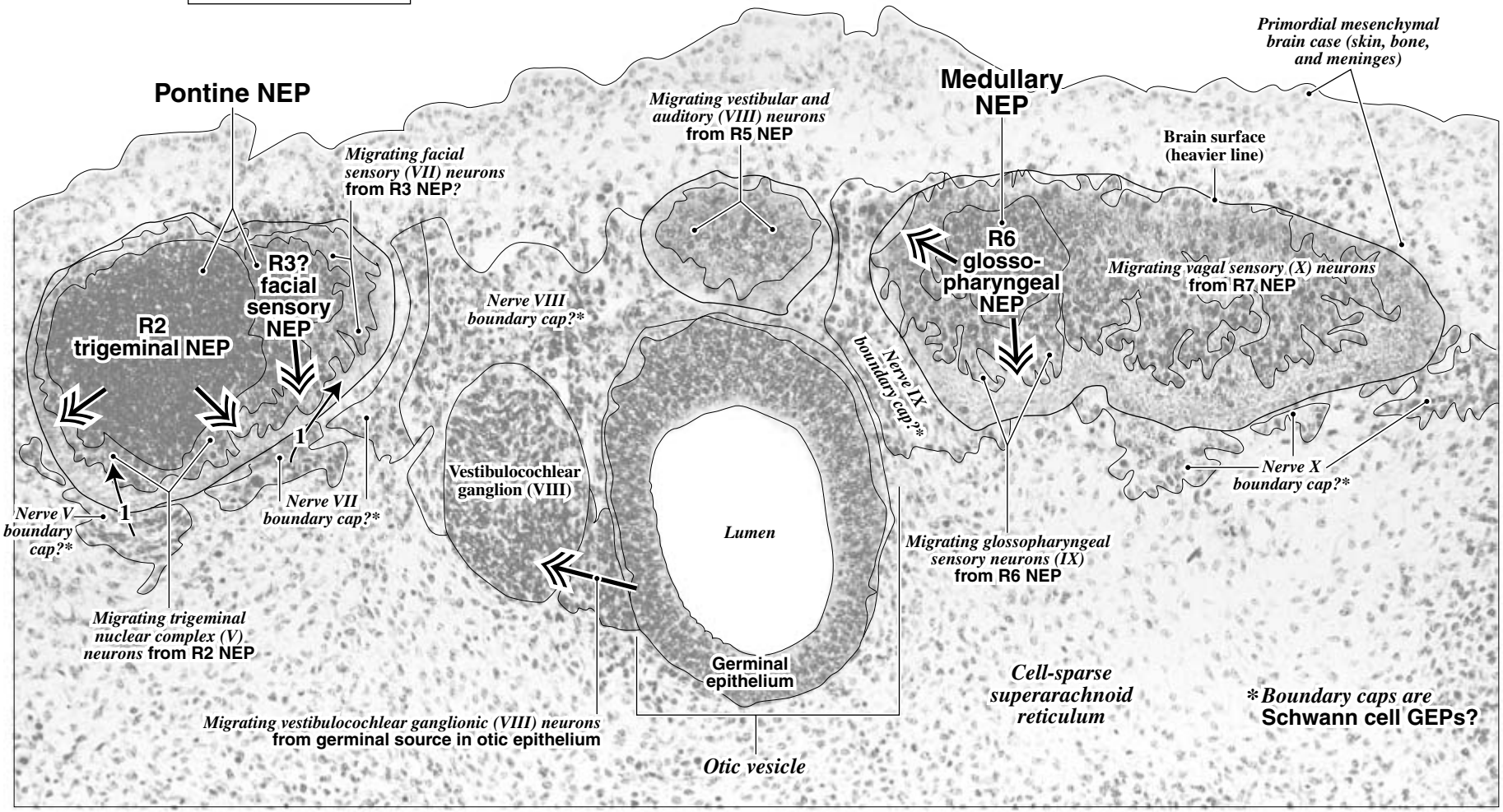
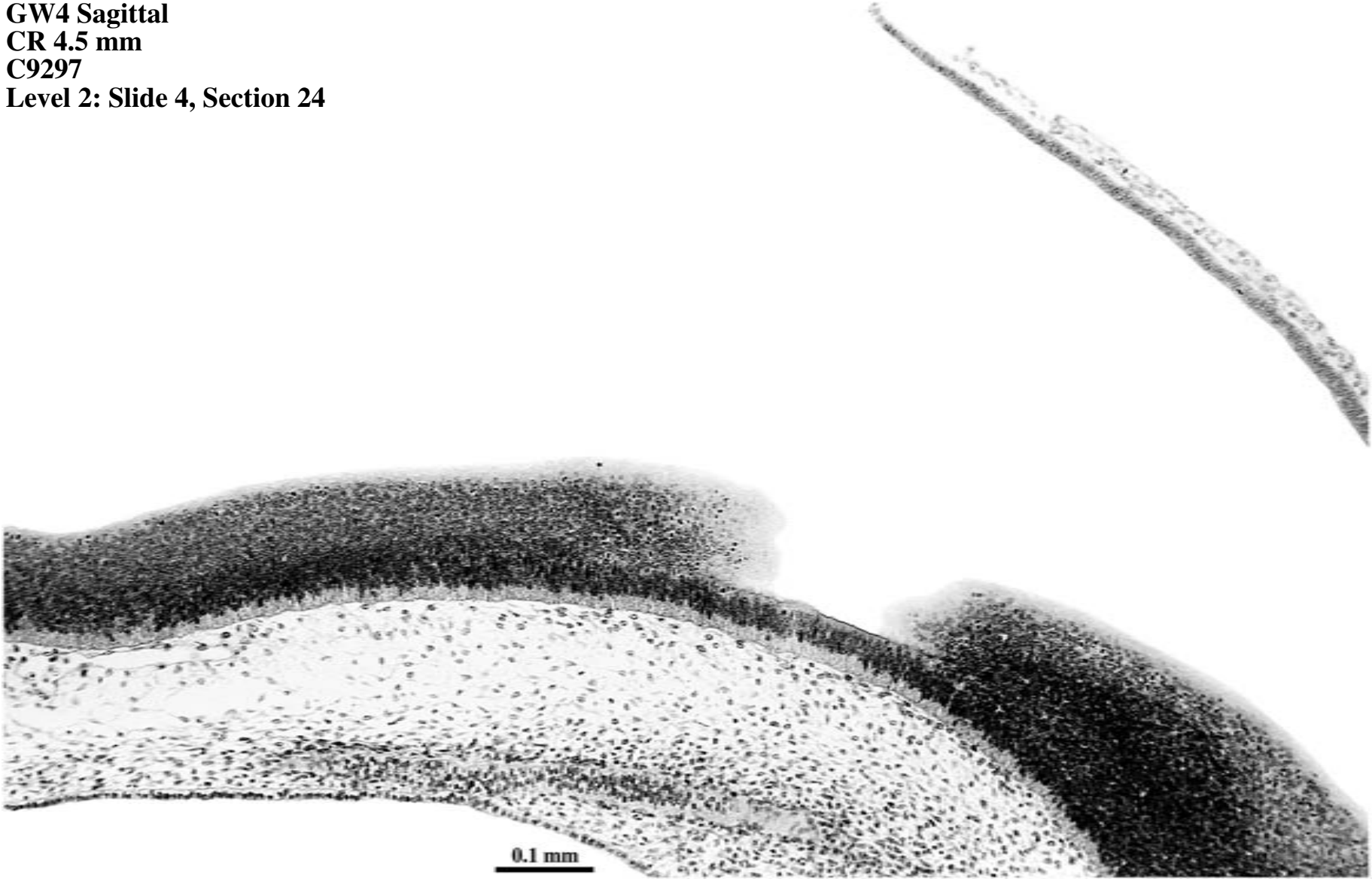


PLATE 160A

LOWER MEDULLA AND SPINAL CORD
(MIDLINE RAPHE GLIAL STRUCTURE)

GW4 Sagittal
CR 4.5 mm
C9297
Level 2: Slide 4, Section 24



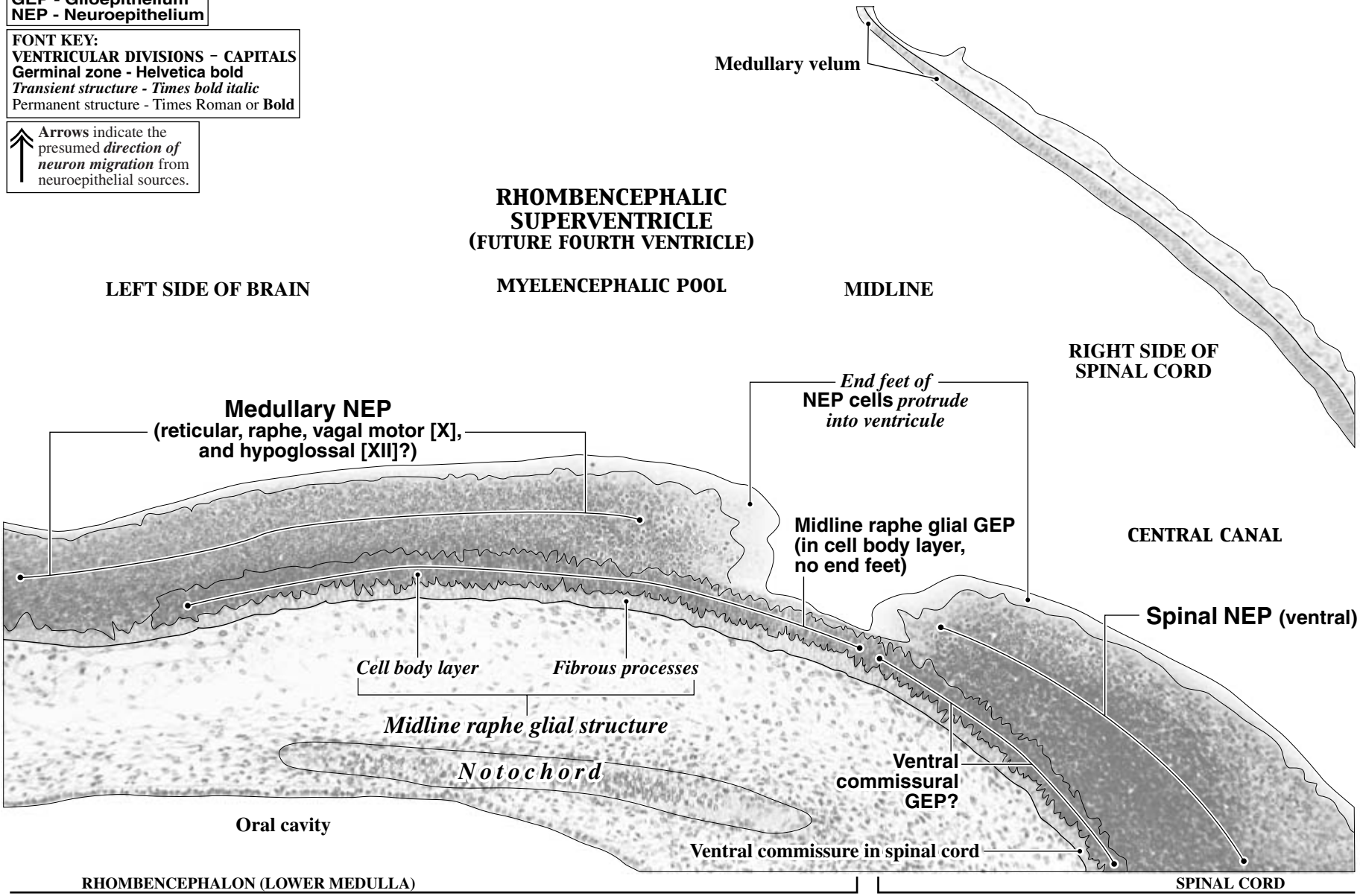
See Level 2 in Plates 148A and B.

PLATE 160B

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.



PART XIII: GW4 CORONAL

Carnegie Collection specimen #836 (designated here as C836) with a 4-mm crown-rump length (CR) is estimated to be at gestational week (GW) 4. C836 was fixed in corrosive acetic acid, embedded in paraffin, and was cut in 15-µm transverse sections that were stained with aluminum cochineal. Sections of the prosencephalon and anterior mesencephalon are cut in the coronal plane, but the plane shifts to predominantly horizontal in the posterior mesencephalon, pons, and medulla. We photographed 36 sections at low magnification from the frontal prominence to the posterior tips of the mesencephalon and medulla. Twelve of these sections are illustrated in **Plates 161AB to 171AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of C836's brain and optic vesicle (**Figure 12**), and to show each illustrated section *in situ* (*insets,* **Plates 161A to 171A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures.

The prosencephalon is considerably smaller than at GW4.5 (**Part XI**) and consists of a stockbuilding neuroepithelium surrounding a small prosencephalic superventricle with paired optic recesses. Anterior sections are tentatively identified as future telencephalic neuroepithelium and include the semicircular olfactory placodes at the embryonic surface. The diencephalic neuroepithelium is located in-between and posterior to the large pair of optic vesicles that form the most prominent prosencephalic feature. A preplacodal epithelium is in the head around the optic vesicles, but a definite lens placode cannot be identified. The preplacodal epithelium is continuous with the thickened olfactory placode anterolaterally and the primordium of Rathke's pouch in the ventral midline.

The mesencephalon contains a stockbuilding neuroepithelium surrounding a small mesencephalic superventricle. A roof (tectum) and floor (tegmentum) can be differentiated in coronally cut anterior sections. It is difficult to distinguish neuroepithelial subdivisions in posterior sections that cut the mesencephalon horizontally. A few pioneer migrating cells are outside the presumptive tegmental and isthmal neuroepithelia posteriorly. The primordial plexiform layer at the brain surface is very thin throughout the entire mesencephalon.

The most prominent neuroepithelial structures in the rhombencephalon are the rhombomeric evaginations. This specimen is one of the best to show the "rippled" neuroepithelium in **Plates 167 to 170**. As in M2300 (**Part XI**), the trigeminal ganglion (sensory axons of V) is attached to the brain surface at rhombomere 2. The vestibulocochlear ganglion (source of VIII axons) is attached to the rhombomere 4 brain surface. The otic vesicle touches the rhombomere 5 brain surface. A glossopharyngeal ganglion is lateral to the brain at rhombomere 6. The short nerve extending from the large vagal ganglion (sensory axons of X) touches the rhombomere 7 brain surface. The facial ganglion is tentatively identified adjacent to a placode in the hyoid arch that lies immediately ventral to the vestibulocochlear ganglion and posteroventral to rhombomere 3. Very few neurons are migrating from the rhombomeres. The small stockbuilding cerebellar neuroepithelium is only identifiable in the most posterior sections of the rhombencephalon and is difficult to distinguish from the mesencephalic tectum.

C836 Computer-aided 3-D Brain Reconstructions

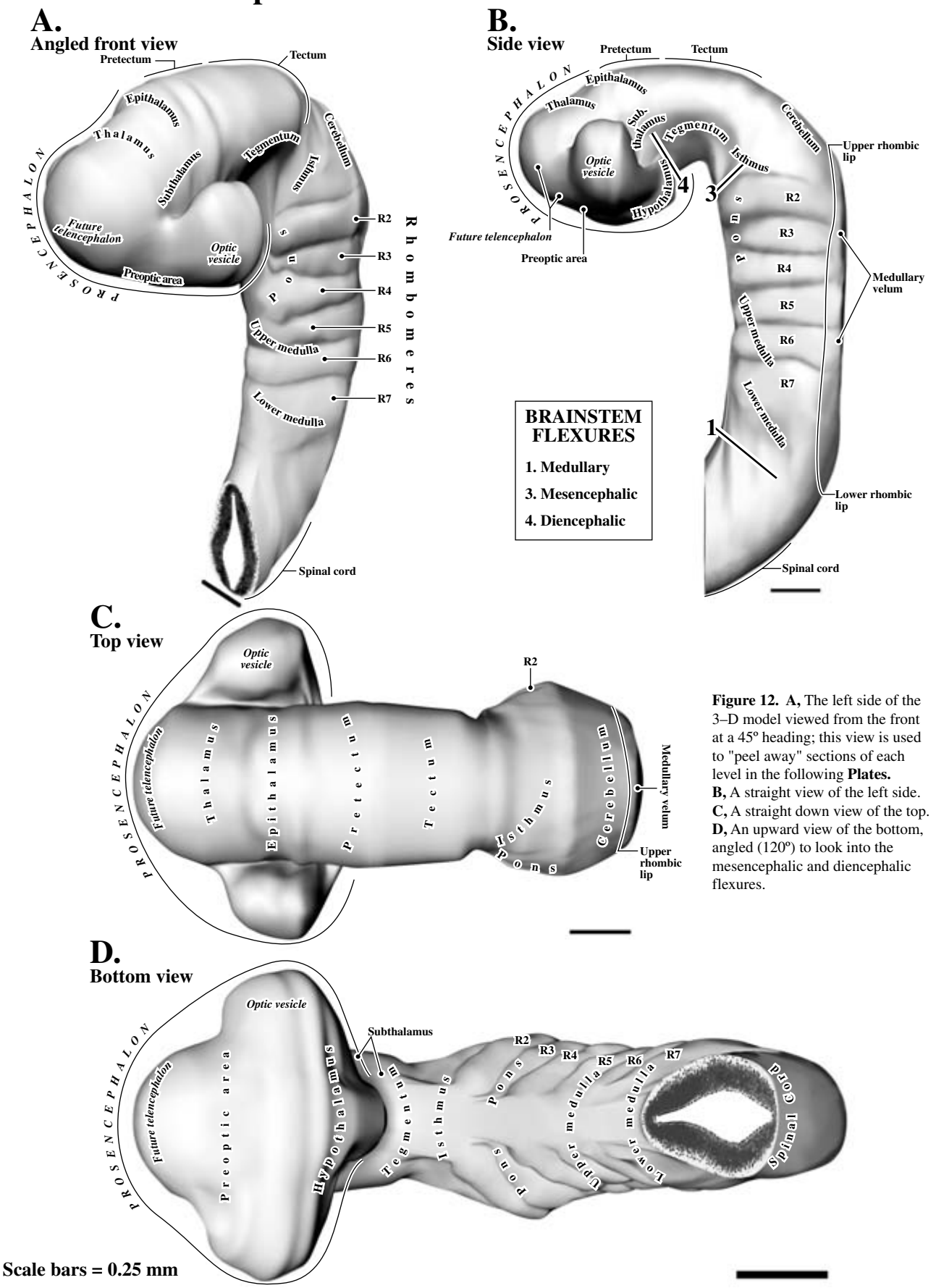


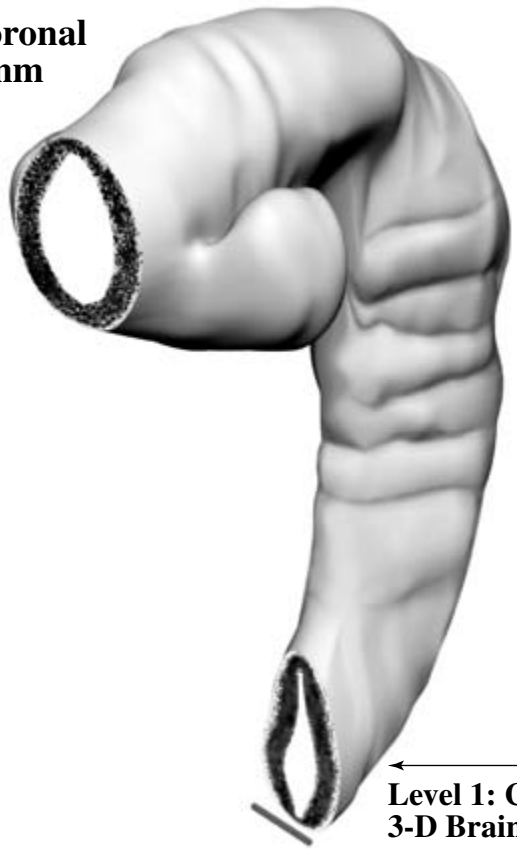
Figure 12. A, The left side of the 3–D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.** **B,** A straight view of the left side. **C,** A straight down view of the top. **D,** An upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures.

Scale bars = 0.25 mm

PLATE 161A

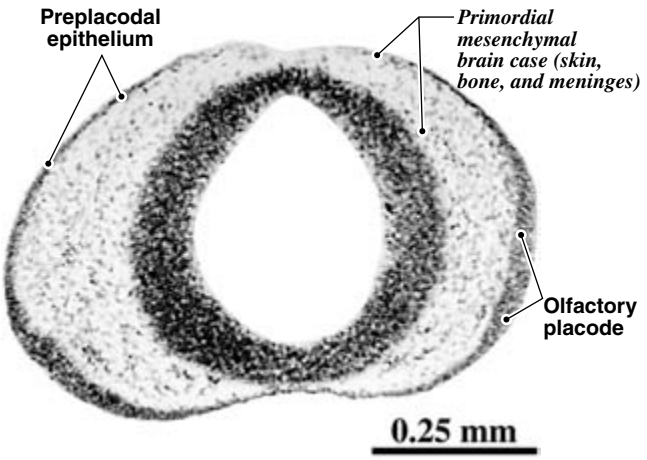
Peripheral neural and non-neural structures labeled

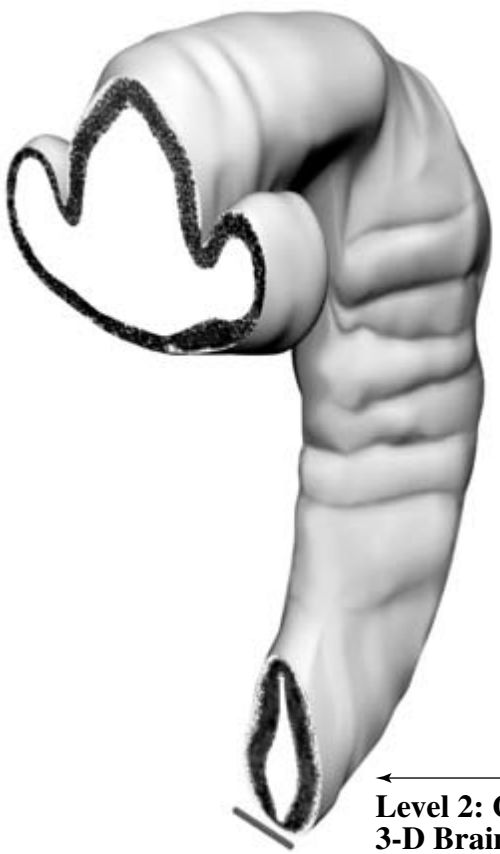
GW4 Coronal
CR 4.0 mm
C836



Level 1: Computer-aided 3-D Brain Reconstruction

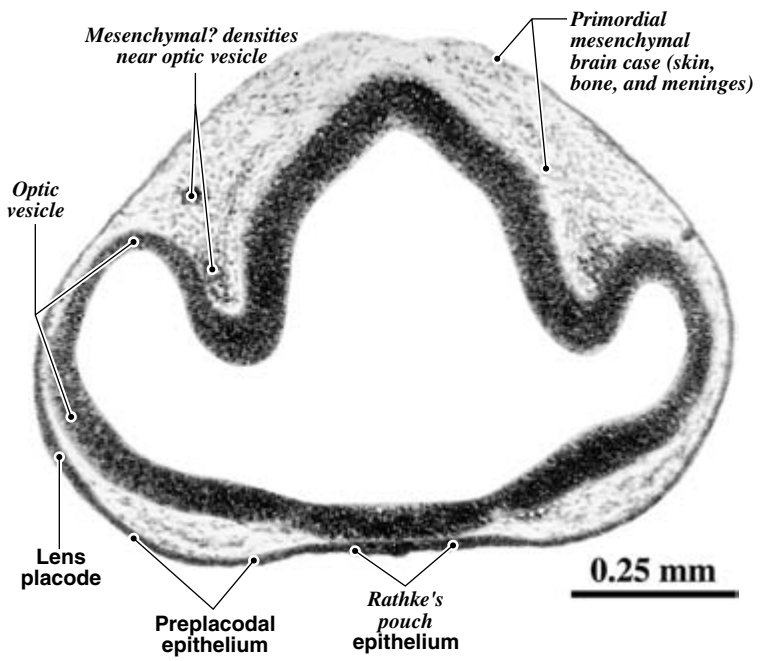
Level 1: Section 9





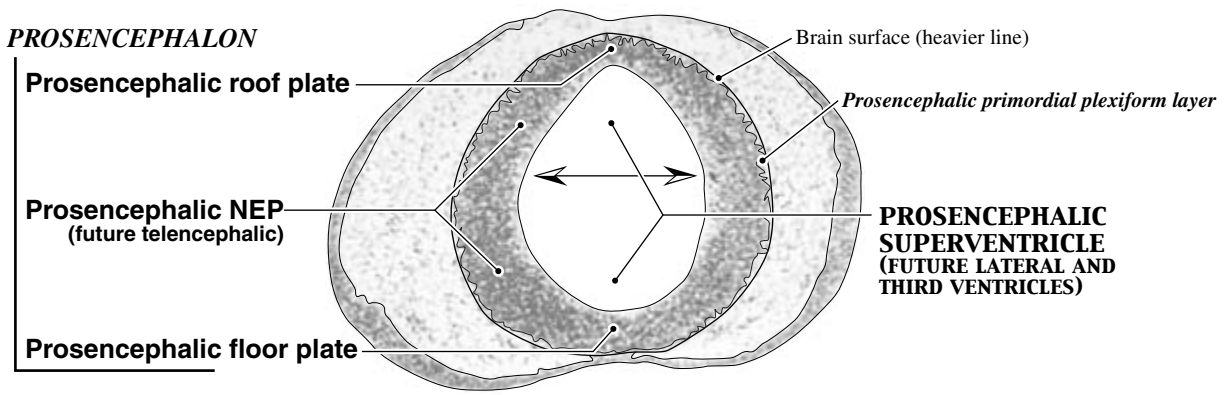
Level 2: Computer-aided 3-D Brain Reconstruction

Level 2: Section 27

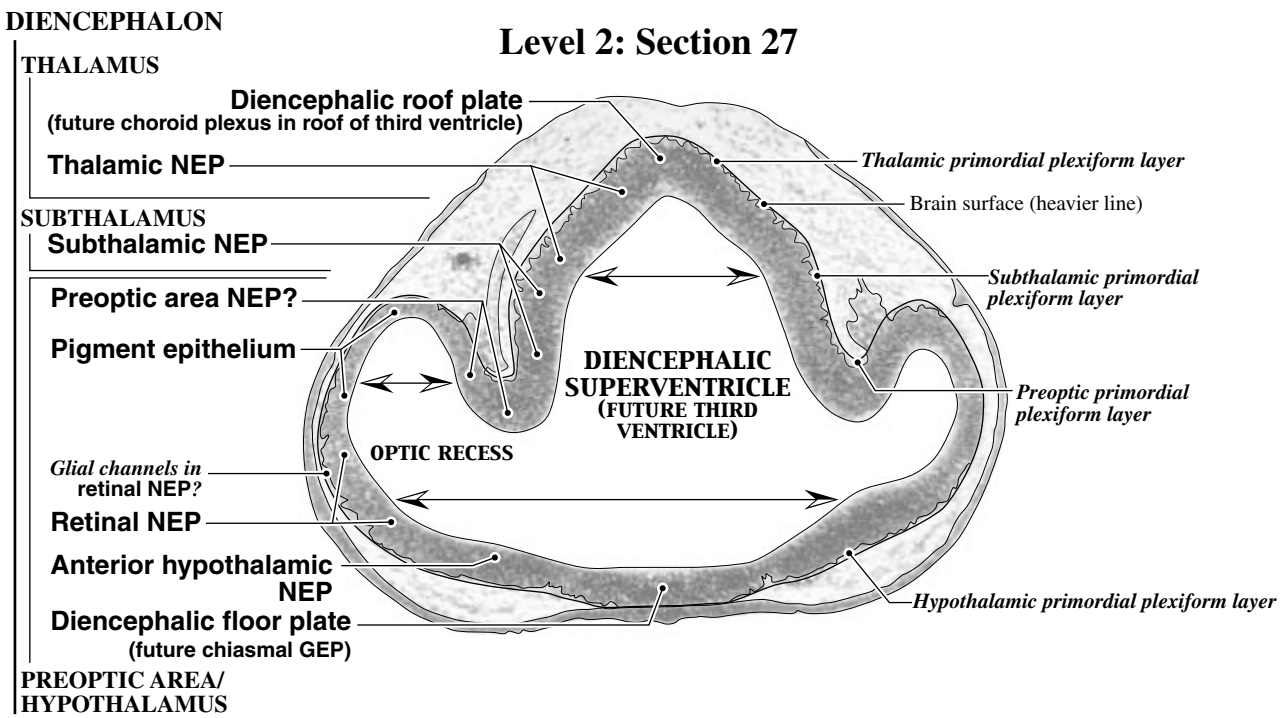


Central neural structures labeled **PLATE 161B**

Level 1: Section 9



Level 2: Section 27



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

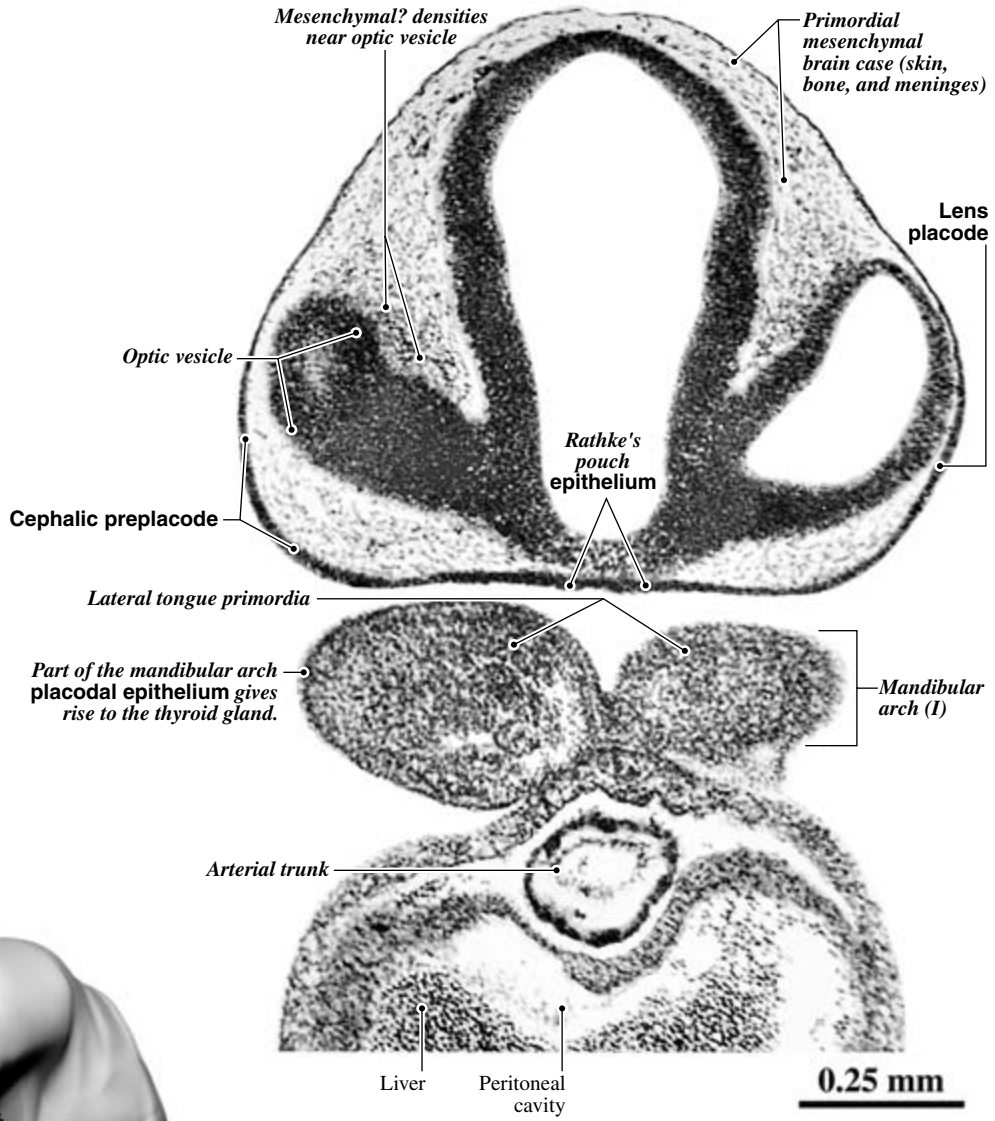
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 162A

Peripheral neural and non-neural structures labeled

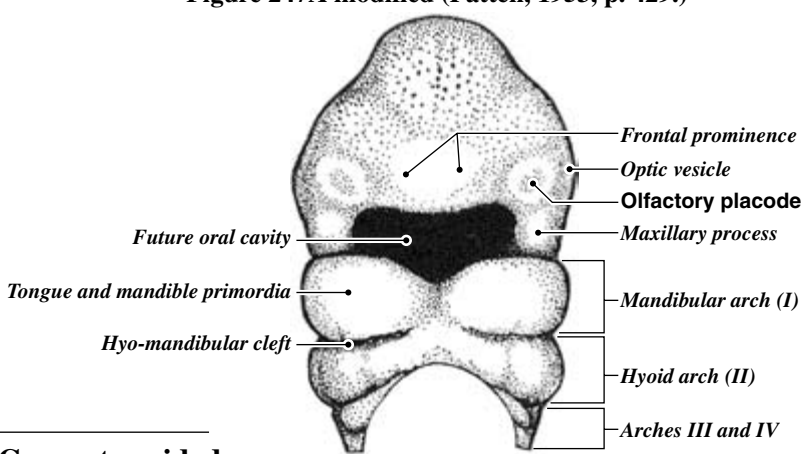
GW4 Coronal
CR 4.0 mm
C836
Level 3: Section 36



Level 3: Computer-aided 3-D Brain Reconstruction

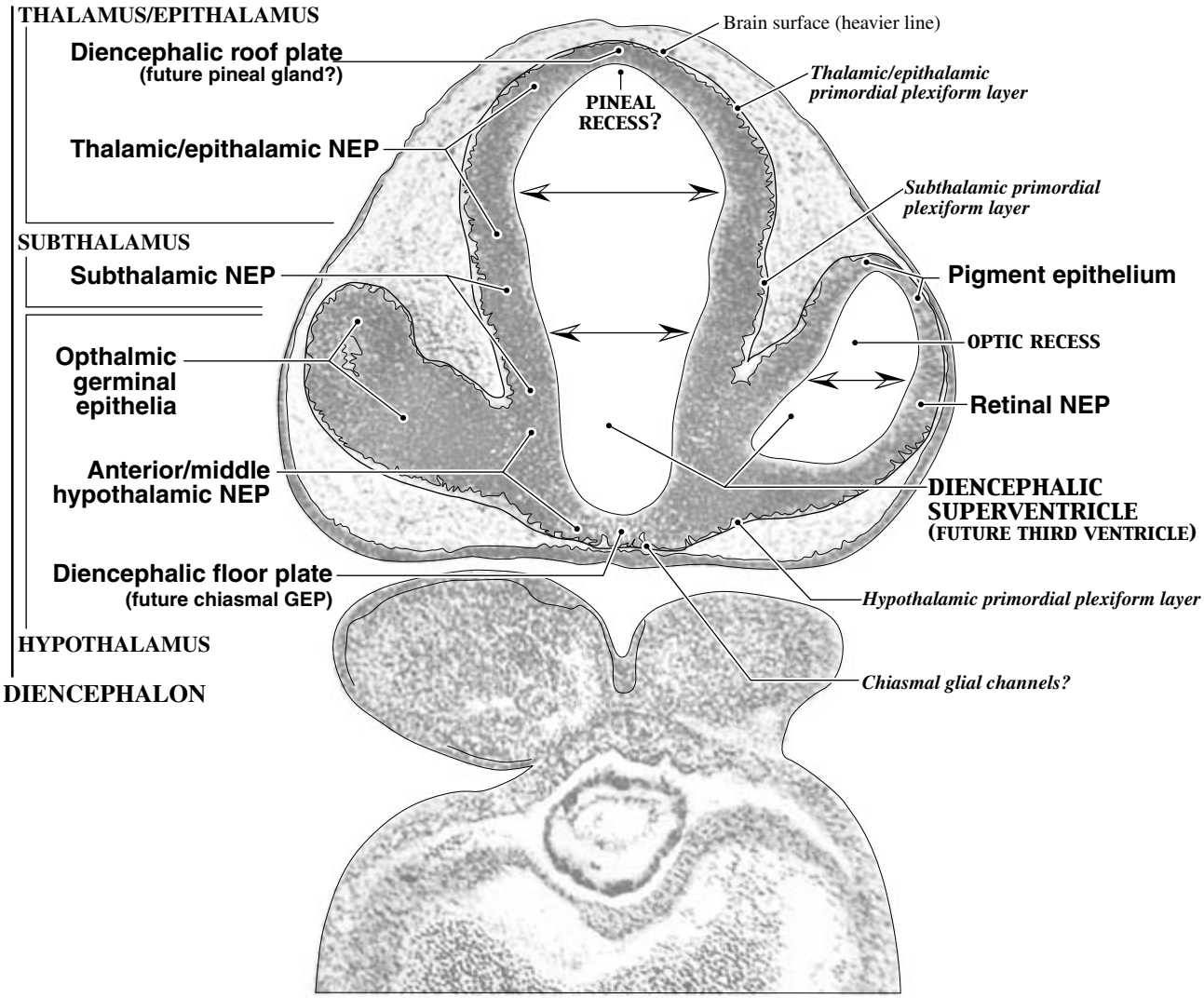
The GW4 Face and Neck

Figure 247A modified (Patten, 1953, p. 429.)



Central neural structures labeled

PLATE 162B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

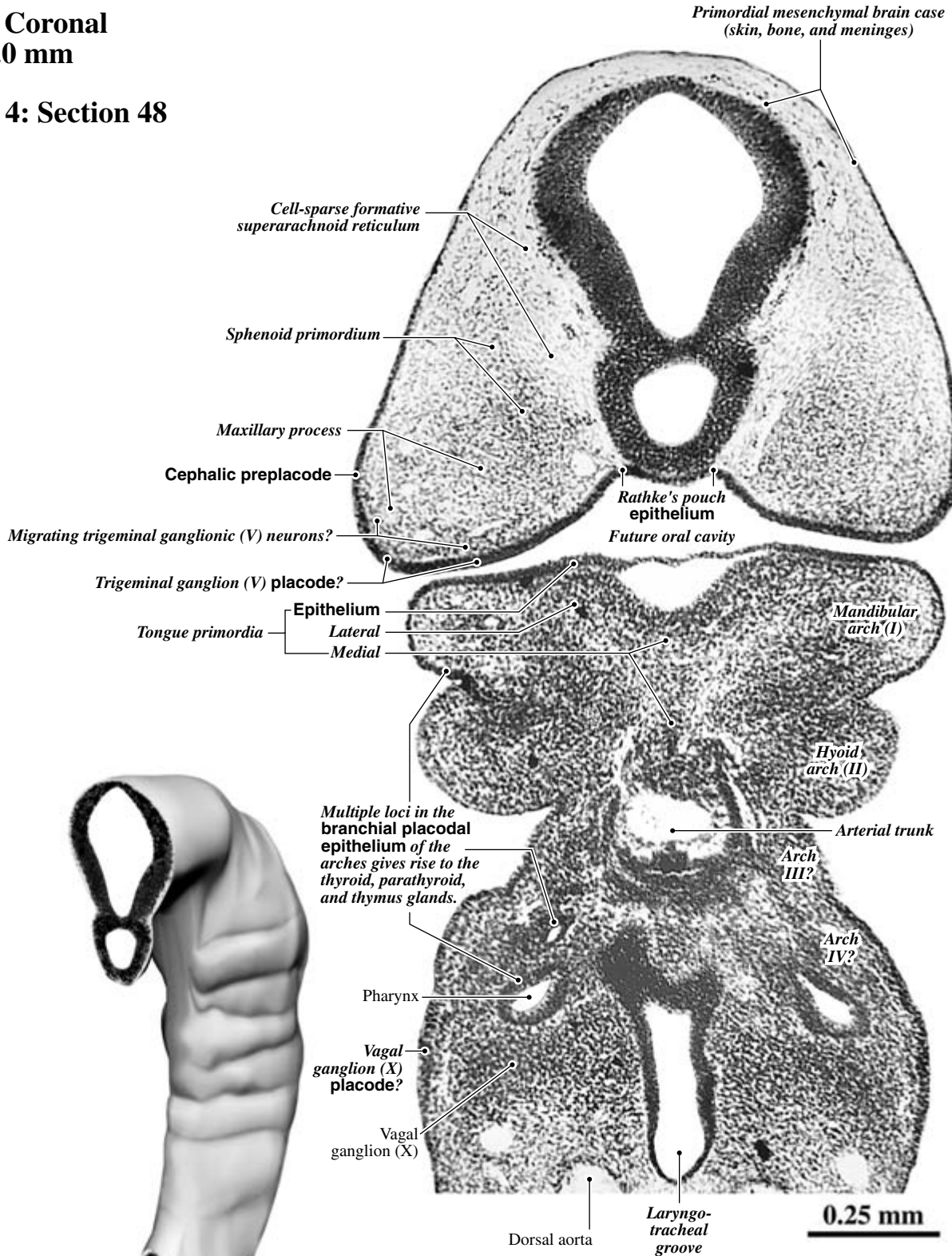
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 163A

Peripheral neural and non-neural structures labeled

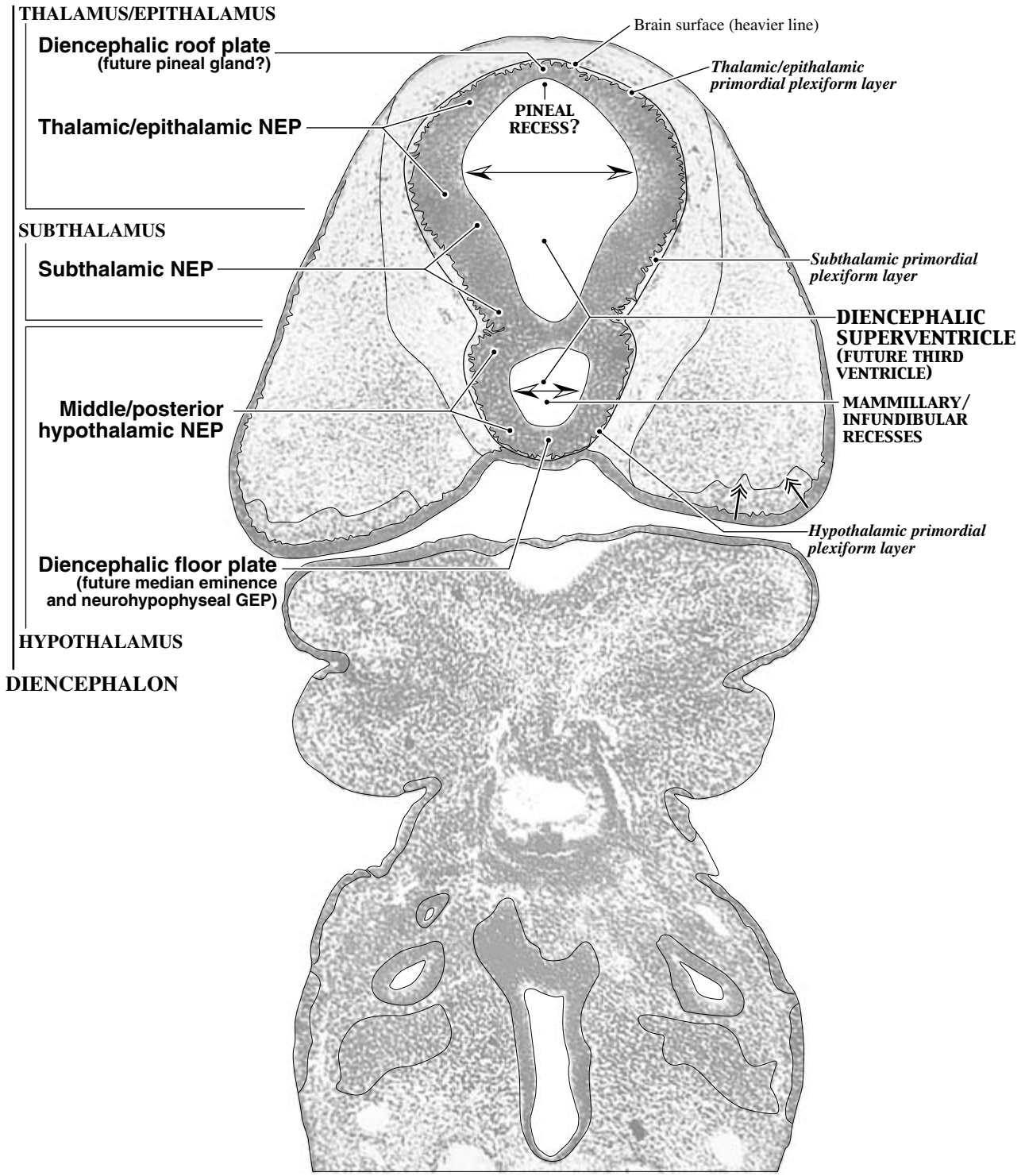
GW4 Coronal
CR 4.0 mm
C836
Level 4: Section 48



Level 4: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 163B



Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

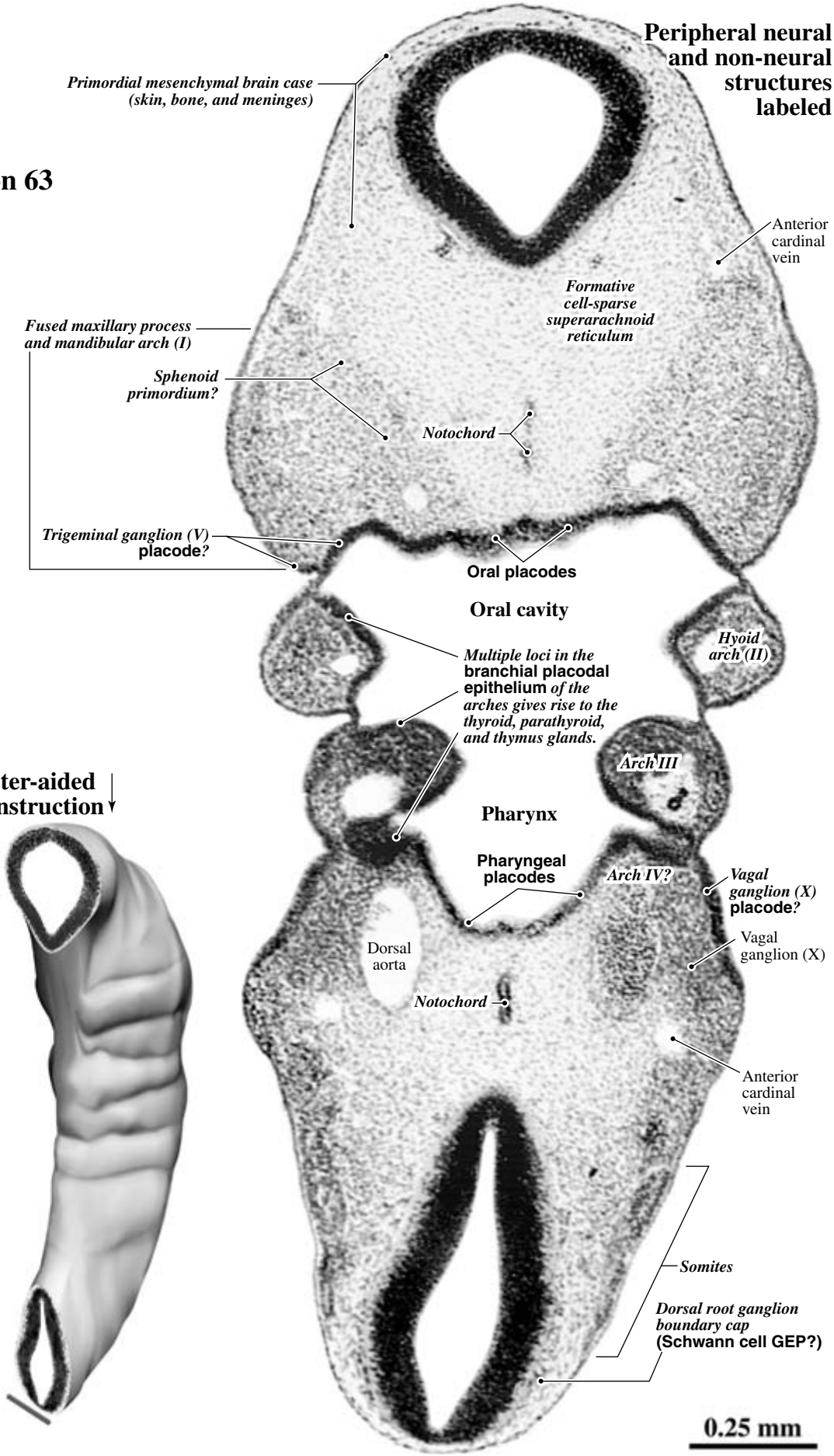
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

PLATE 164A

GW4 Coronal
CR 4.0 mm
C836
Level 5: Section 63

Peripheral neural and non-neural structures labeled



Level 5: Computer-aided 3-D Brain Reconstruction

PLATE 164B

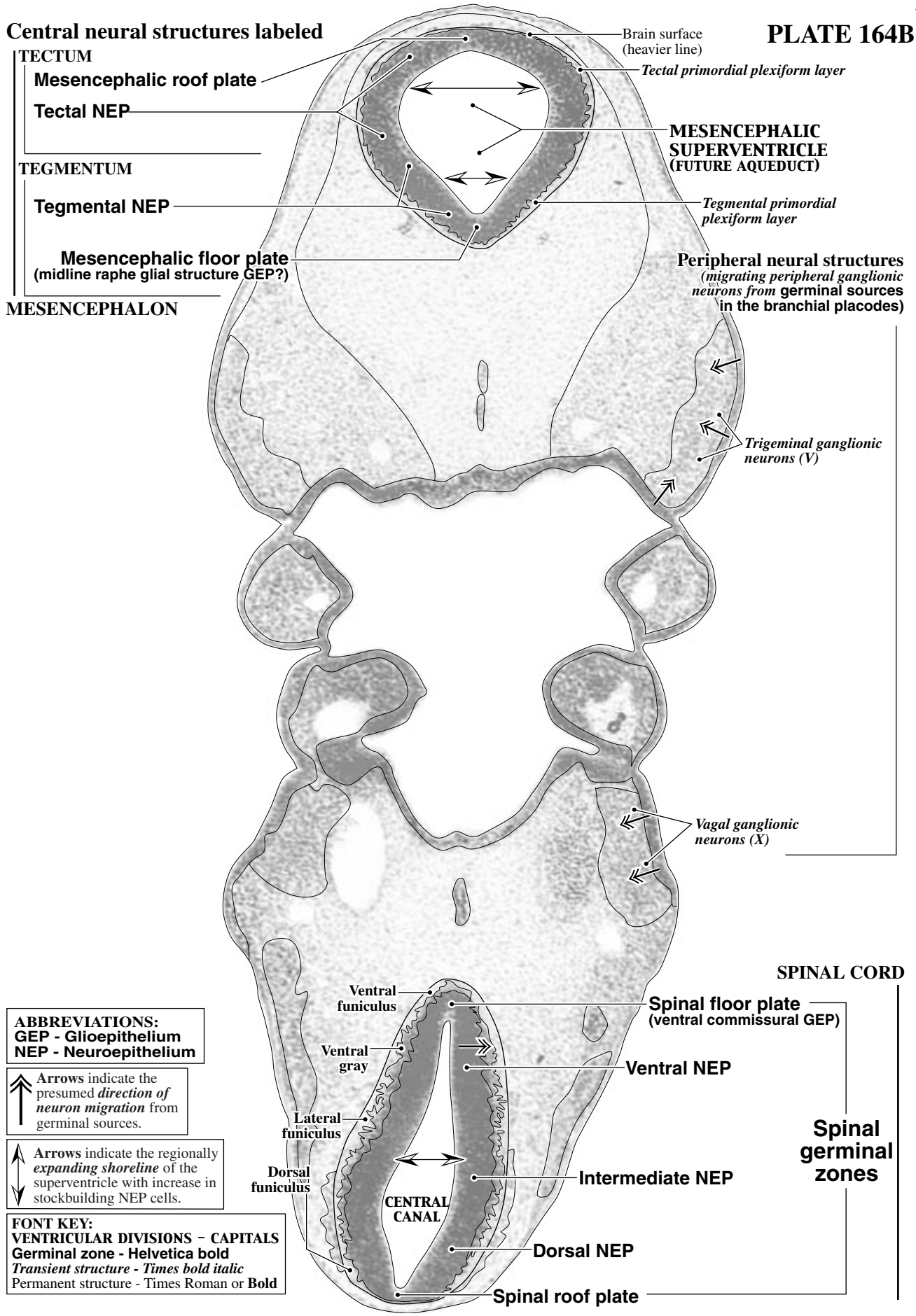
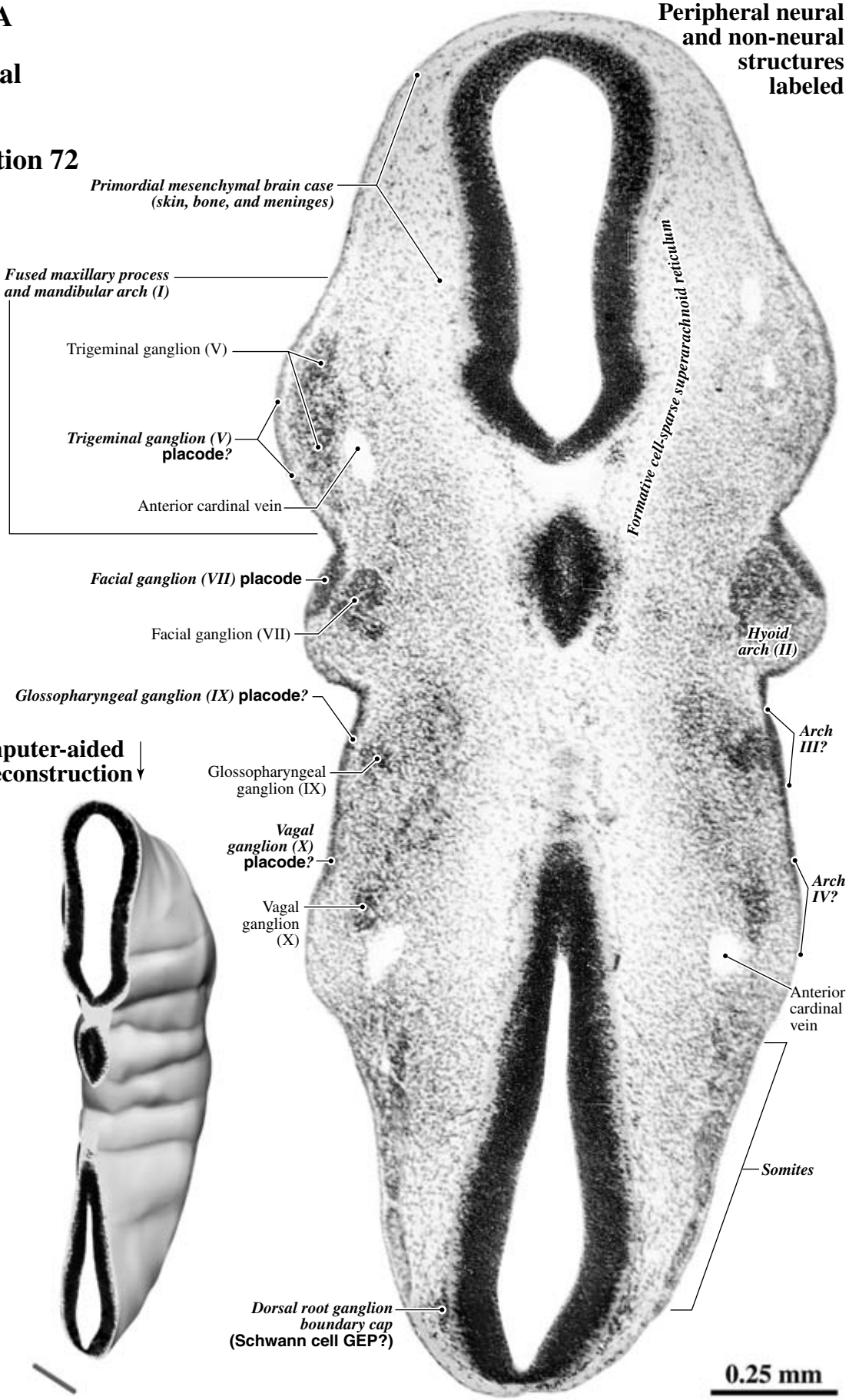

Central neural structures labeled
TECTUM
Mesencephalic roof plate
Tectal NEP
TEGMENTUM
Tegmental NEP
Mesencephalic floor plate
(midline raphe glial structure GEP?)
MESENCEPHALON
Brain surface
(heavier line)
Tectal primordial plexiform layer
MESENCEPHALIC
SUPERVENTRICLE
(FUTURE AQUEDUCT)
Tegmental primordial
plexiform layer
Peripheral neural structures
(migrating peripheral ganglionic
neurons from germinal sources
in the branchial placodes)
Trigeminal ganglionic
neurons (V)
Vagal ganglionic
neurons (X)
SPINAL CORD
Ventral
funiculus
Spinal floor plate
(ventral commissural GEP)
Ventral
gray
Ventral NEP
Lateral
funiculus
Dorsal
funiculus
Intermediate NEP
CENTRAL
CANAL
Dorsal NEP
Spinal roof plate
Spinal
germinal
zones
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
Arrows indicate the
presumed direction of
neuron migration from
germinal sources.
Arrows indicate the regionally
expanding shoreline of the
superventricle with increase in
stockbuilding NEP cells.
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold

PLATE 165A

GW4 Coronal
CR 4.0 mm
C836
Level 6: Section 72

Peripheral neural and non-neural structures labeled



Level 6: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 165B

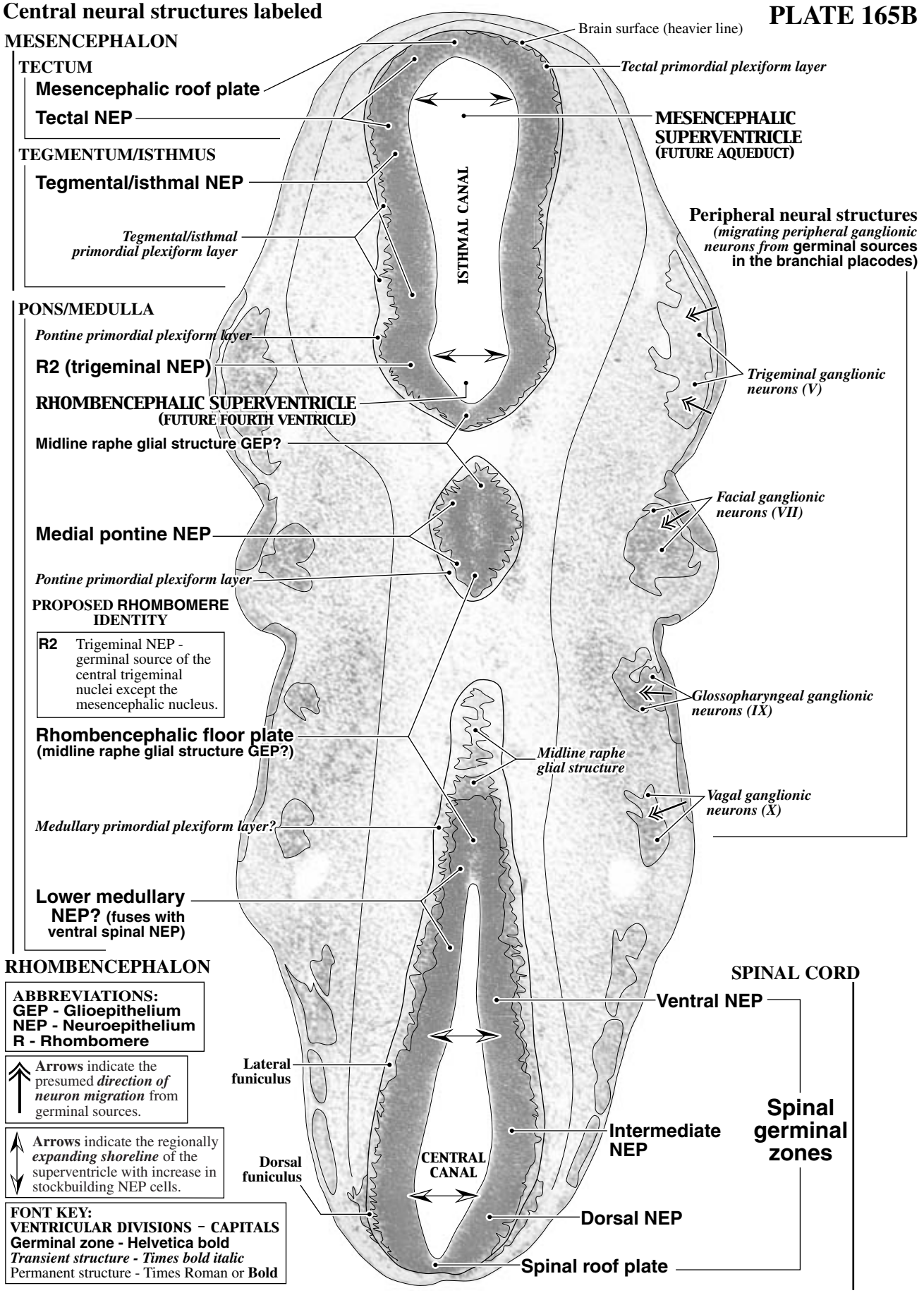
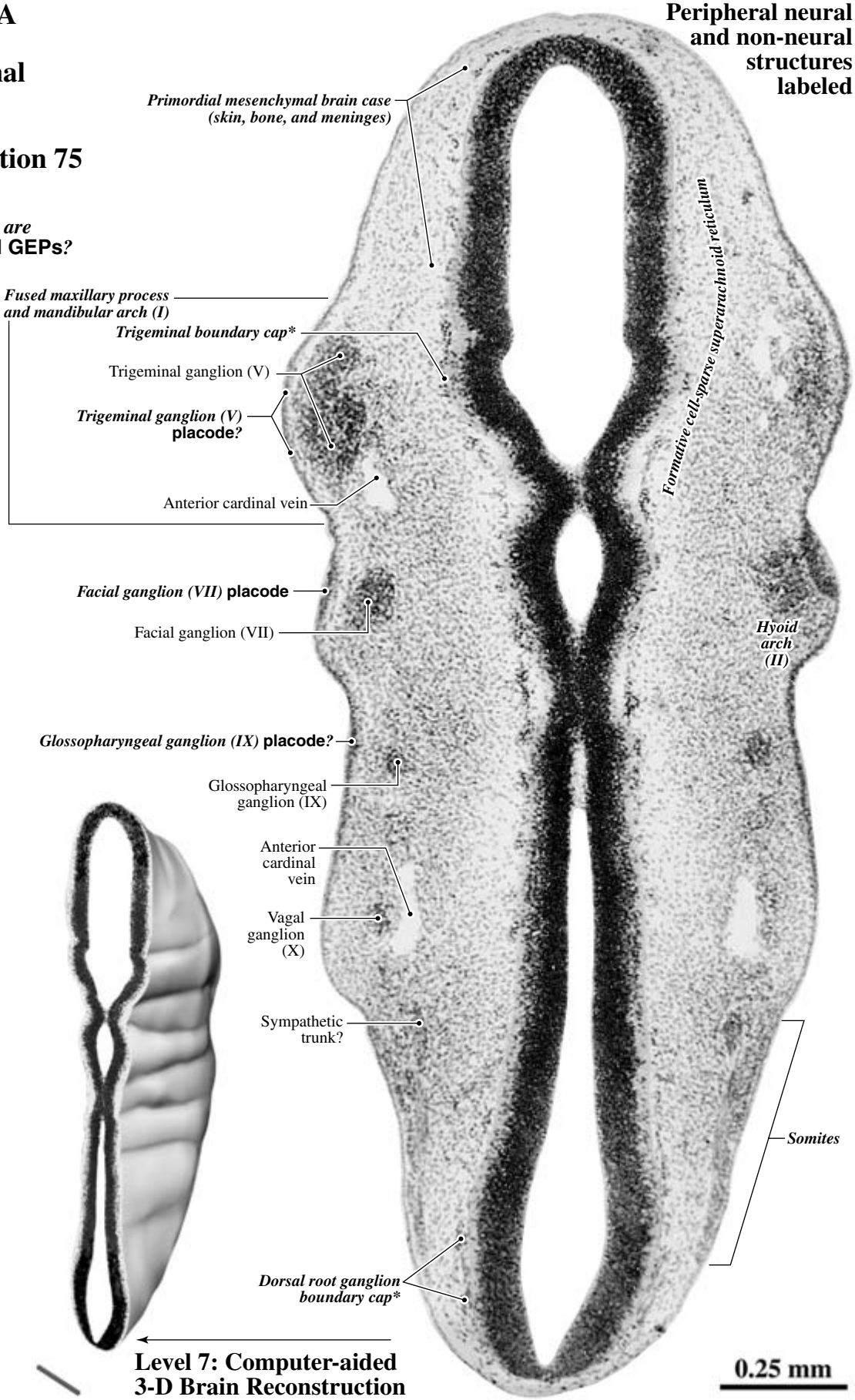


PLATE 166A

GW4 Coronal
CR 4.0 mm
C836
Level 7: Section 75

*** *Boundary caps are* Schwann cell GEPs*?***

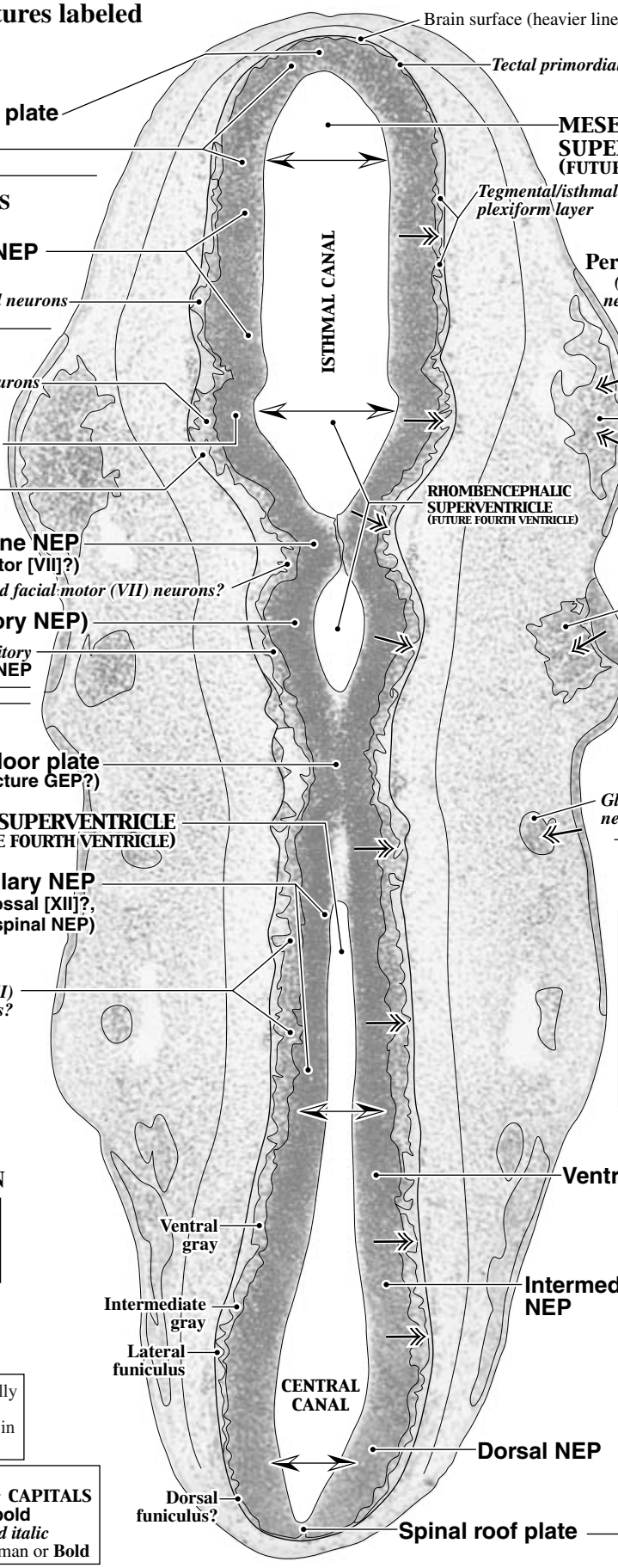
Peripheral neural and non-neural structures labeled



Level 7: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 166B



MESENCEPHALON

TECTUM

Mesencephalic roof plate

Tectal NEP

TEGMENTUM/ISTHMUS

Tegmental/isthmal NEP

Migrating tegmental/isthmal neurons

PONS

Migrating trigeminal (V) neurons

R2 (trigeminal NEP)

Central trigeminal tract

Medial pontine NEP
(abducens [VI], facial motor [VII]?)

Migrating abducens (VI) and facial motor (VII) neurons?

R4 (vestibulo-auditory NEP)

Migrating vestibulo-auditory neurons from R4 NEP

Rhombencephalic floor plate
(midline raphe glial structure GEP?)

RHOMBENCEPHALIC SUPERVENTRICLE
(FUTURE FOURTH VENTRICLE)

Medial medullary NEP
(vagal motor [X], hypoglossal [XII]?, blends with ventral spinal NEP)

Migrating hypoglossal (XII) and vagal motor (X) neurons?

MEDULLA

RHOMBENCEPHALON

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

SPINAL CORD

Spinal germinal zones

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

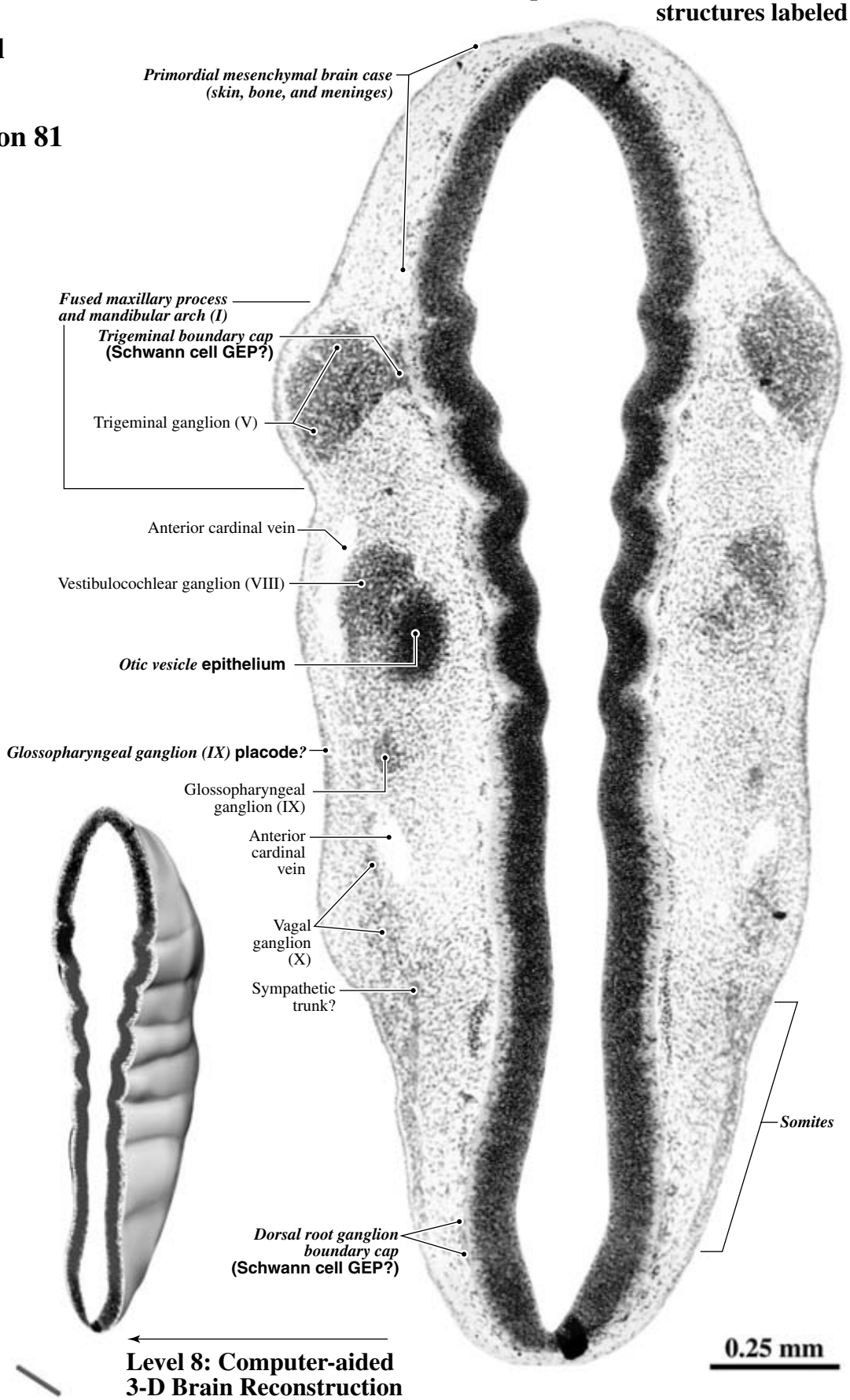
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 167A

Peripheral neural and non-neural structures labeled

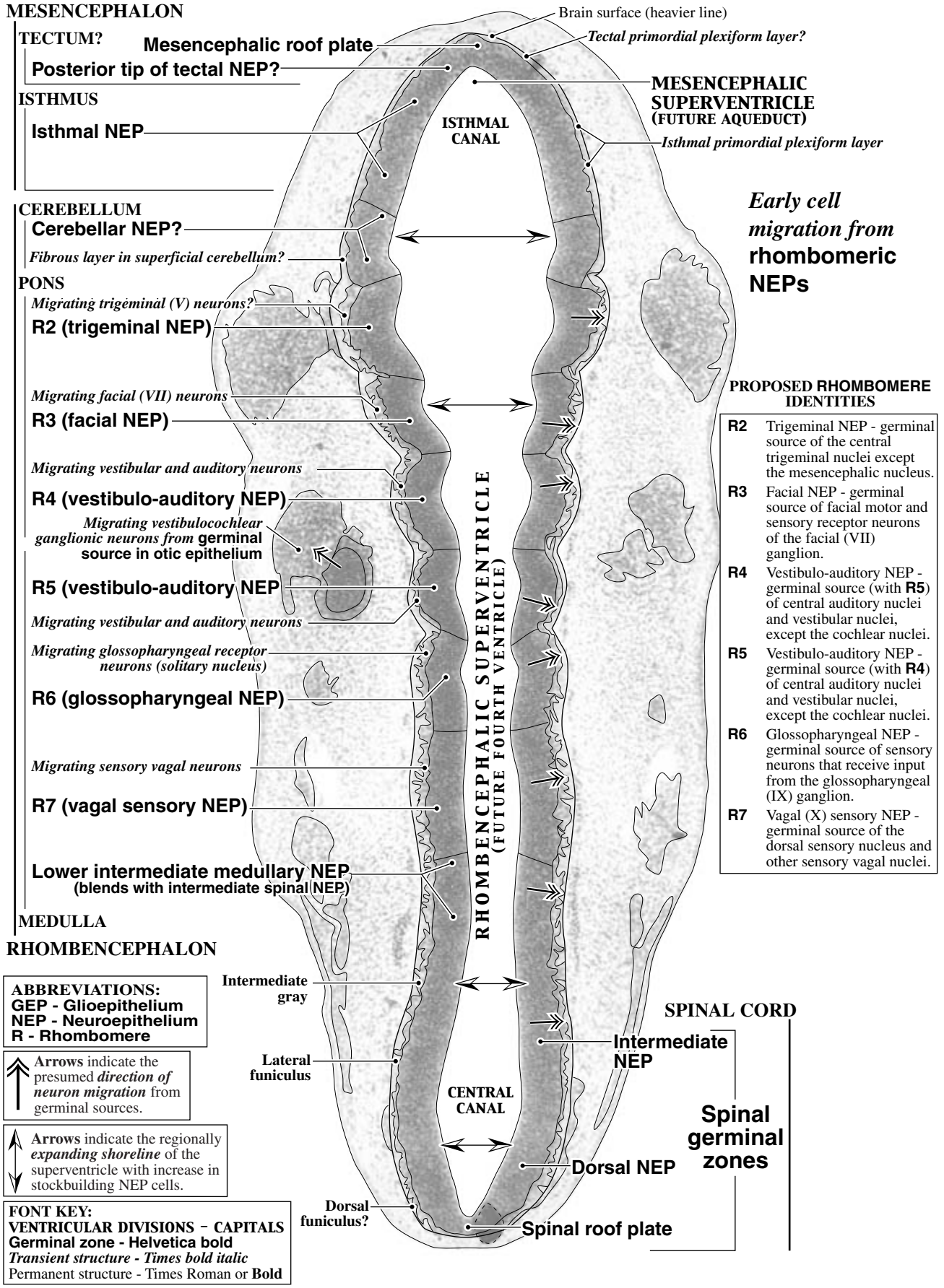
GW4 Coronal
CR 4.0 mm
C836
Level 8: Section 81



Level 8: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 167B



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

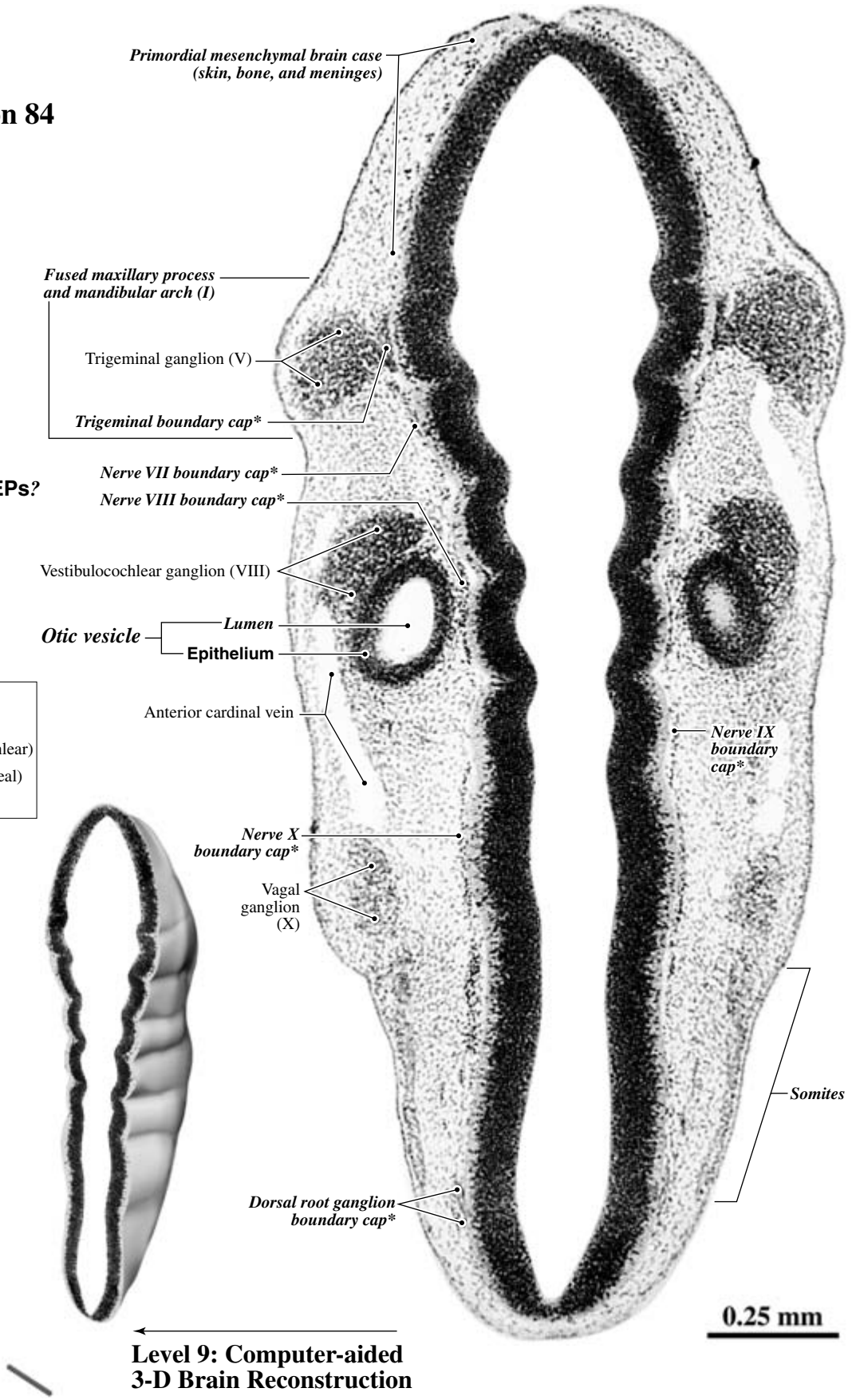
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 168A

Peripheral neural and non-neural structures labeled

GW4 Coronal
CR 4.0 mm
C836
Level 9: Section 84



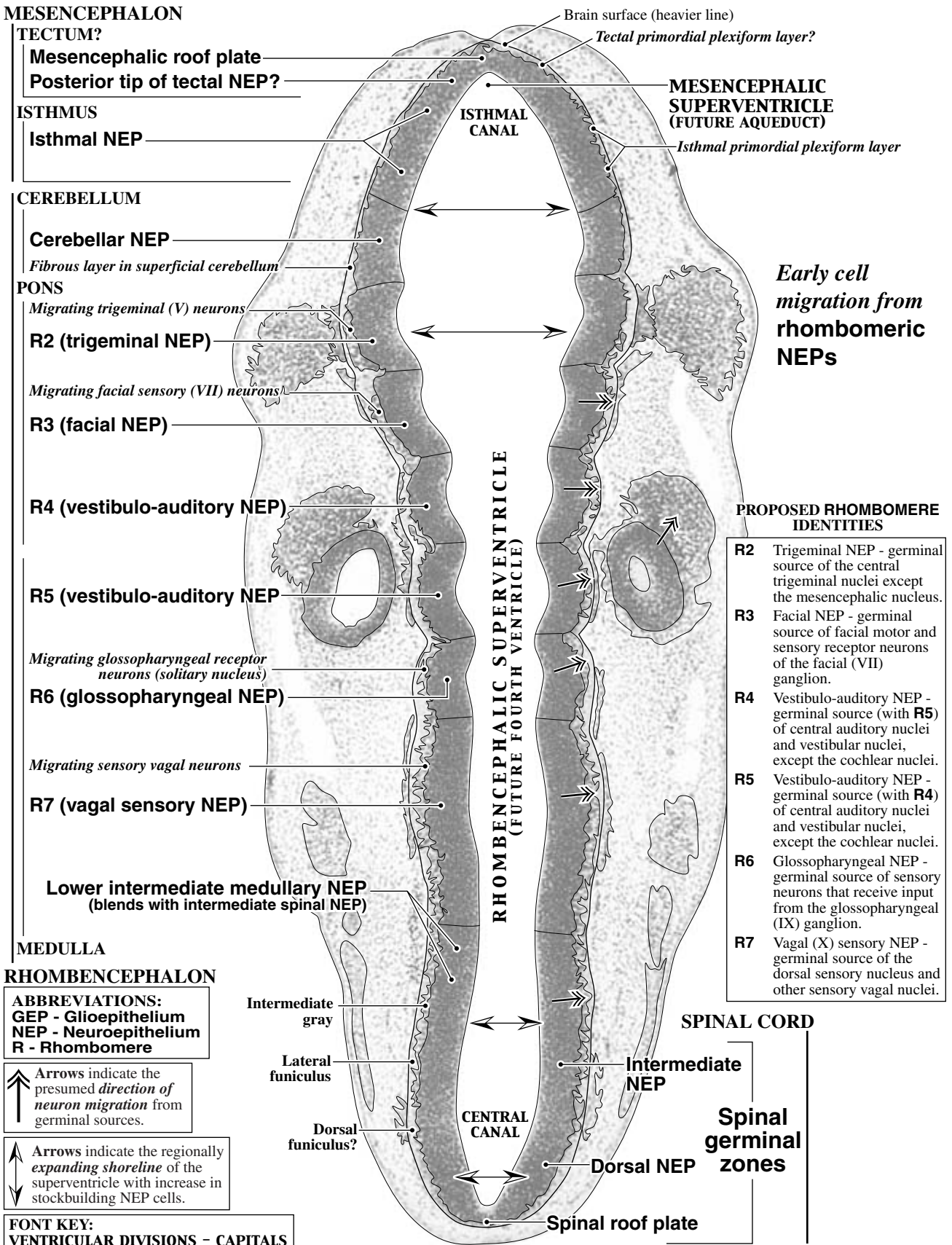
*Boundary caps are Schwann cell GEPs?

Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Nerve X (vagus)

Level 9: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 168B



***Early cell migration from* rhombomeric NEPs**

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

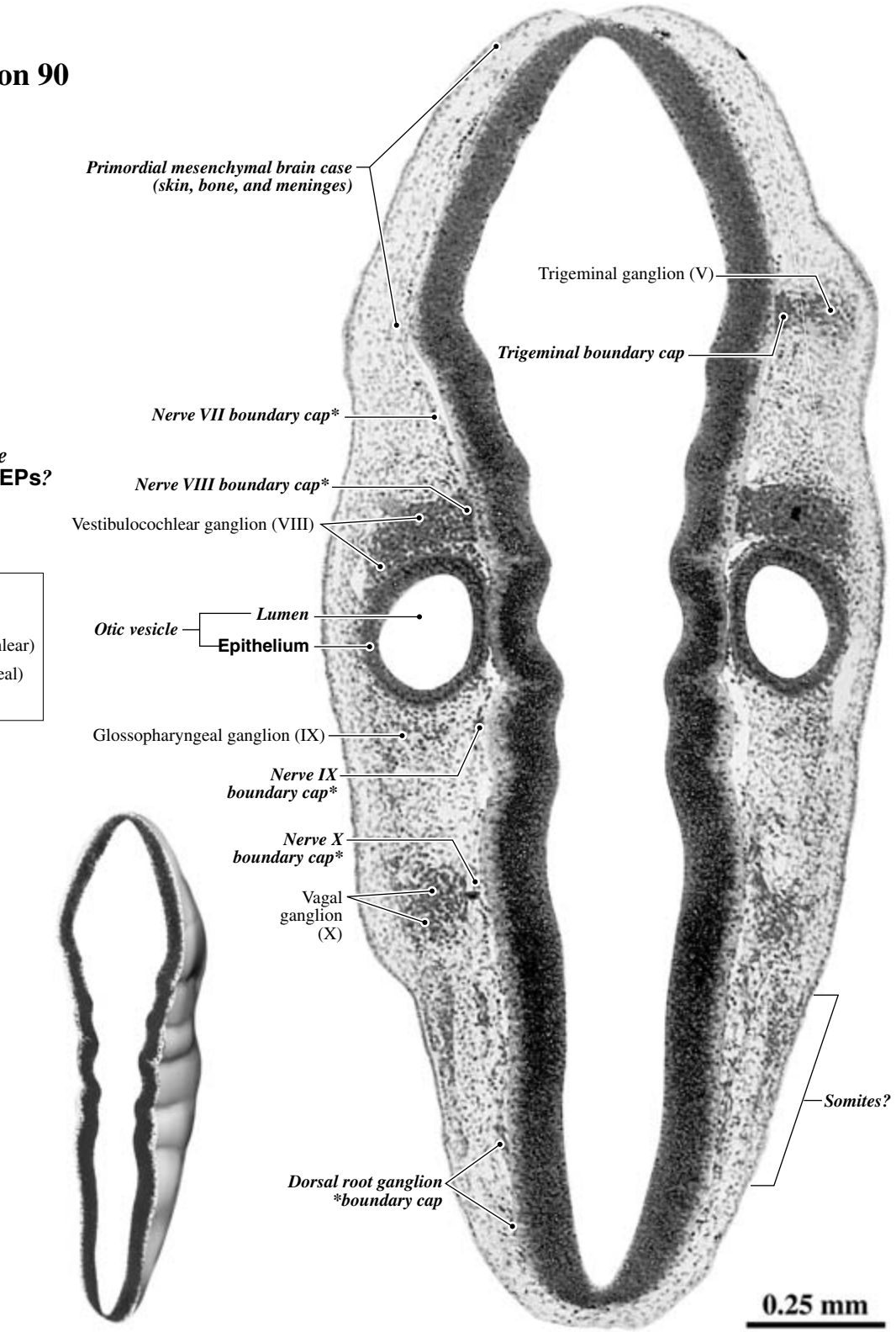
Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 169A

Peripheral neural and non-neural structures labeled

GW4 Coronal
CR 4.0 mm
C836
Level 10: Section 90



*Boundary caps are Schwann cell GEPs?

Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Nerve X (vagus)

Level 10: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 169B

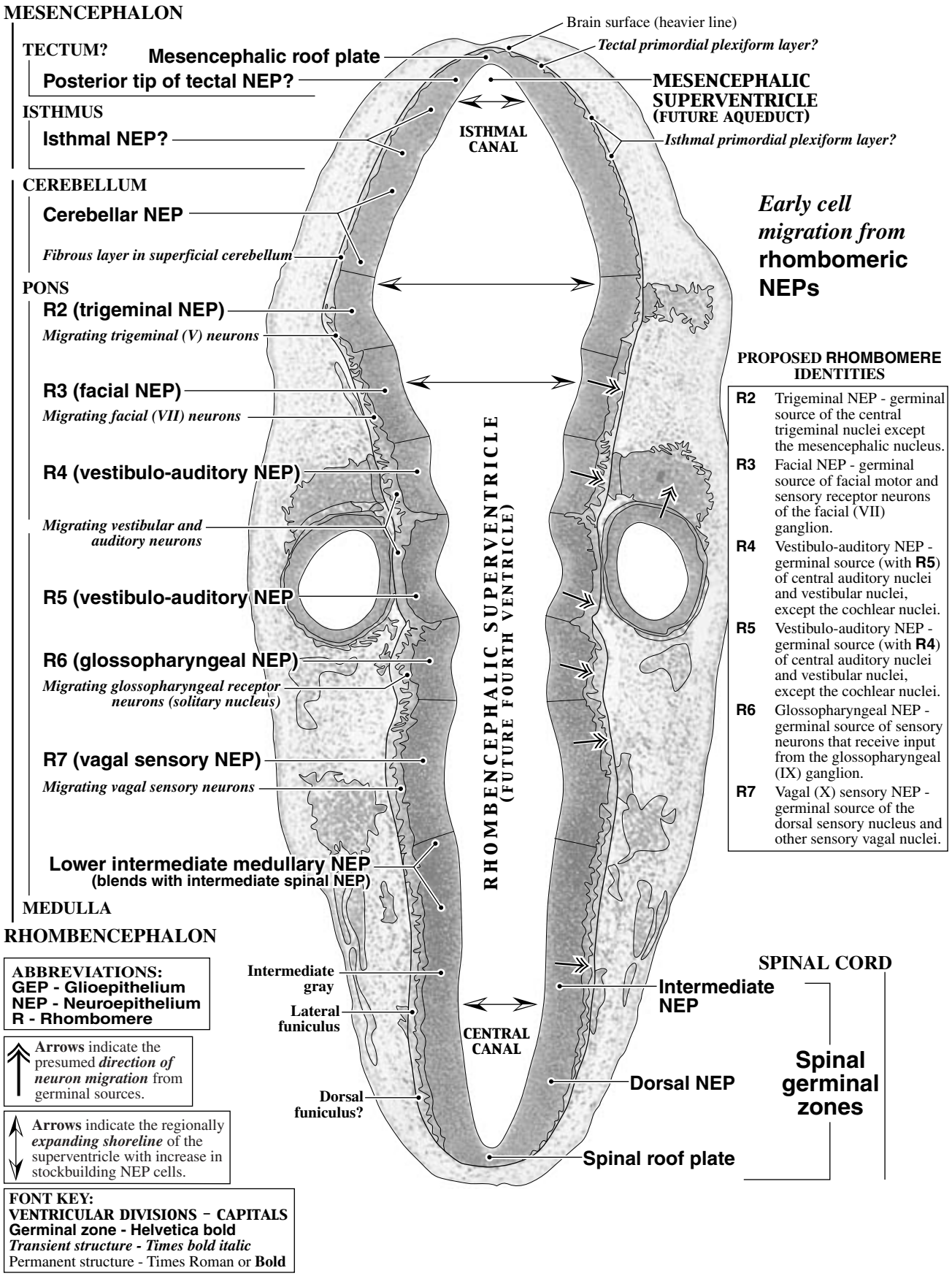
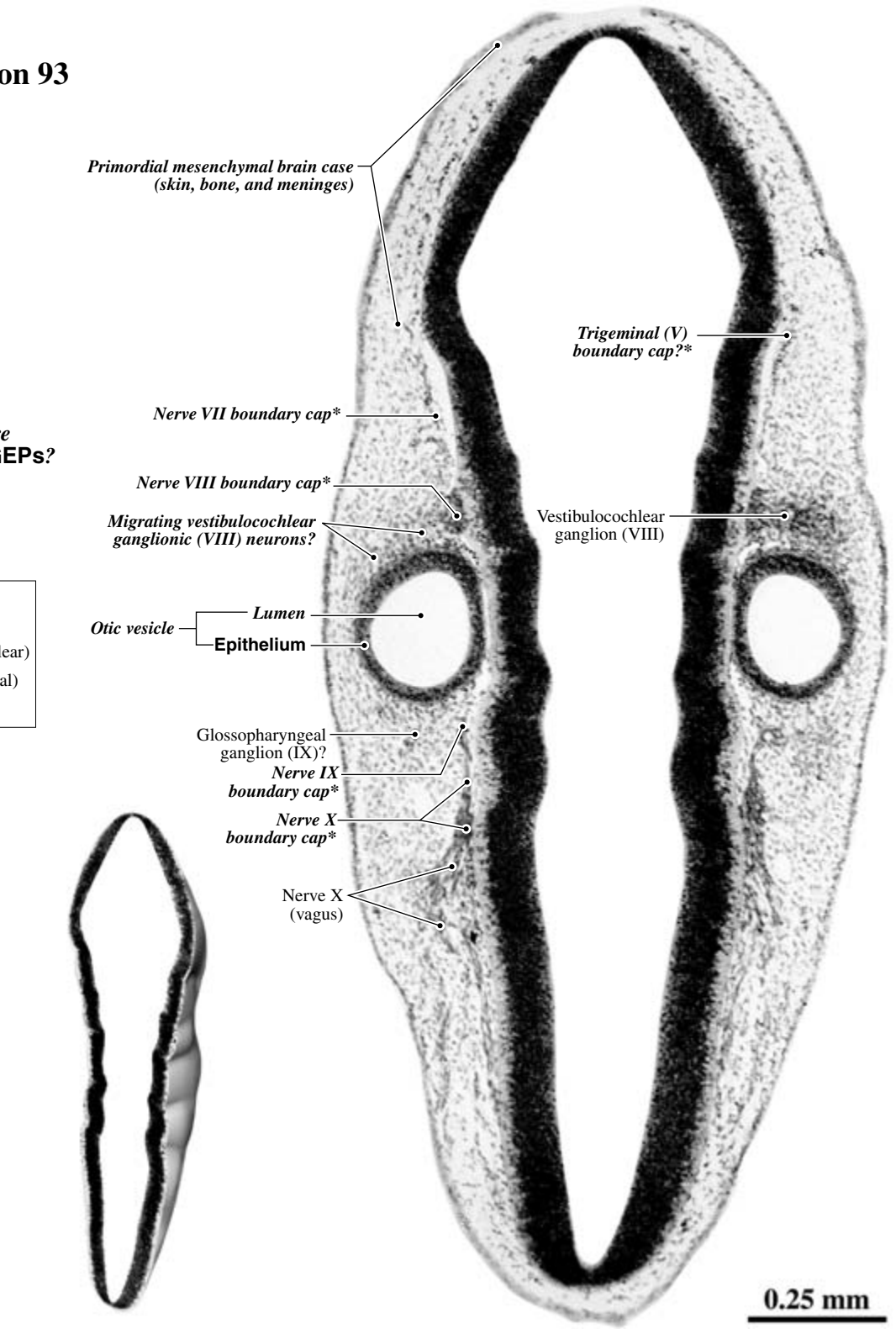


PLATE 170A

Peripheral neural and non-neural structures labeled

GW4 Coronal
CR 4.0 mm
C836
Level 11: Section 93



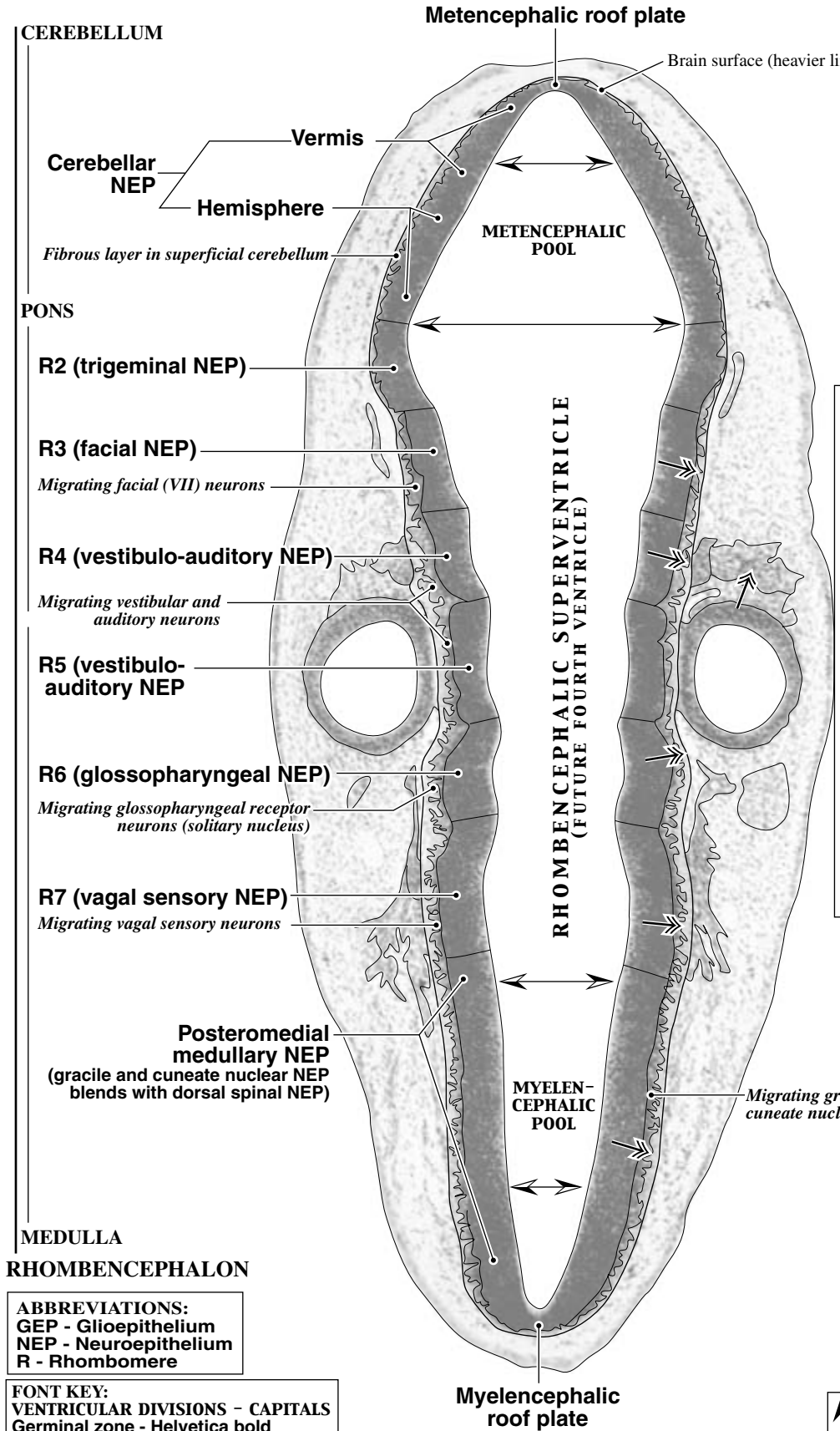
* *Boundary caps are* **Schwann cell GEPs*?***

Nerve V (trigeminal)
Nerve VII (facial)
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)
Nerve X (vagus)

Level 11: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 170B



***Early cell migration from* rhombomeric NEPs**

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

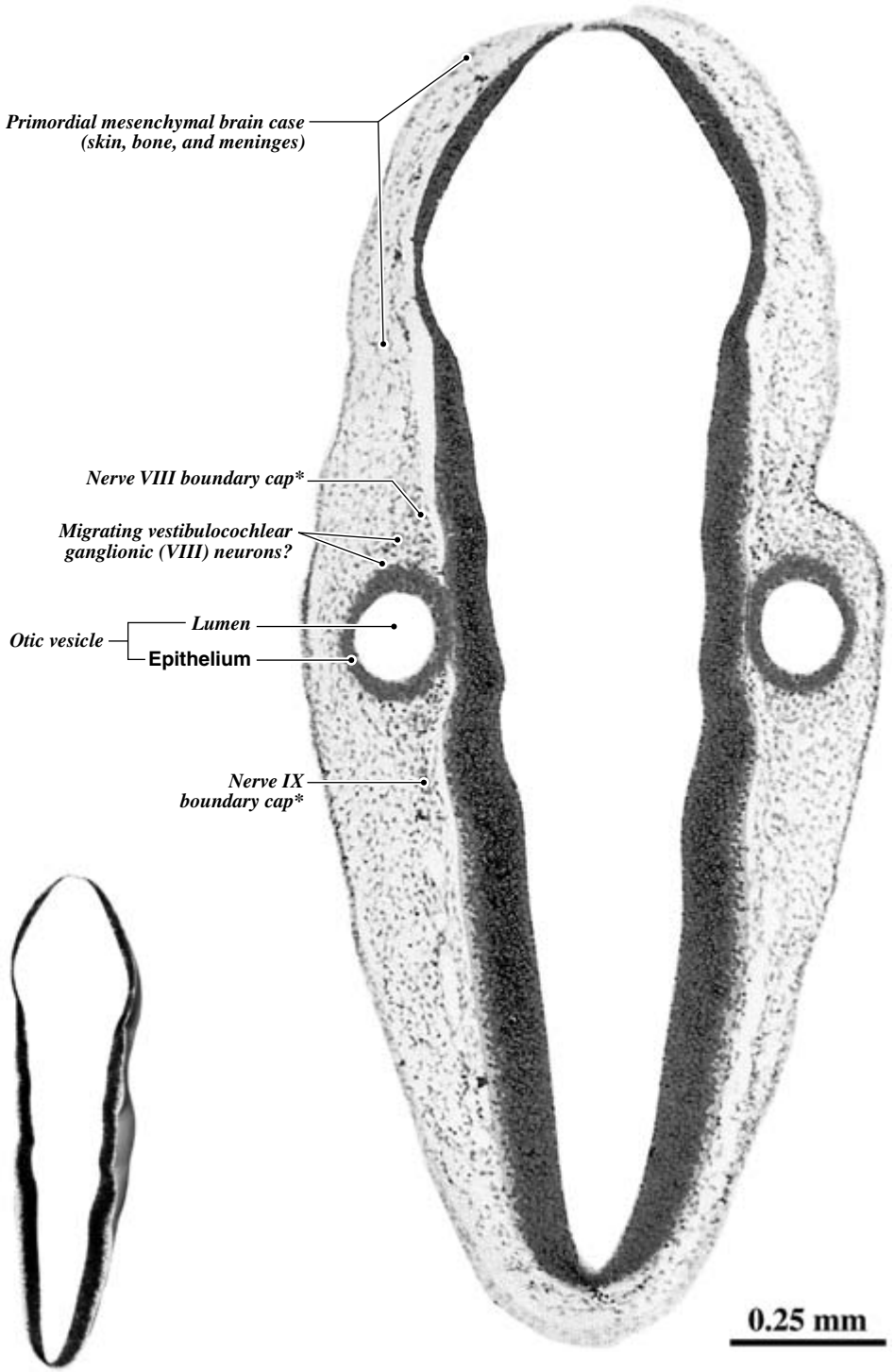
Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PLATE 171A

Peripheral neural and non-neural structures labeled

GW4 Coronal
CR 4.0 mm
C836
Level 12: Section 99



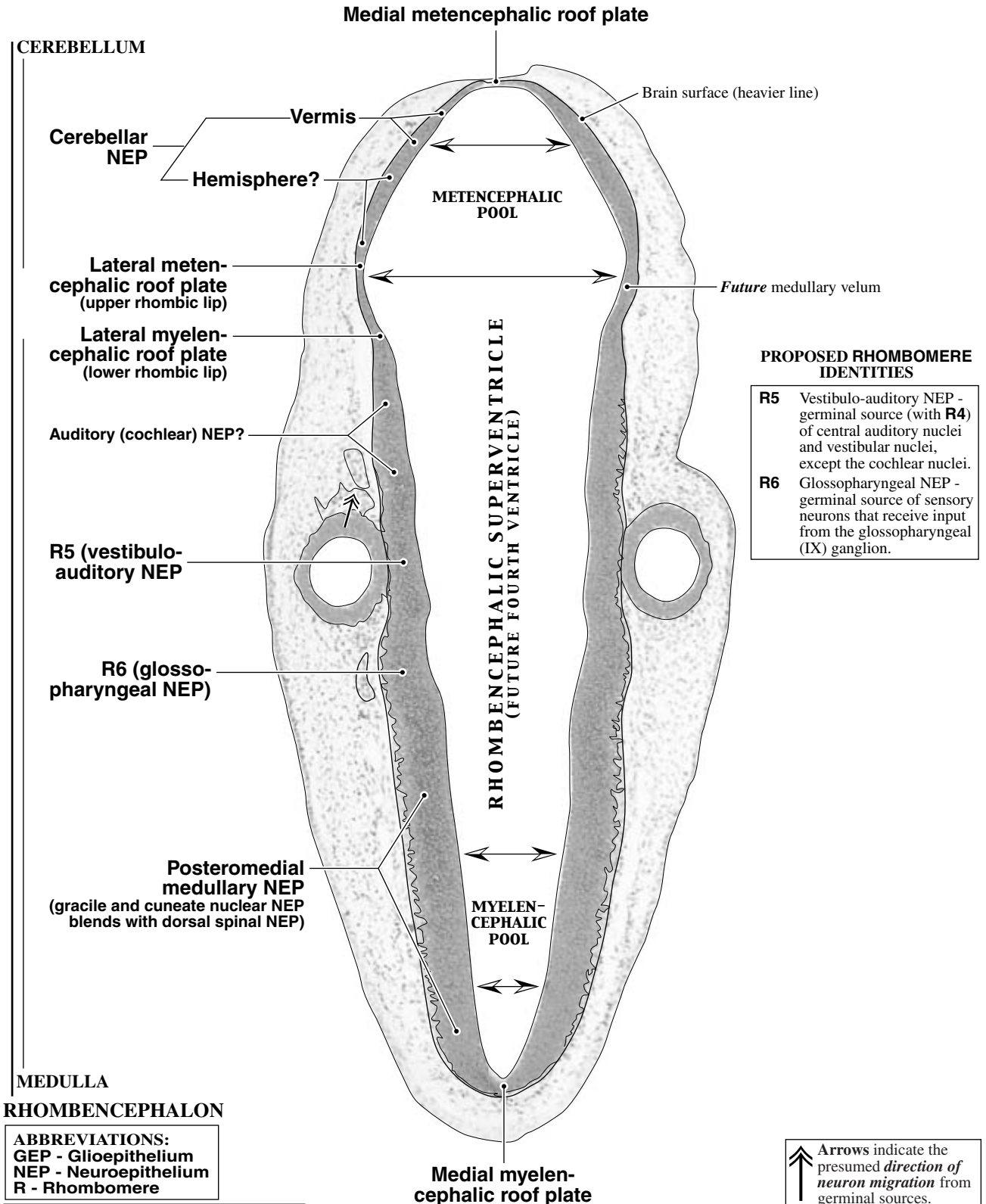
Nerve VIII (vestibulocochlear)
Nerve IX (glossopharyngeal)

* *Boundary caps are* **Schwann cell GEPs***?*

Level 12: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 171B



PROPOSED RHOMBOMERE IDENTITIES

R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the superventricle with increase in stockbuilding NEP cells.

PART XIV: GW3.8 SAGITTAL

Carnegie Collection specimen #7724 (designated here as C7724) has a 4-mm crown-rump length (CR). However, at this early stage, CR length is an unreliable estimate of gestational age. The right side of the body has clearly separated 24 to 25 somites with both anterior and posterior neuropores closed. Using the timetables in Patten (1953) and Hamilton et al. (1959), we estimate that C7724 is at gestational week (GW) 3.8. C7724 was fixed in formalin, was embedded in a celloidin/paraffin mix, and was cut in 8-µm sagittal sections that were stained with hematoxylin and eosin. Various orientations of the computer-aided 3-D reconstruction of C836's brain are used to show the gross external features of a GW4 brain (**Figure 13**). Like most sagittally cut specimens, C7724's sections are not parallel to the midline; **Figure 13** shows the approximate rotations in front (**B**) and back views (**C**). We photographed 24 sections at low magnification from the left to right sides of the body. Eight of the sections, mainly from the left side of the body, are illustrated in **Plates 172AB to 179AB**. Each illustrated section shows the entire embryo. Labels in **A Plates** (normal-contrast images) identify the approximate midline, non-neural structures, peripheral neural structures, and brain ventricular divisions; labels in **B Plates** (low-contrast images) identify central neural structures. **Plates 180AB to 184AB** show high-magnification views of several parts of the brain.

The prosencephalon is the smallest major brain structure with little distinction between a future telencephalon and diencephalon. The entire prosencephalic neuroepithelium is rapidly stockbuilding its various populations of neuronal and glial stem cells surrounding a small prosencephalic protoventricle. The ventral and lateral prosencephalon is surrounded by cephalic preplacodes at the surface (for example, the anterolateral olfactory placode) that are continuous with those extending into the roof of the developing oral cavity (for example, Rathke's pouch).

The mesencephalon is smaller than at GW4 but has similar developmental features. The stockbuilding pretectal and tectal neuroepithelia have a relatively short anteroposterior length and blend with the presumptive cerebellar neuroepithelium in the dorsomedial rhombencephalon. The stockbuilding tegmental and isthmal neuroepithelia form a distinctive arch between the mesencephalic and diencephalic flexures. These neuroepithelia surround a small mesencephalic protoventricle. There is a very thin subpial fiber band in the tegmentum and isthmus.

The rhombencephalon is the largest brain structure. Rhombomeres 2 through 7 form well-defined swellings in the lateral neuroepithelium (**Plate 176**). As in the GW4 specimens, most sensory cranial ganglia and the otic vesicle are located directly lateral to the rhombomeres with which they interact. The trigeminal ganglion (source of sensory V axons) appears in sections lateral to the last section that contains rhombomere 2. The vestibulocochlear ganglion (VIII afferents) and the otic vesicle are lateral to the last section that contains rhombomeres 4 and 5. The presumptive glossopharyngeal ganglion (IX afferents) is ventrolateral to the last section with rhombomere 6, and the presumptive vagal nerve (X afferents) is lateral to the last section with rhombomere 7. The presumptive facial ganglion (VII afferents) is near a branchial placode in the hyoid arch, slightly posterior and ventrolateral to rhombomere 3. Each rhombomere has a thin layer of pioneer migrating neurons that are only visible in most lateral sections, where the outer edges of the rhombomeric neuroepithelium are cut tangentially. Sections through the midline show a smooth neuroepithelium. Some migrating cells are outside the lower medullary neuroepithelium. The primordial white matter in the spinal cord extends into the lower medulla. The cerebellum stands out as the most immature and smallest rhombencephalic structure that blends with the isthmal neuroepithelium laterally and the presumptive tectal neuroepithelium medially.

EXTERNAL FEATURES OF THE GW4.0 BRAIN

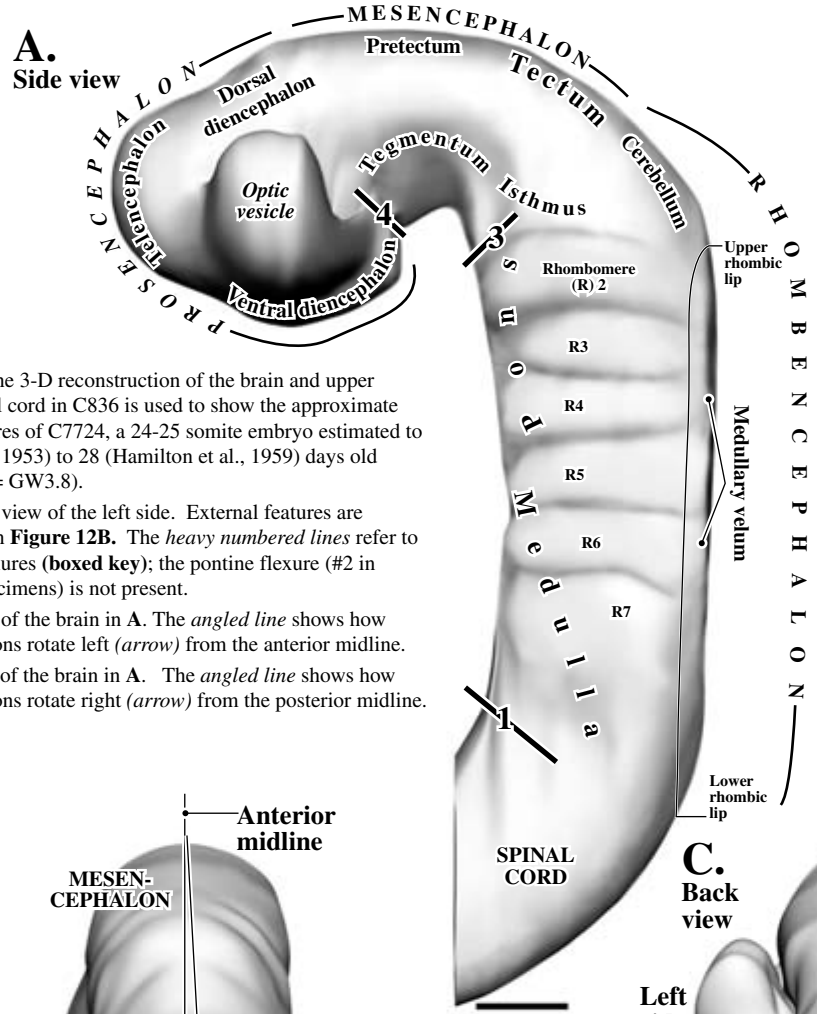


Figure 13. The 3-D reconstruction of the brain and upper cervical spinal cord in C836 is used to show the approximate external features of C7724, a 24-25 somite embryo estimated to be 25 (Patten, 1953) to 28 (Hamilton et al., 1959) days old (average age = GW3.8).

A, The lateral view of the left side. External features are identified as in **Figure 12B.** The *heavy numbered lines* refer to brainstem flexures **(boxed key)**; the pontine flexure (#2 in preceding specimens) is not present.

B, Front view of the brain in **A**. The *angled line* shows how C7724's sections rotate left *(arrow)* from the anterior midline.

C, Back view of the brain in **A**. The *angled line* shows how C7724's sections rotate right *(arrow)* from the posterior midline.

A perfect sagittal cut through the brain is parallel to the midline from anterior to posterior.

Sections of C7724's brain rotate an estimated 6.6º counterclockwise from the midline, 3.3º to the left side of the anterior midline (B, front view), and 3.3º to the right side of the posterior midline (C, back view).

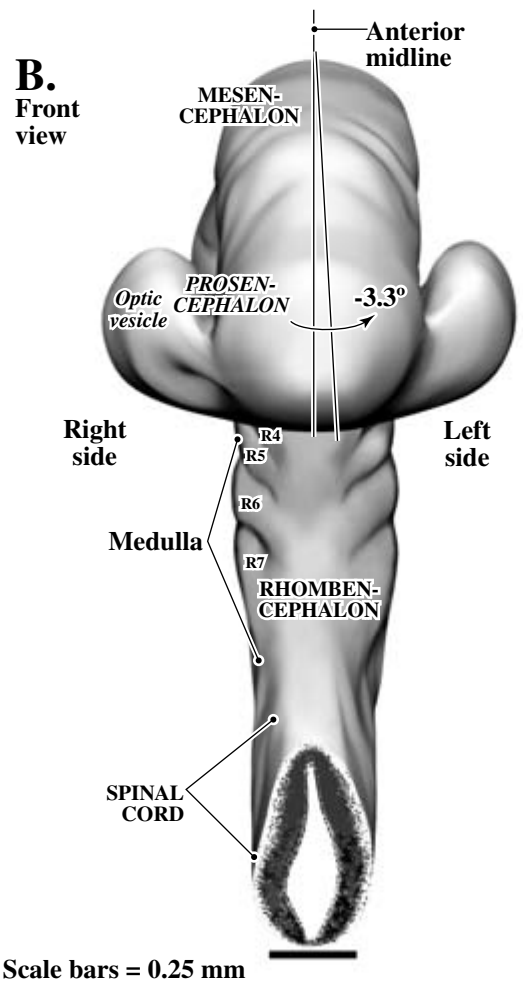
In the sections illustrated on the following pages, anterior parts (top and left) are tilted toward the observer, while posterior parts (bottom and right) are tilted away from the observer. The lower part of the spinal cord (not shown in this reconstruction) has a concave curve, and the sacral tip is cut in the coronal plane.

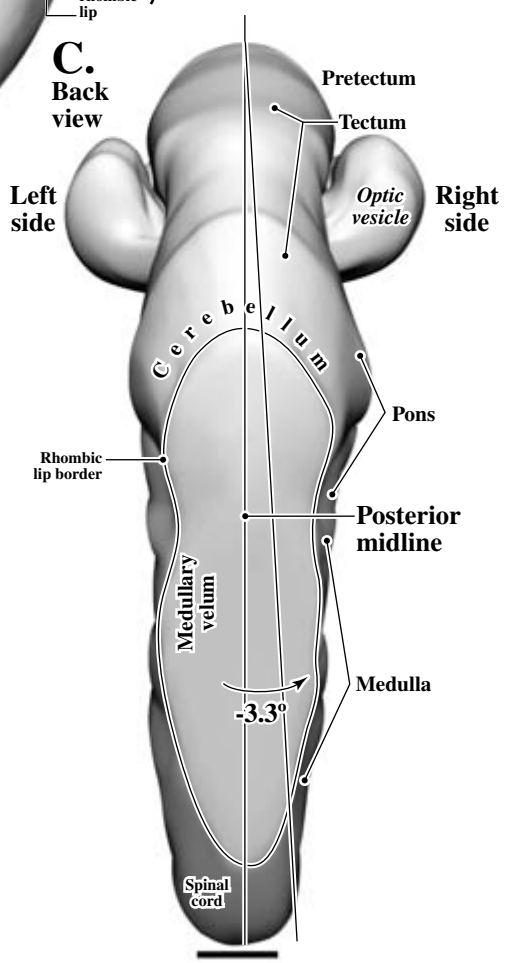
BRAINSTEM FLEXURES

1. Medullary

3. Mesencephalic

4. Diencephalic

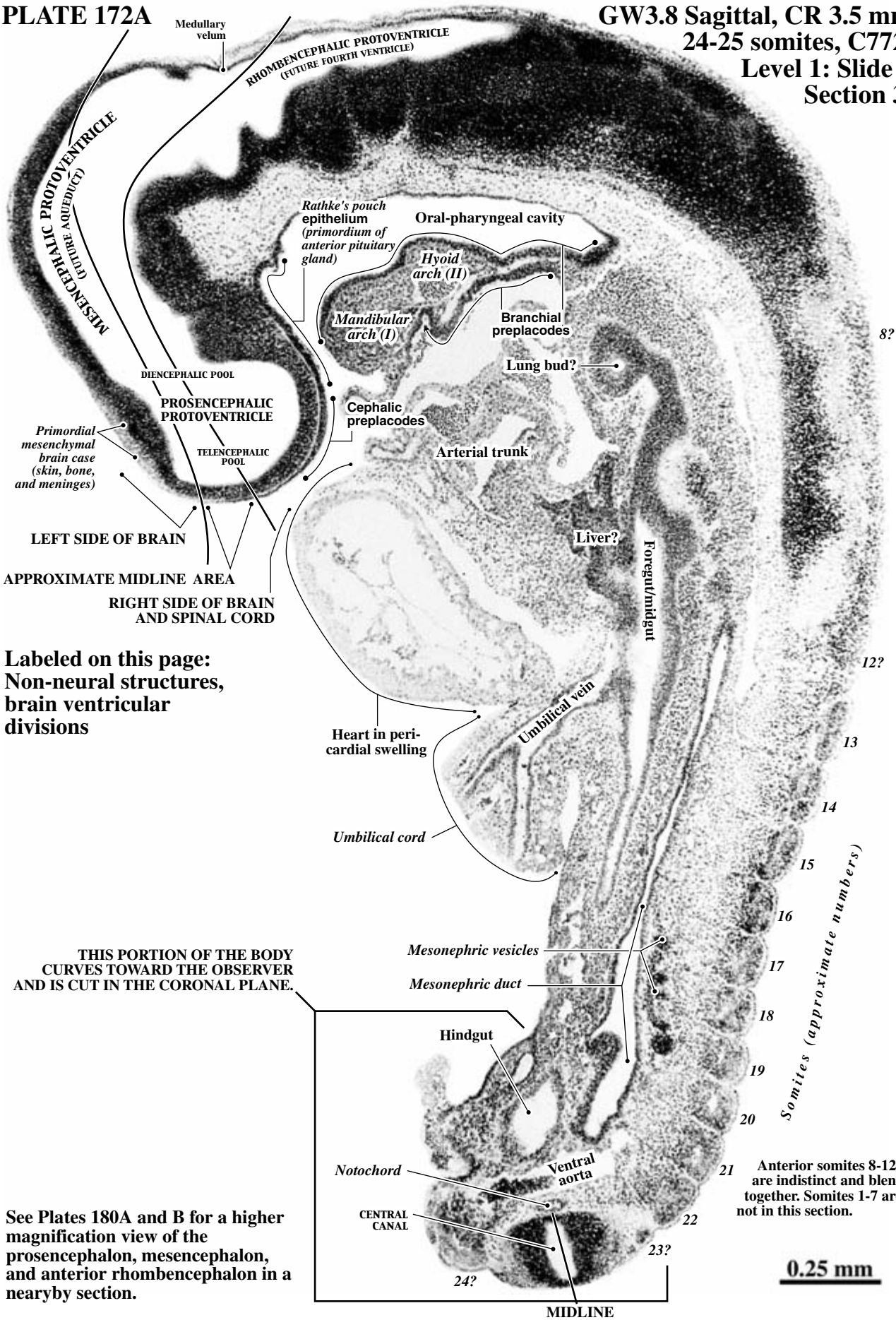




Scale bars = 0.25 mm

PLATE 172A

GW3.8 Sagittal, CR 3.5 mm, 24-25 somites, C7724 Level 1: Slide 2, Section 30

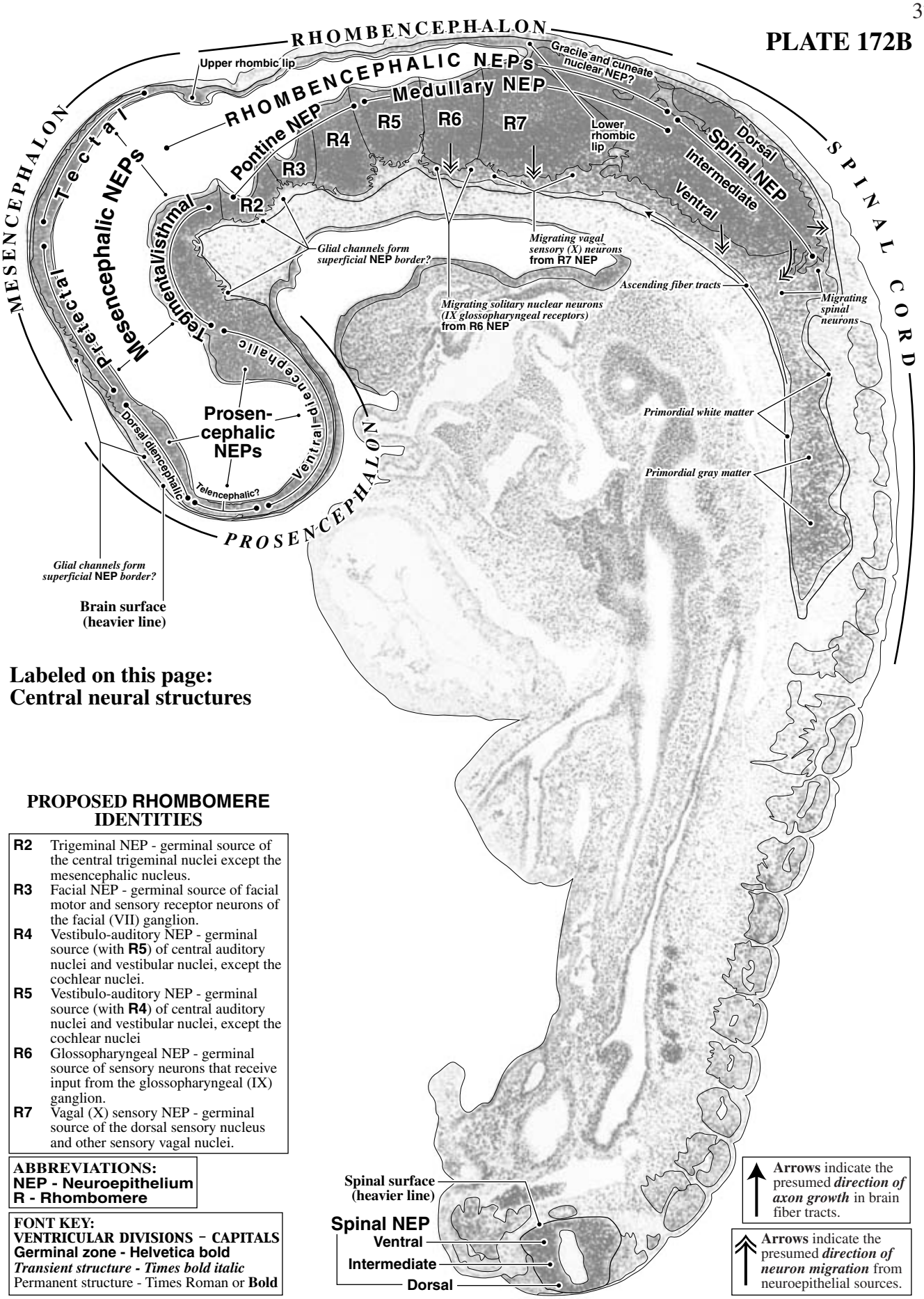


Labeled on this page: Non-neural structures, brain ventricular divisions

See Plates 180A and B for a higher magnification view of the prosencephalon, mesencephalon, and anterior rhombencephalon in a nearyby section.

Anterior somites 8-12 are indistinct and blend together. Somites 1-7 are not in this section.

PLATE 172B



Labeled on this page:
Central neural structures

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

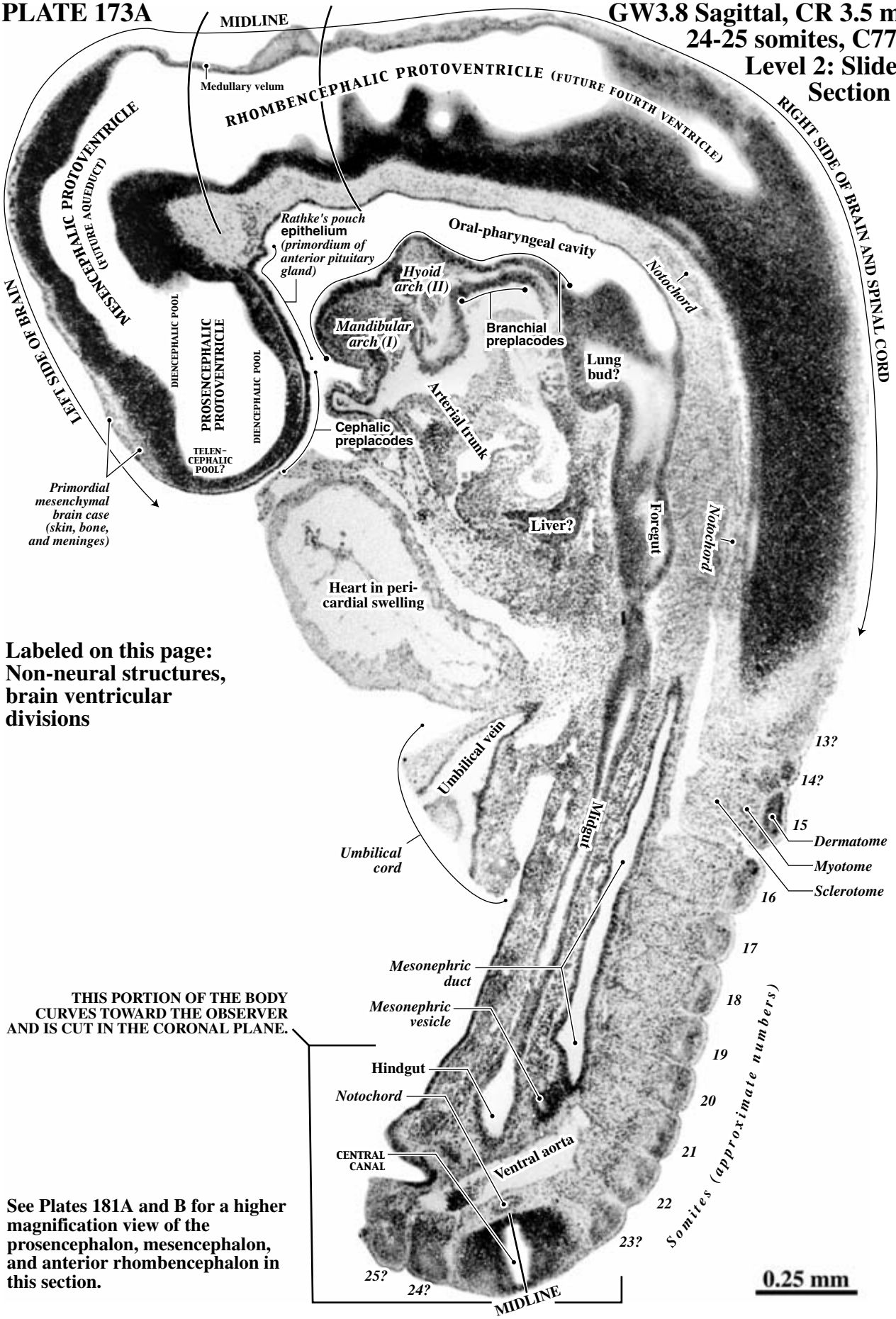
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of axon growth*** in brain fiber tracts.

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 173A

GW3.8 Sagittal, CR 3.5 mm 24-25 somites, C7724 Level 2: Slide 2, Section 24

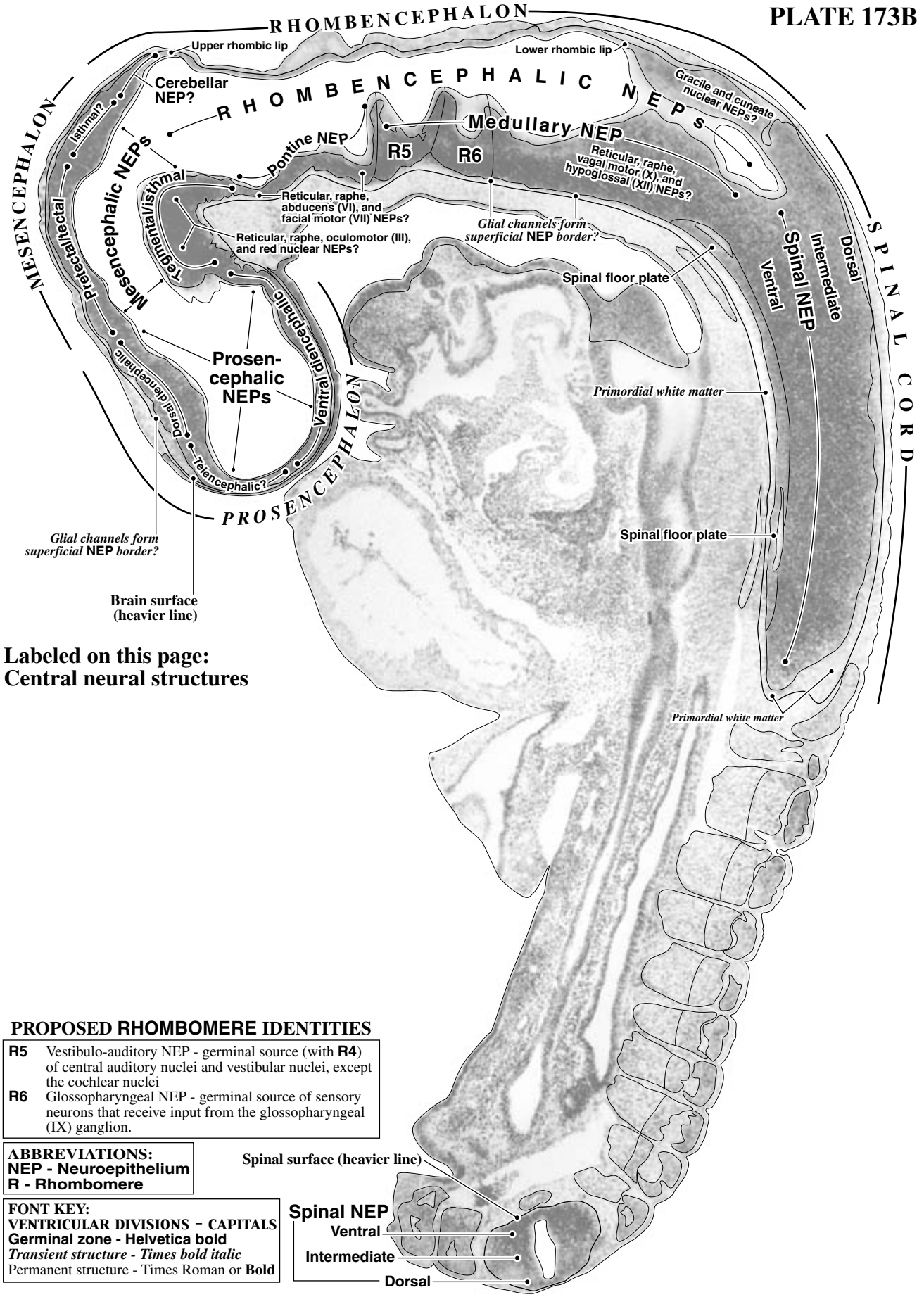


Labeled on this page: Non-neural structures, brain ventricular divisions

THIS PORTION OF THE BODY CURVES TOWARD THE OBSERVER AND IS CUT IN THE CORONAL PLANE.

See Plates 181A and B for a higher magnification view of the prosencephalon, mesencephalon, and anterior rhombencephalon in this section.

PLATE 173B



Labeled on this page:
Central neural structures

PROPOSED RHOMBOMERE IDENTITIES

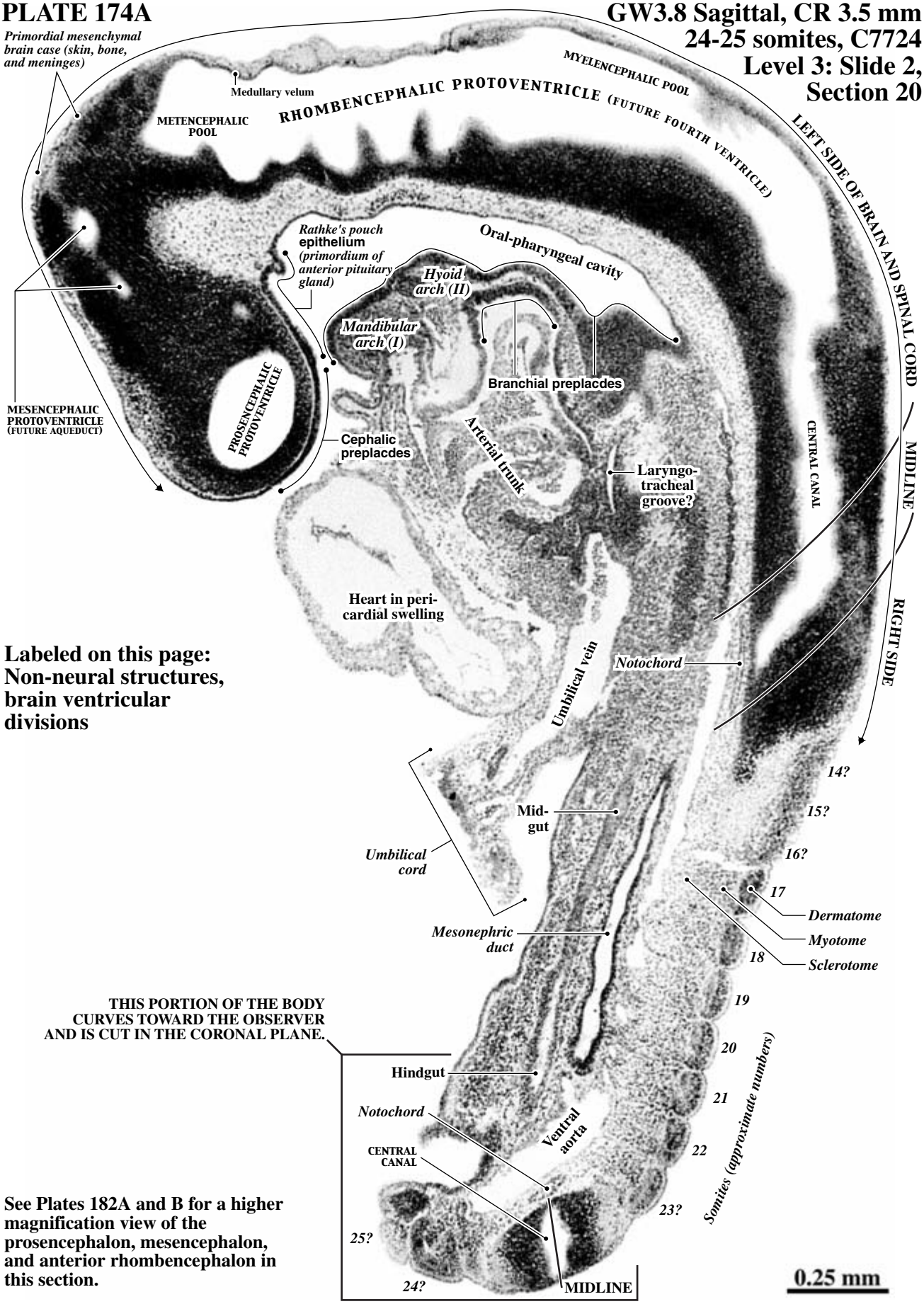
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 174A

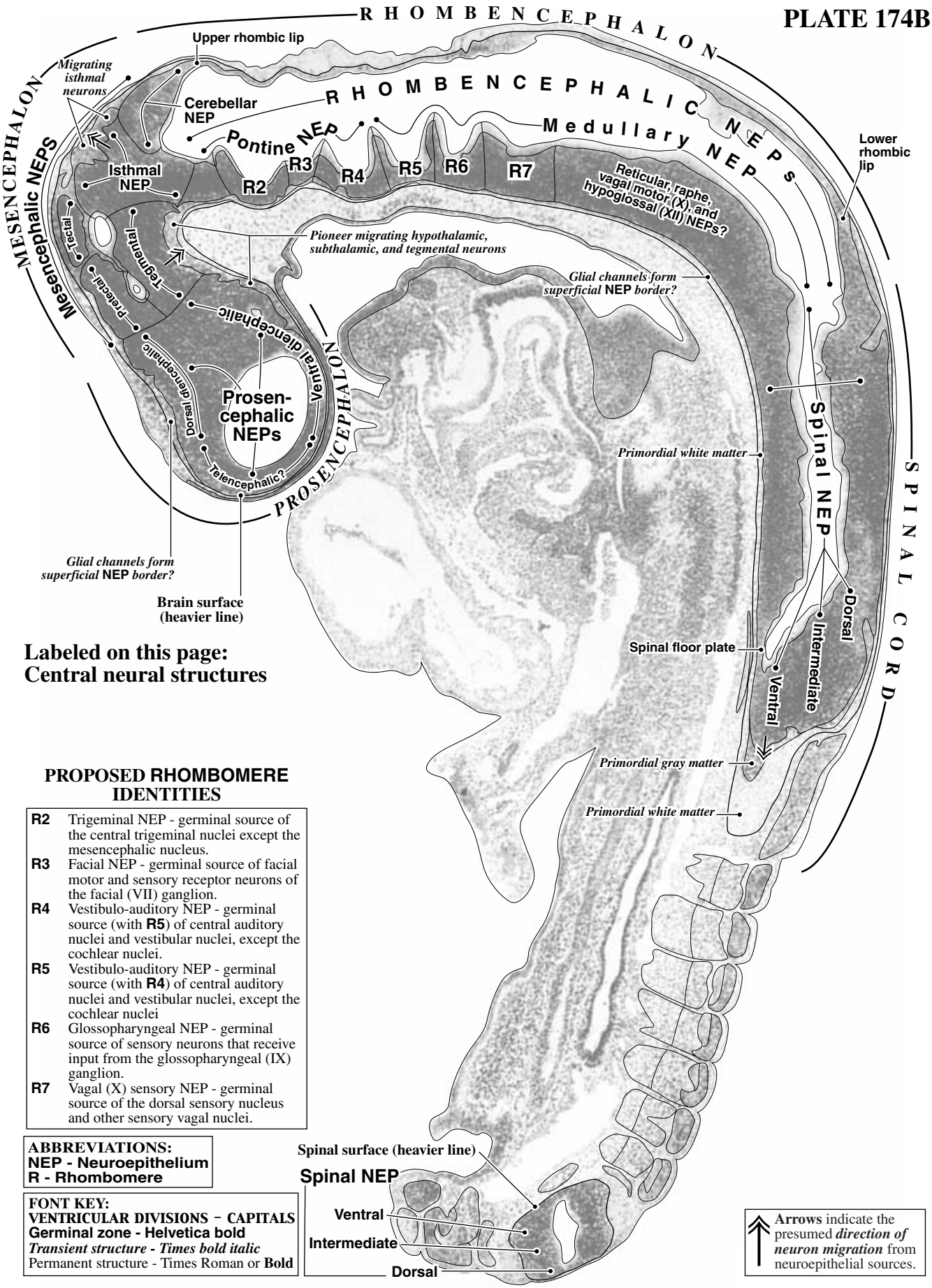
GW3.8 Sagittal, CR 3.5 mm 24-25 somites, C7724 Level 3: Slide 2, Section 20



Labeled on this page: Non-neural structures, brain ventricular divisions

See Plates 182A and B for a higher magnification view of the prosencephalon, mesencephalon, and anterior rhombencephalon in this section.

PLATE 174B



Labeled on this page:
Central neural structures

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

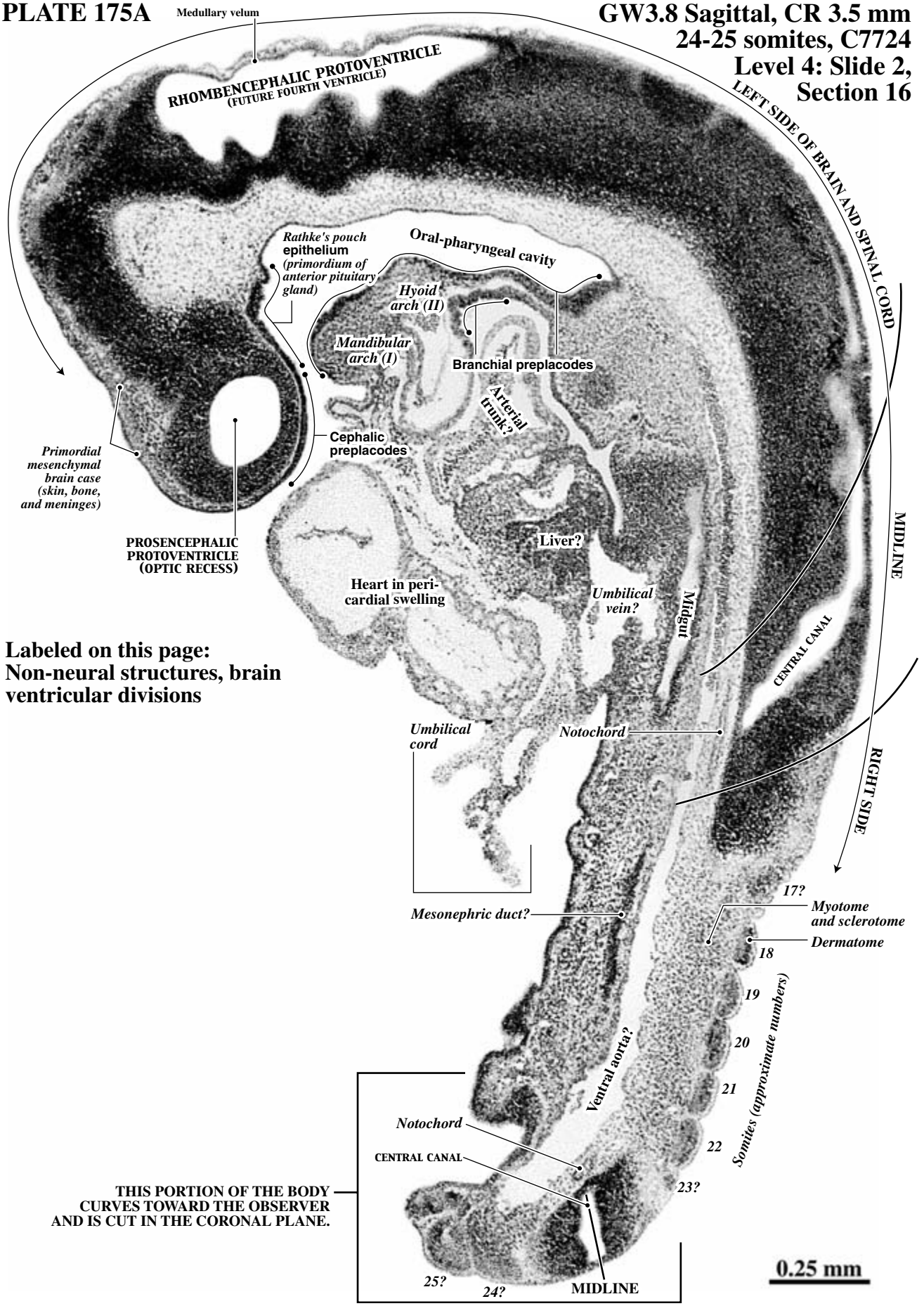
ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

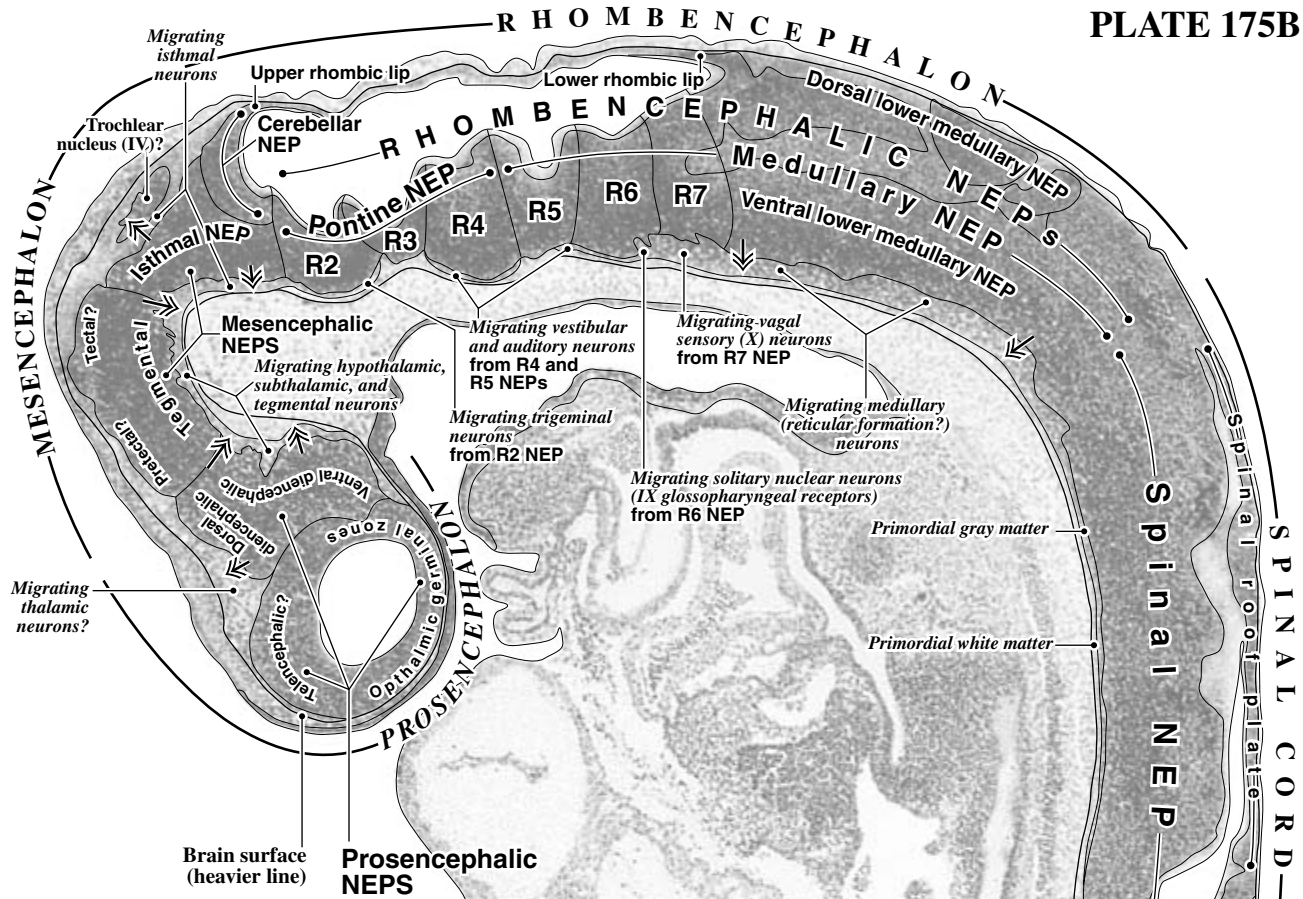
PLATE 175A

GW3.8 Sagittal, CR 3.5 mm 24-25 somites, C7724 Level 4: Slide 2, Section 16



Labeled on this page:
Non-neural structures, brain ventricular divisions

PLATE 175B



Labeled on this page:
Central neural structures

PROPOSED RHOMBOMERE IDENTITIES

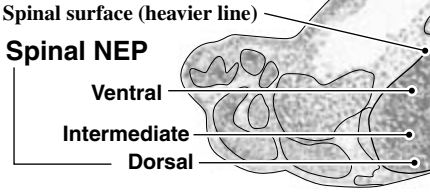
R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

The **dorsal lower medullary NEP** contains cells that will expand later into a more defined mosaic including the **cochlear nuclear NEP, the precerebellar NEP, and the gracile and cuneate nuclear NEPs.**

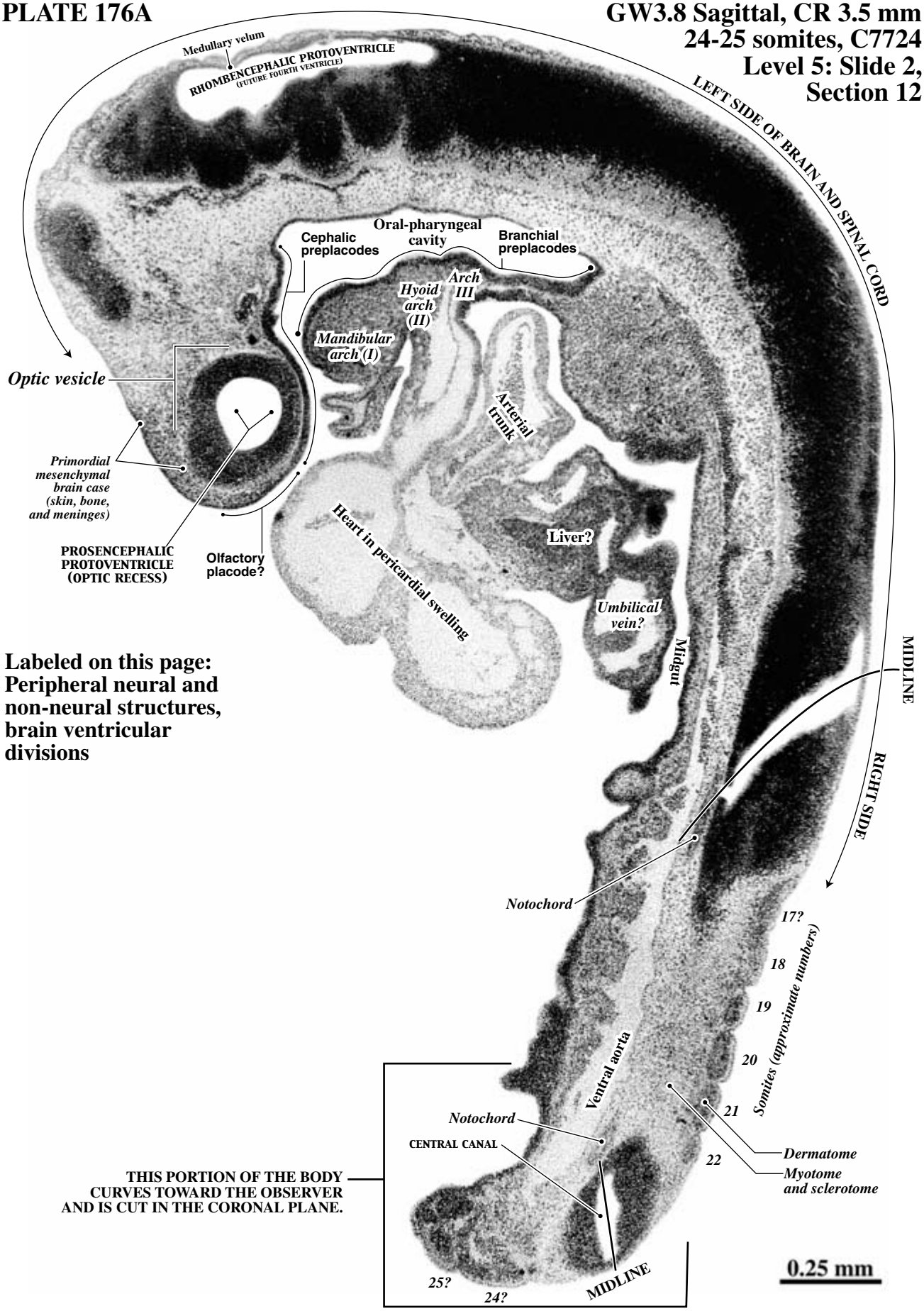
The **ventral lower medullary NEP** contains cells that will expand later into a more defined mosaic including the following **NEPs: raphe nuclear, vagal motor (X), hypoglossal (XII), prepositus nuclear, and reticular formation.**



Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

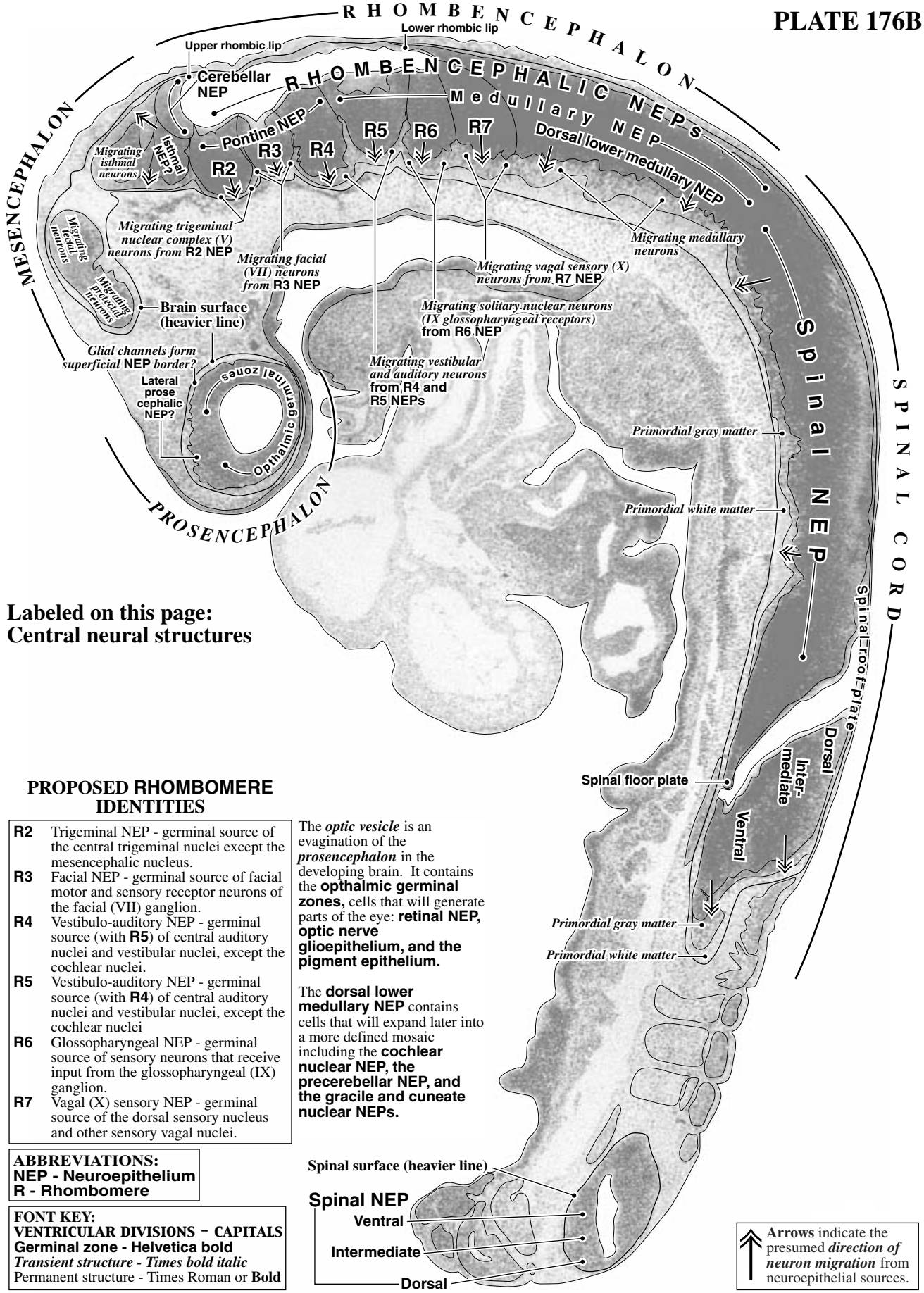
PLATE 176A

GW3.8 Sagittal, CR 3.5 mm 24-25 somites, C7724 Level 5: Slide 2, Section 12



Labeled on this page:
Peripheral neural and non-neural structures, brain ventricular divisions

PLATE 176B



Labeled on this page:
Central neural structures

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

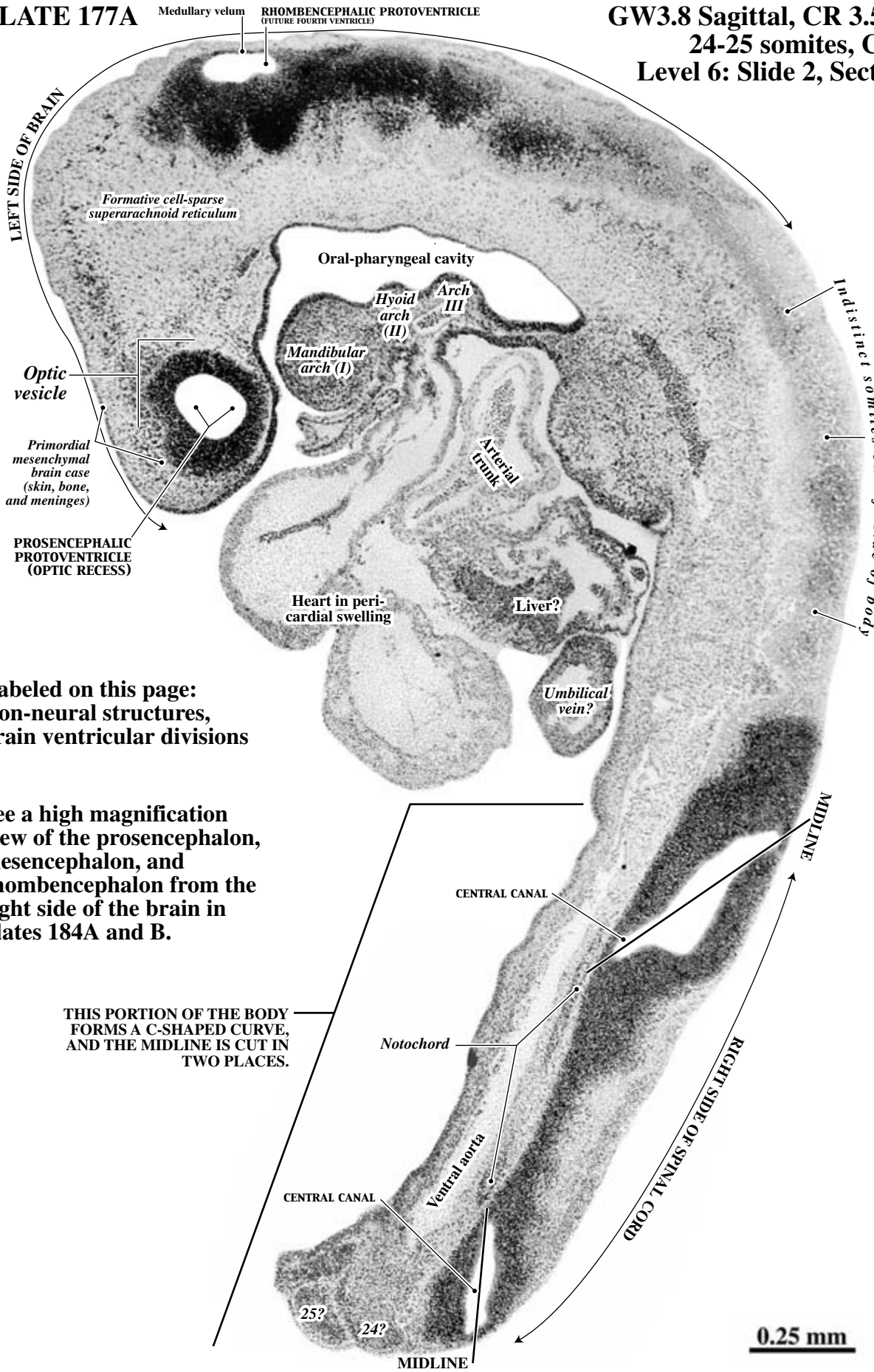
The ***optic vesicle*** is an evagination of the ***prosencephalon*** in the developing brain. It contains the **opthalmic germinal zones,** cells that will generate parts of the eye: **retinal NEP, optic nerve glioepithelium, and the pigment epithelium.**

The **dorsal lower medullary NEP** contains cells that will expand later into a more defined mosaic including the **cochlear nuclear NEP, the precerebellar NEP, and the gracile and cuneate nuclear NEPs.**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 177A

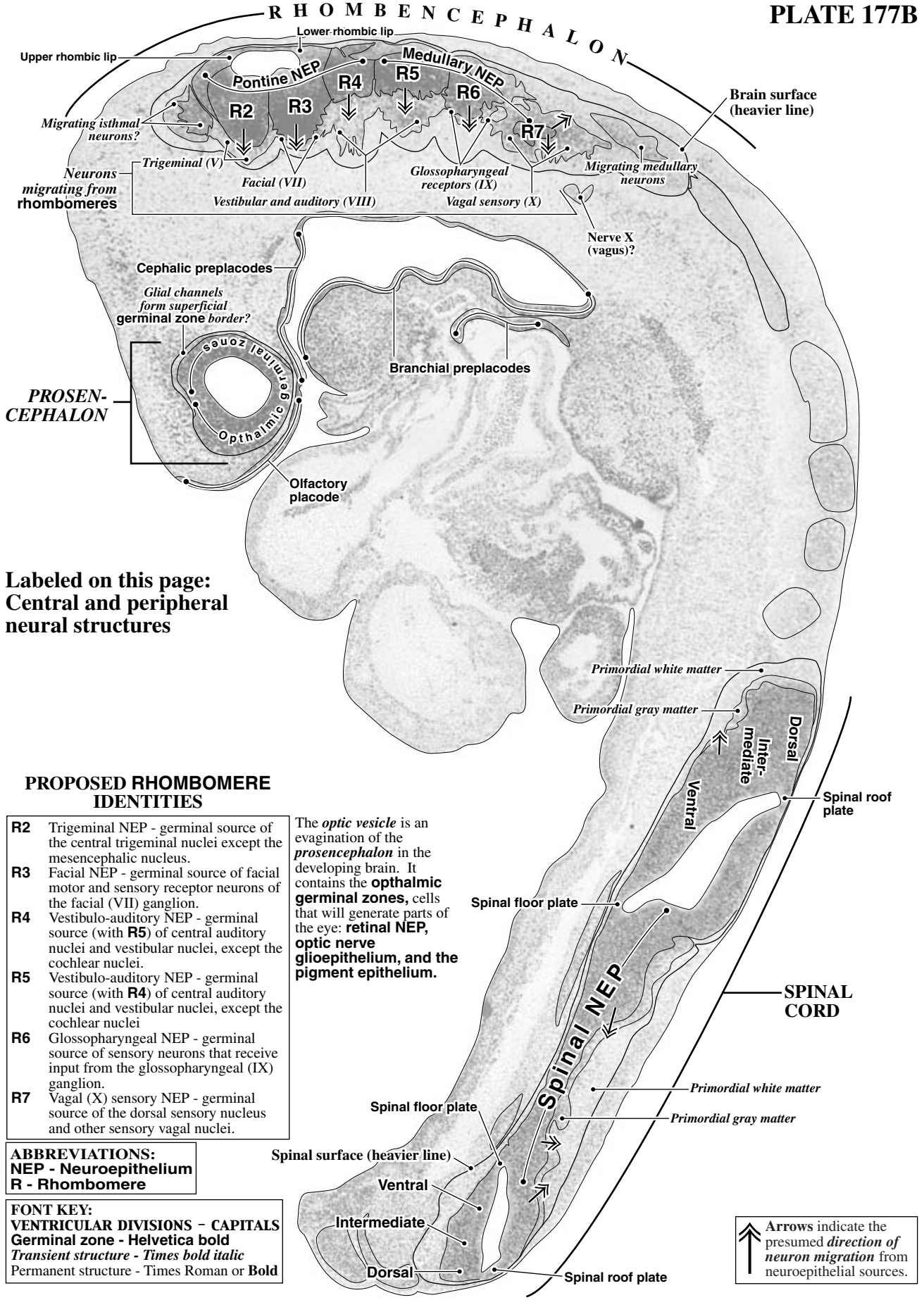
GW3.8 Sagittal, CR 3.5 mm
24-25 somites, C7724
Level 6: Slide 2, Section 8



Labeled on this page:
Non-neural structures, brain ventricular divisions

See a high magnification view of the prosencephalon, mesencephalon, and rhombencephalon from the right side of the brain in Plates 184A and B.

PLATE 177B



Labeled on this page: Central and peripheral neural structures

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

The ***optic vesicle*** is an evagination of the ***prosencephalon*** in the developing brain. It contains the **opthalmic germinal zones,** cells that will generate parts of the eye: **retinal NEP, optic nerve glioepithelium, and the pigment epithelium.**

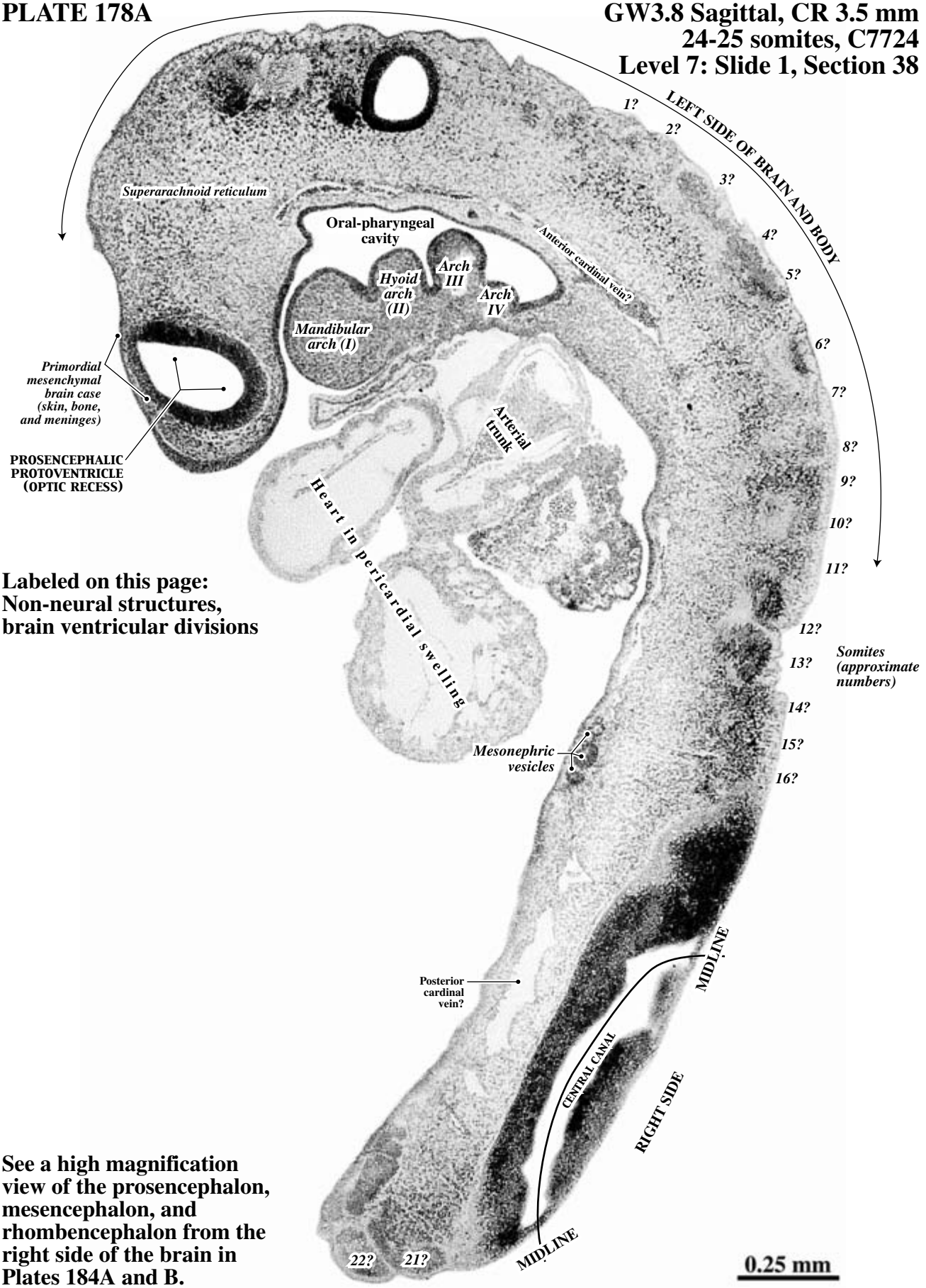
ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

PLATE 178A

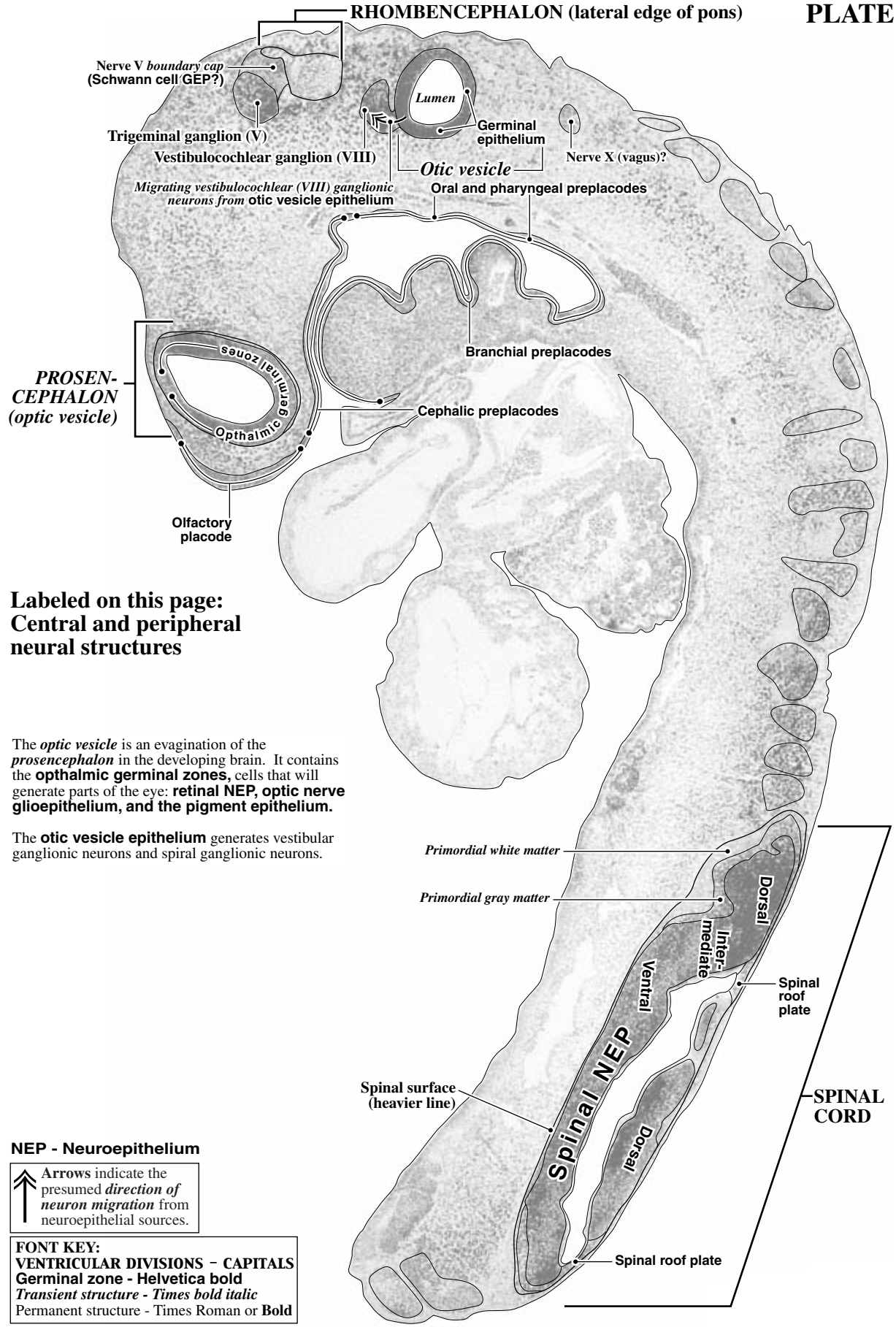
GW3.8 Sagittal, CR 3.5 mm
24-25 somites, C7724
Level 7: Slide 1, Section 38



Labeled on this page:
Non-neural structures, brain ventricular divisions

See a high magnification view of the prosencephalon, mesencephalon, and rhombencephalon from the right side of the brain in Plates 184A and B.

PLATE 178B



Labeled on this page:
Central and peripheral neural structures

The ***optic vesicle*** is an evagination of the ***prosencephalon*** in the developing brain. It contains the **opthalmic germinal zones,** cells that will generate parts of the eye: **retinal NEP, optic nerve glioepithelium, and the pigment epithelium.**

The **otic vesicle epithelium** generates vestibular ganglionic neurons and spiral ganglionic neurons.

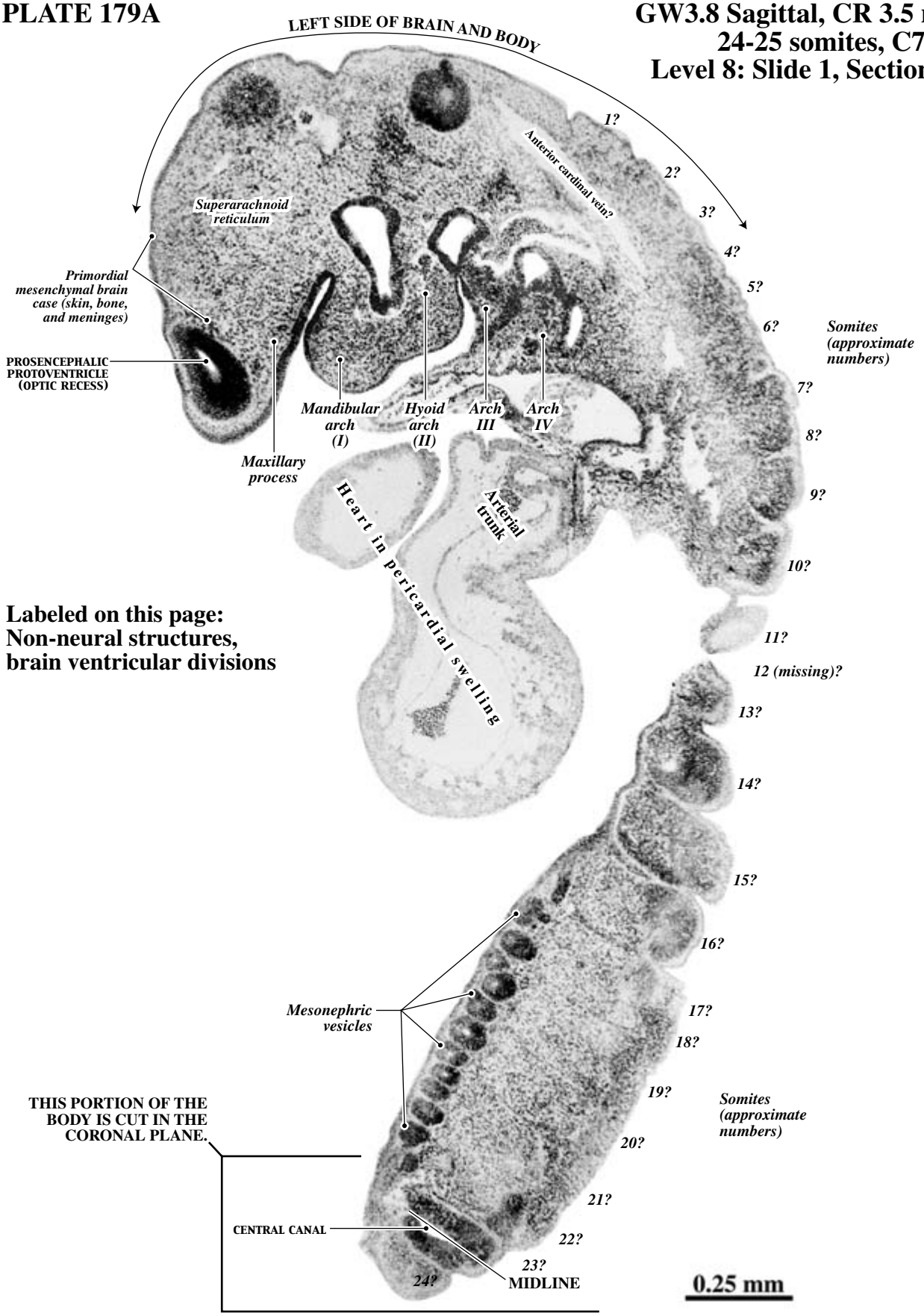
NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

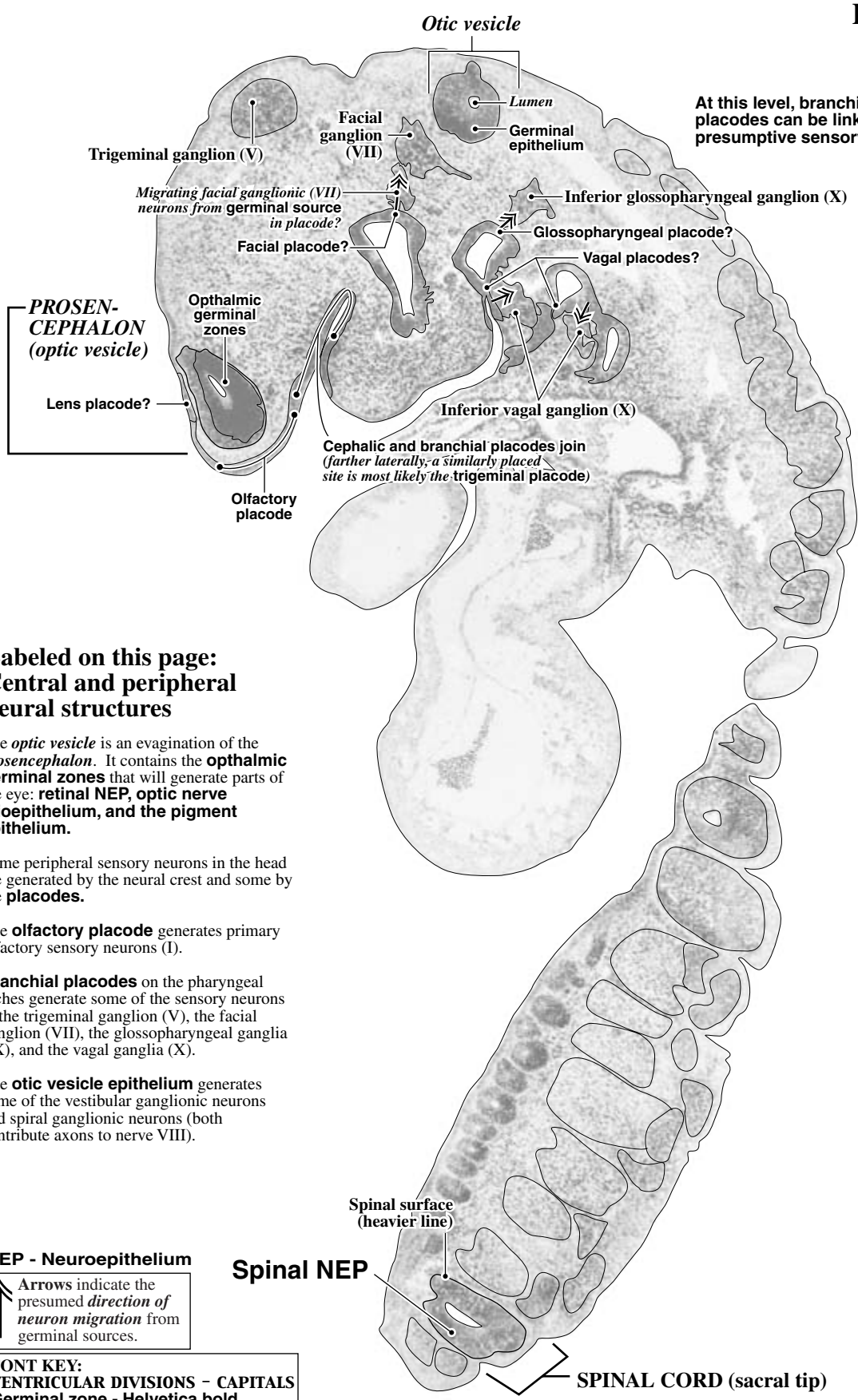
PLATE 179A

GW3.8 Sagittal, CR 3.5 mm
24-25 somites, C7724
Level 8: Slide 1, Section 30



Labeled on this page:
Non-neural structures, brain ventricular divisions

PLATE 179B



Labeled on this page: Central and peripheral neural structures

The ***optic vesicle*** is an evagination of the ***prosencephalon***. It contains the **opthalmic germinal zones** that will generate parts of the eye: **retinal NEP, optic nerve glioepithelium, and the pigment epithelium.**

Some peripheral sensory neurons in the head are generated by the neural crest and some by the **placodes.**

The **olfactory placode** generates primary olfactory sensory neurons (I).

Branchial placodes on the pharyngeal arches generate some of the sensory neurons in the trigeminal ganglion (V), the facial ganglion (VII), the glossopharyngeal ganglia (IX), and the vagal ganglia (X).

The **otic vesicle epithelium** generates some of the vestibular ganglionic neurons and spiral ganglionic neurons (both contribute axons to nerve VIII).

NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

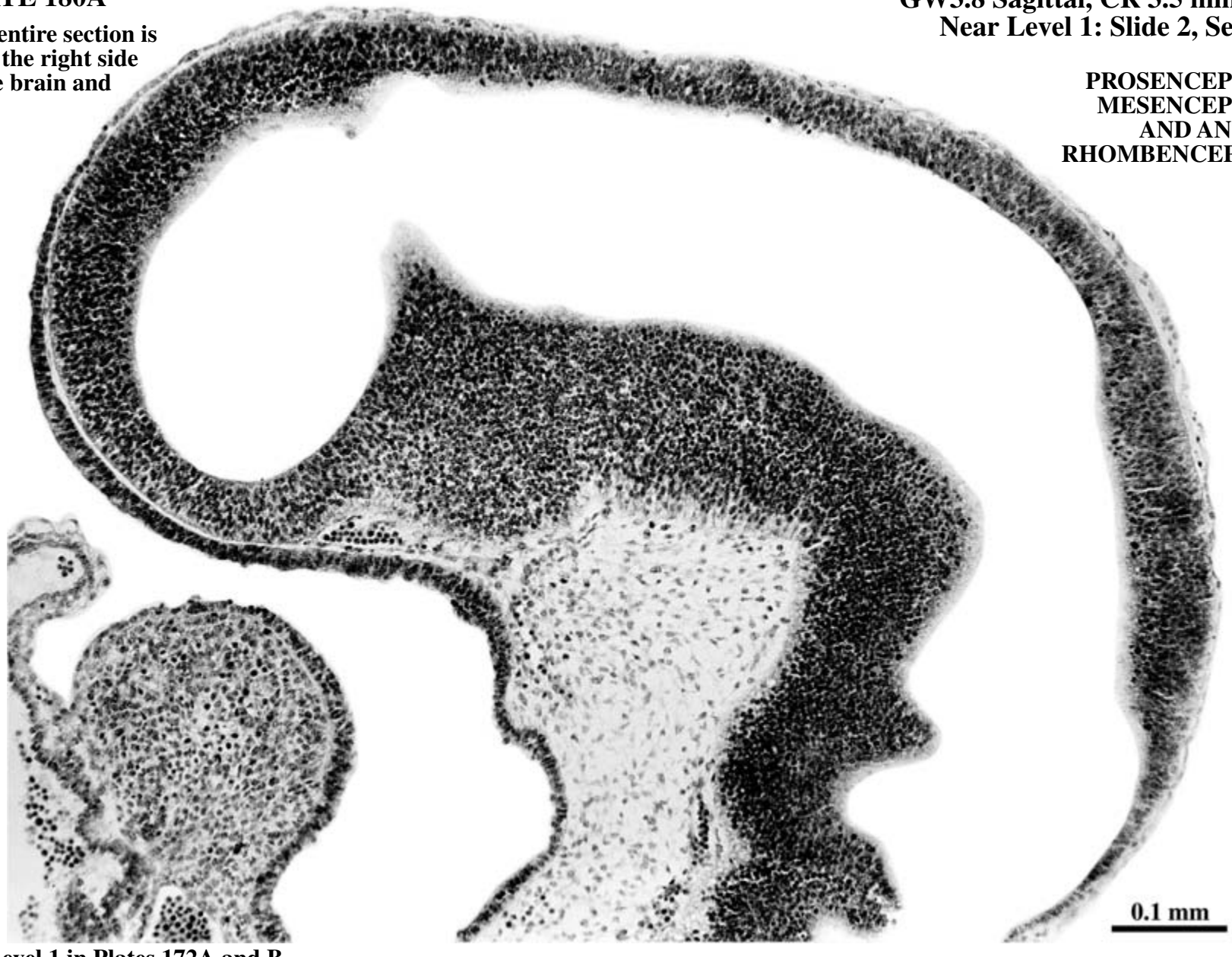
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 180A

This entire section is from the right side of the brain and body.

GW3.8 Sagittal, CR 3.5 mm, C7724
Near Level 1: Slide 2, Section 33

PROSENCEPHALON, MESENCEPHALON, AND ANTERIOR RHOMBENCEPHALON



See Level 1 in Plates 172A and B.

PLATE 180B

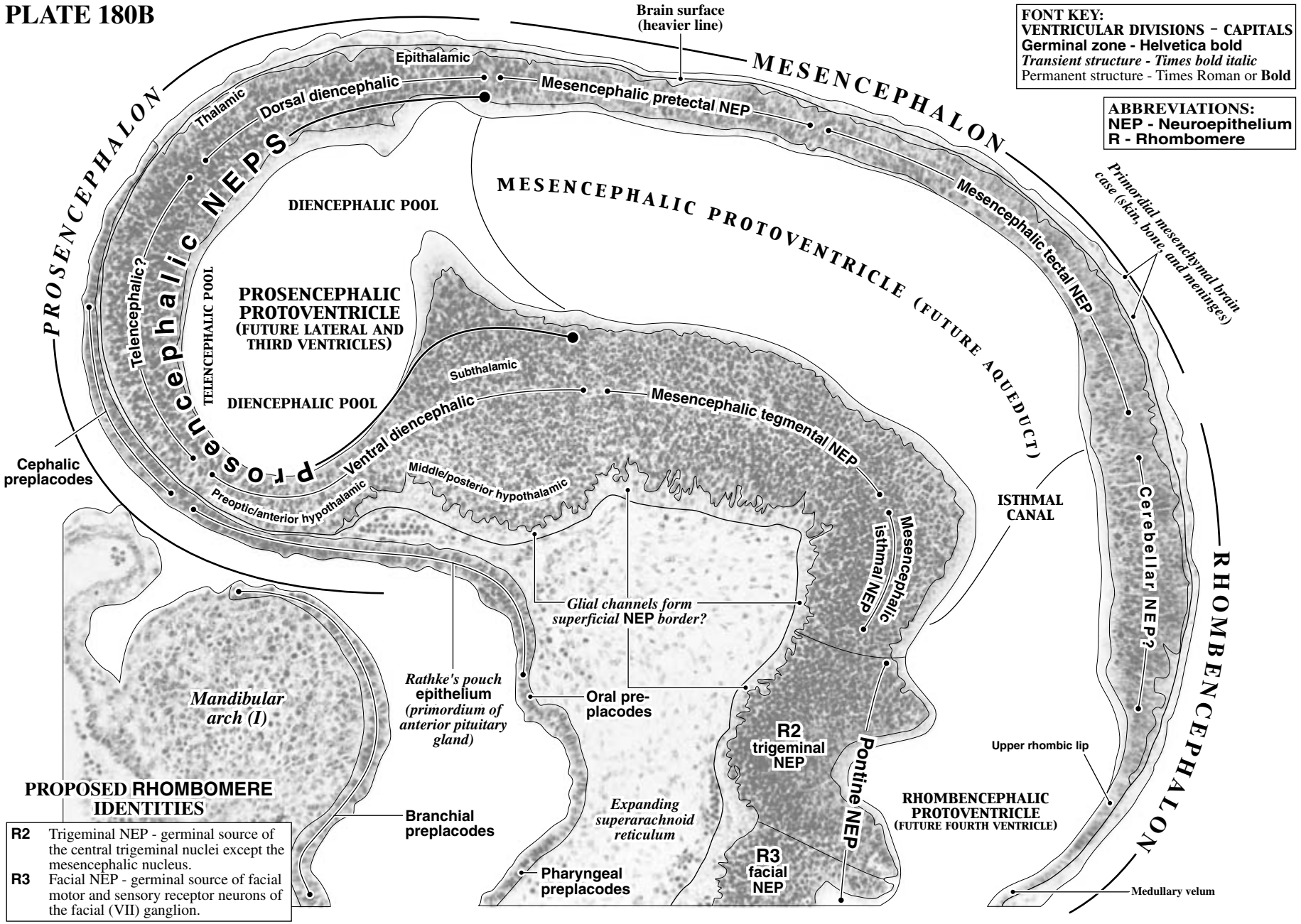

Brain surface
(heavier line)
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere
PROSENCEPHALON
MESENCEPHALON
RHOMBENCEPHALON
Epithalamic
Thalamic
Dorsal diencephalic
Mesencephalic pretectal NEP
Mesencephalic tectal NEP
Primordial mesenchymal brain case (skin, bone, and meninges)
Telencephalic?
Prosencephalic NEPS
TELENCEPHALIC POOL
DIENCEPHALIC POOL
PROSENCEPHALIC PROTOVENTRICLE (FUTURE LATERAL AND THIRD VENTRICLES)
MESENCEPHALIC PROTOVENTRICLE (FUTURE AQUEDUCT)
DIENCEPHALIC POOL
Subthalamic
Ventral diencephalic
Mesencephalic tegmental NEP
Cephalic preplacodes
Middle/posterior hypothalamic
Preoptic/anterior hypothalamic
ISTHMAL CANAL
Mesencephalic isthmal NEP
Cerebellar NEP?
Glial channels form superficial NEP border?
Rathke's pouch epithelium (primordium of anterior pituitary gland)
Mandibular arch (I)
Oral pre-placodes
R2 trigeminal NEP
Pontine NEP
Upper rhombic lip
PROPOSED RHOMBOMERE IDENTITIES
R2 Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3 Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
Branchial preplacodes
Expanding superarachnoid reticulum
RHOMBENCEPHALIC PROTOVENTRICLE (FUTURE FOURTH VENTRICLE)
R3 facial NEP
Pharyngeal preplacodes
Medullary velum

PLATE 181A

GW3.8 Sagittal, CR 3.5 mm, C7724
Level 2: Slide 2, Section 24

PROSENCEPHALON, MESENCEPHALON, AND ANTERIOR RHOMBENCEPHALON

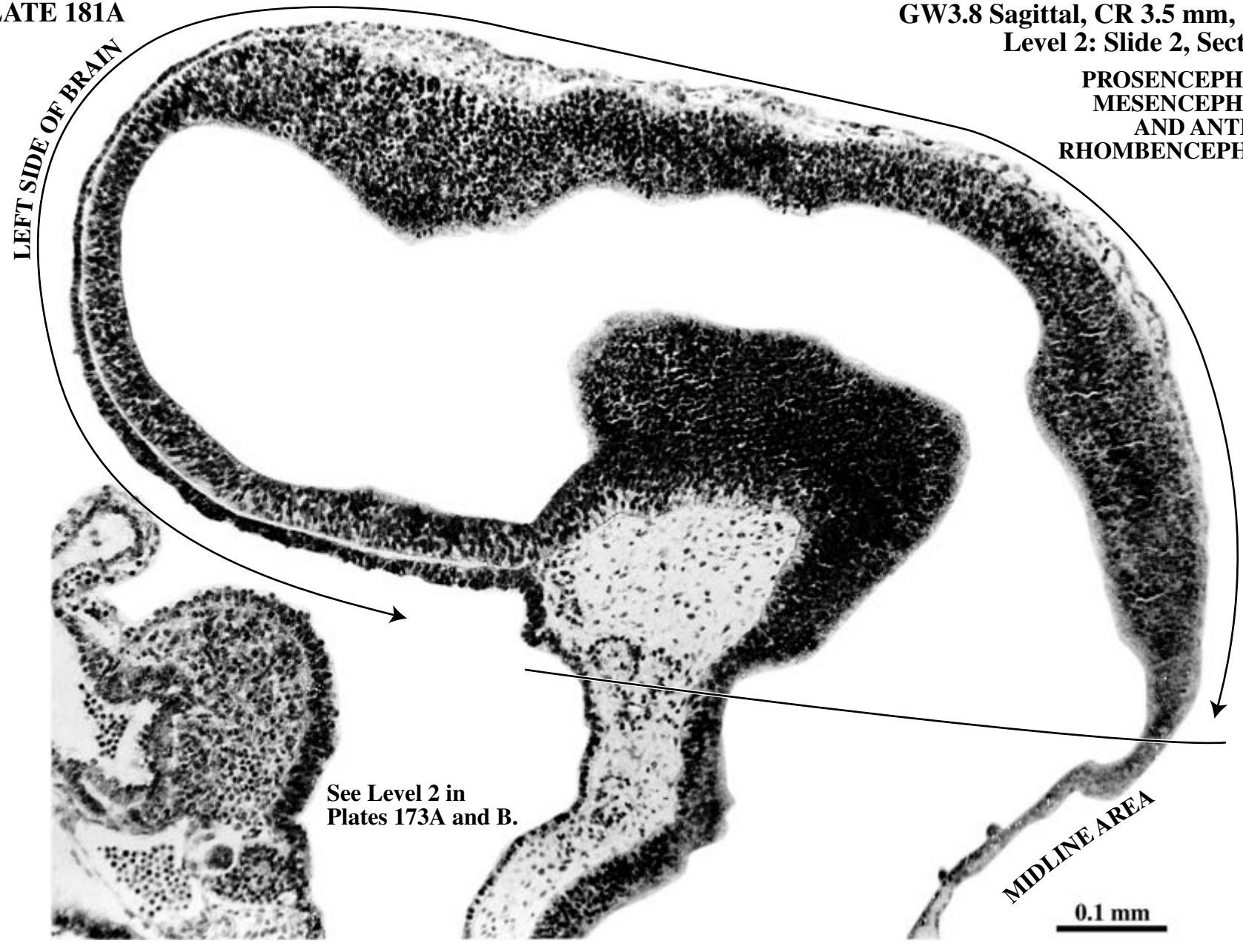


PLATE 181B

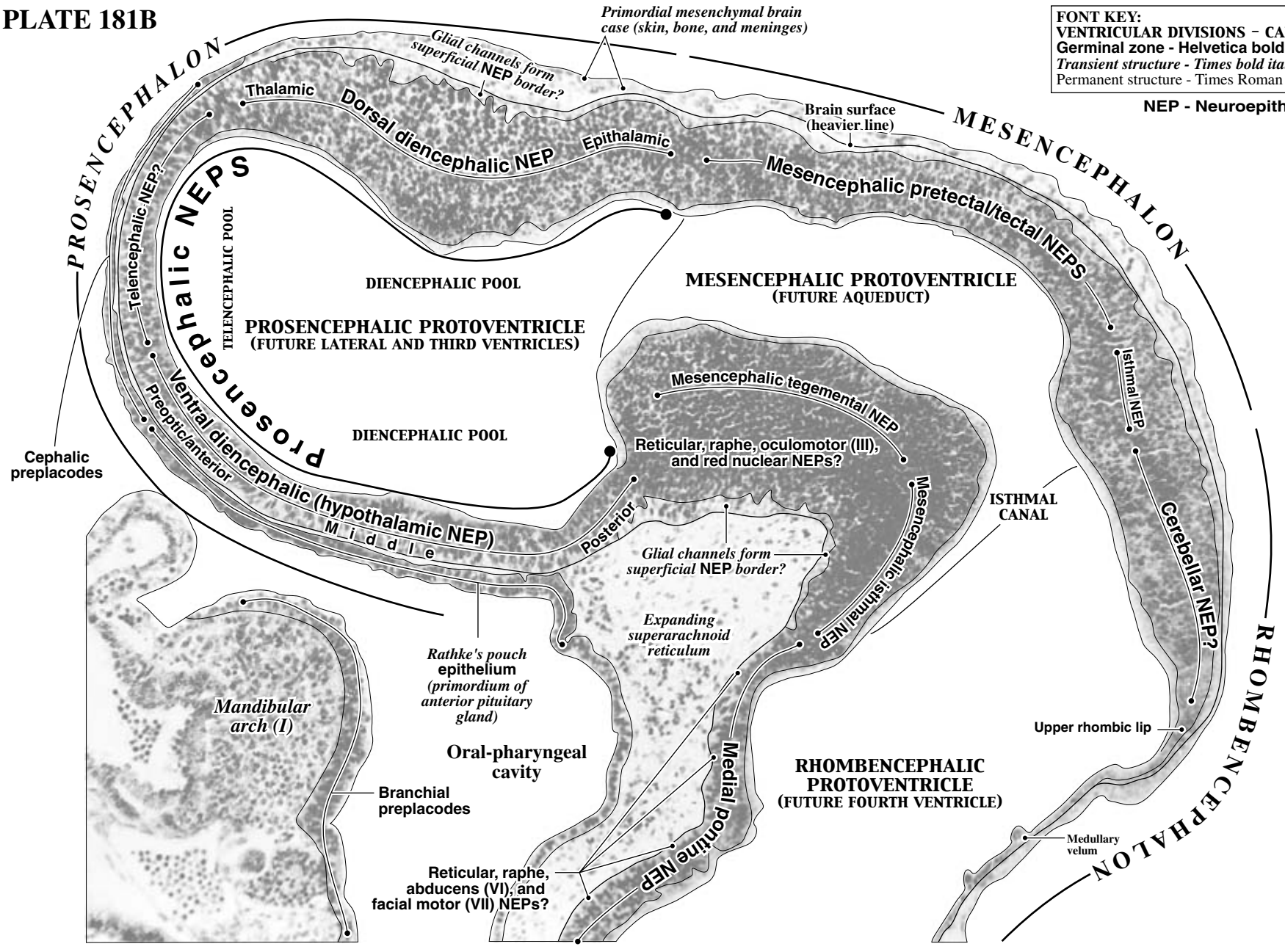
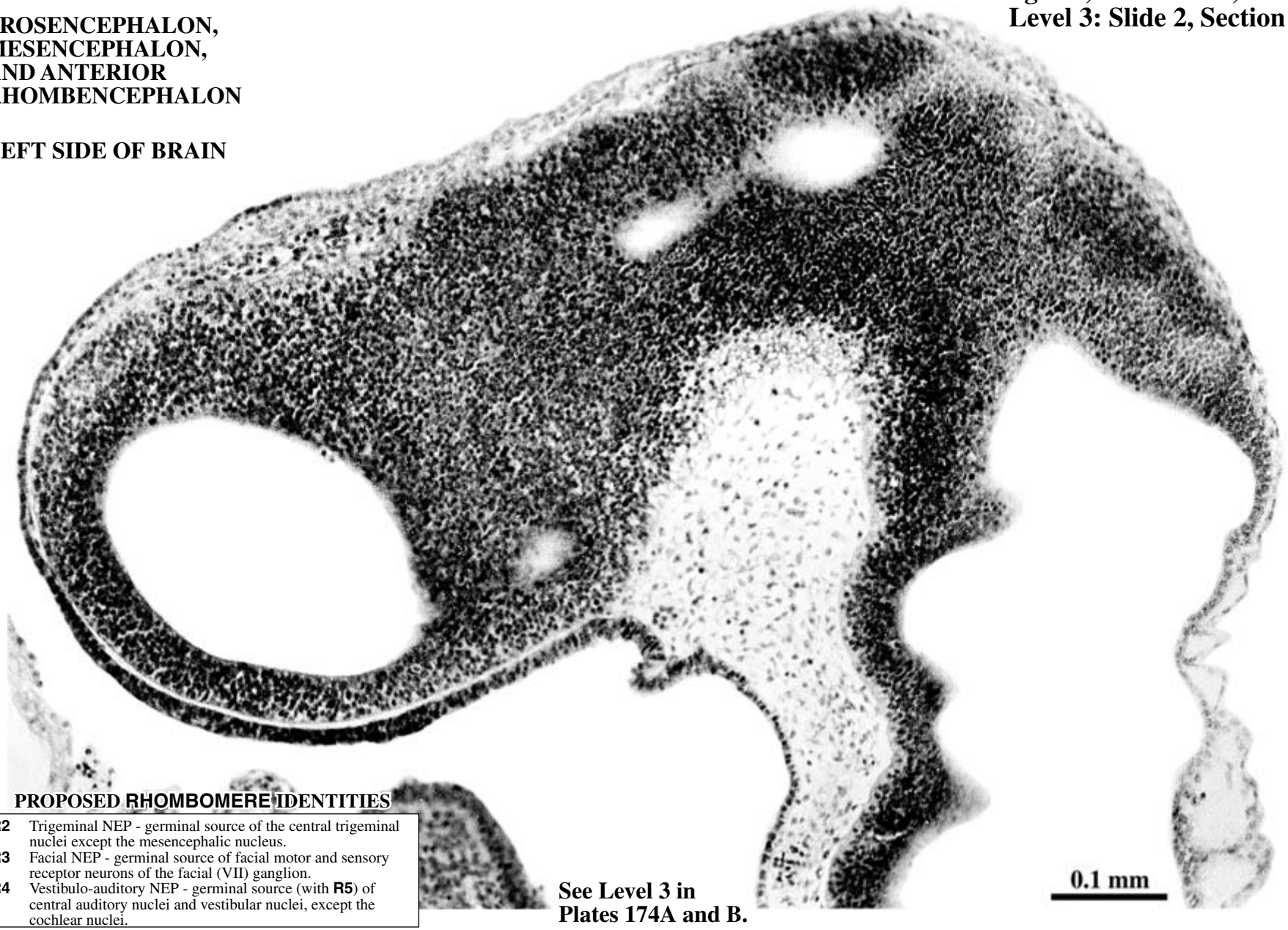

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
NEP - Neuroepithelium
Primordial mesenchymal brain case (skin, bone, and meninges)
Glial channels form superficial NEP border?
Brain surface (heavier line)
PROSENCEPHALON
MESENCEPHALON
RHOMBENCEPHALON
Thalamic
Dorsal diencephalic NEP
Epithalamic
Mesencephalic pretectal/tectal NEPS
Telencephalic NEP?
Prosencephalic NEPS
TELENCEPHALIC POOL
DIENCEPHALIC POOL
PROSENCEPHALIC PROTOVENTRICLE
(FUTURE LATERAL AND THIRD VENTRICLES)
MESENCEPHALIC PROTOVENTRICLE
(FUTURE AQUEDUCT)
Isthmal NEP
Mesencephalic tegemental NEP
Reticular, raphe, oculomotor (III), and red nuclear NEPs?
Cephalic preplacodes
Preoptic/anterior
Ventral diencephalic (hypothalamic NEP)
Middle
Posterior
DIENCEPHALIC POOL
ISTHMAL CANAL
Mesencephalic isthmal NEP
Cerebellar NEP?
Glial channels form superficial NEP border?
Expanding superarachnoid reticulum
Rathke's pouch epithelium (primordium of anterior pituitary gland)
Mandibular arch (I)
Oral-pharyngeal cavity
Upper rhombic lip
RHOMBENCEPHALIC PROTOVENTRICLE
(FUTURE FOURTH VENTRICLE)
Branchial preplacodes
Medial pontine NEP
Medullary velum
Reticular, raphe, abducens (VI), and facial motor (VII) NEPs?

PLATE 182A

PROSENCEPHALON, MESENCEPHALON, AND ANTERIOR RHOMBENCEPHALON

LEFT SIDE OF BRAIN

GW3.8 Sagittal, CR 3.5 mm, C7724
Level 3: Slide 2, Section 20



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

See Level 3 in Plates 174A and B.

PLATE 182B

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - Neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.

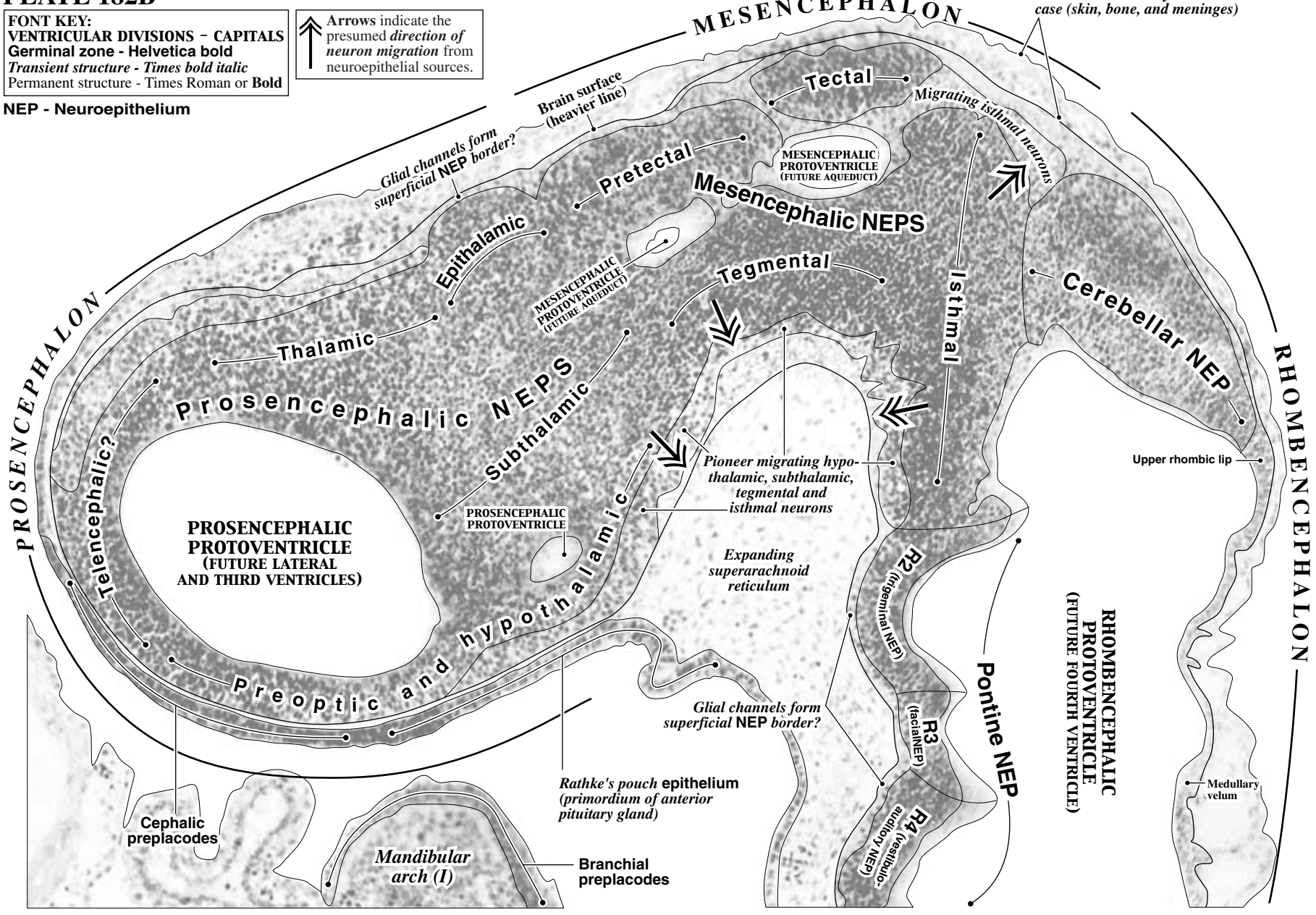


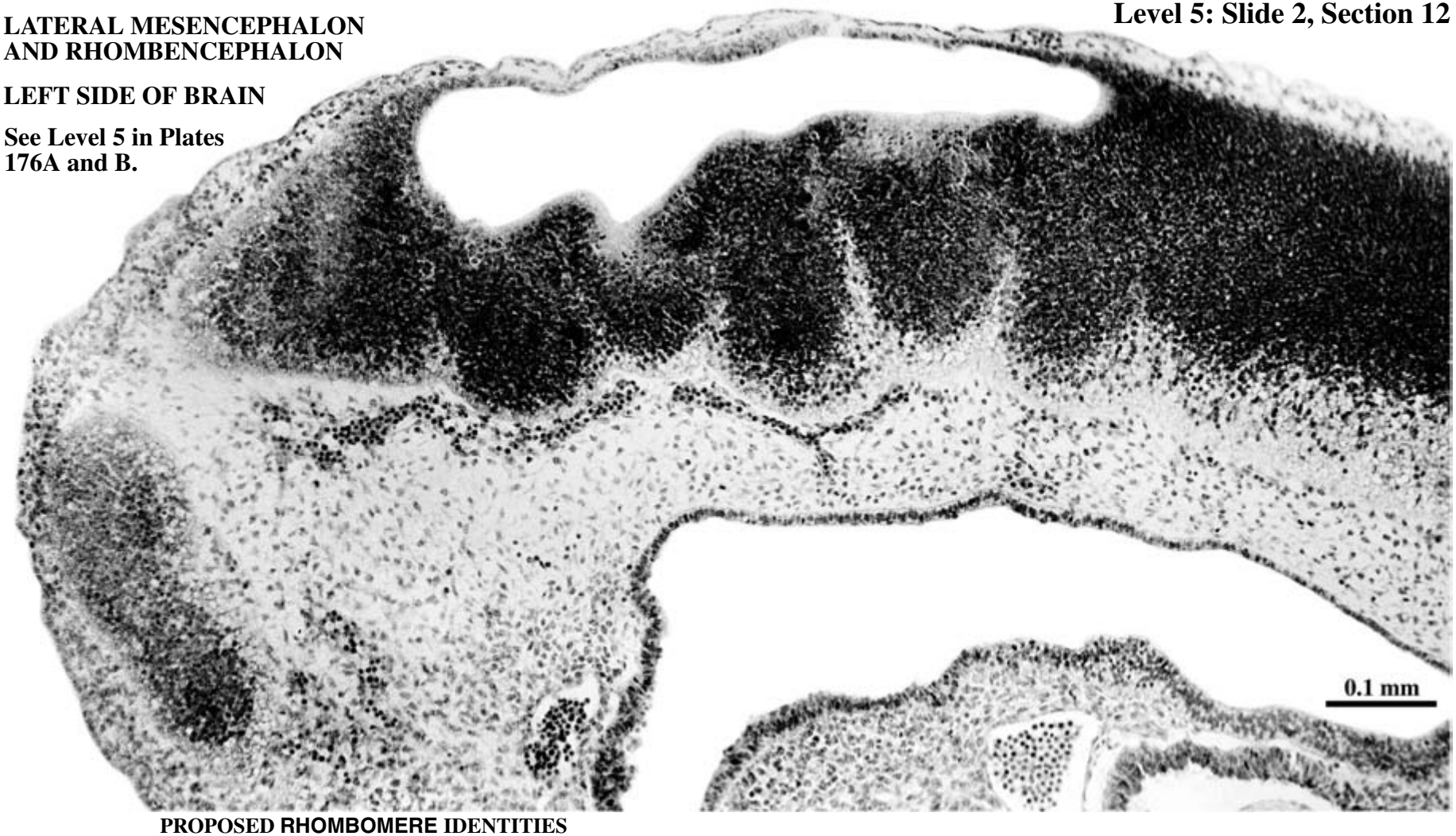
PLATE 183A

LATERAL MESENCEPHALON AND RHOMBENCEPHALON

LEFT SIDE OF BRAIN

See Level 5 in Plates 176A and B.

GW3.8 Sagittal, CR 3.5 mm, C7724
Level 5: Slide 2, Section 12



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

PLATE 183B

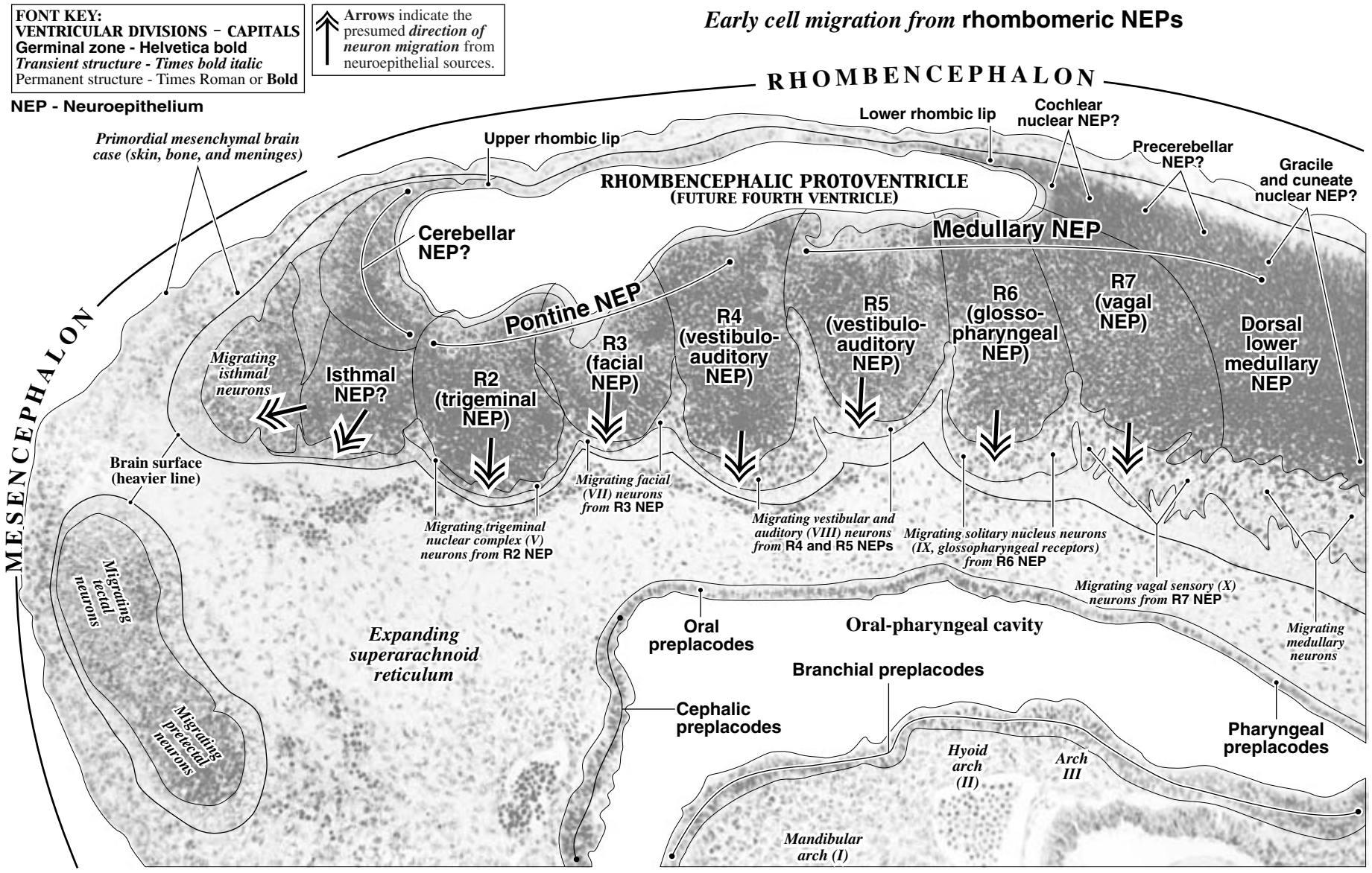
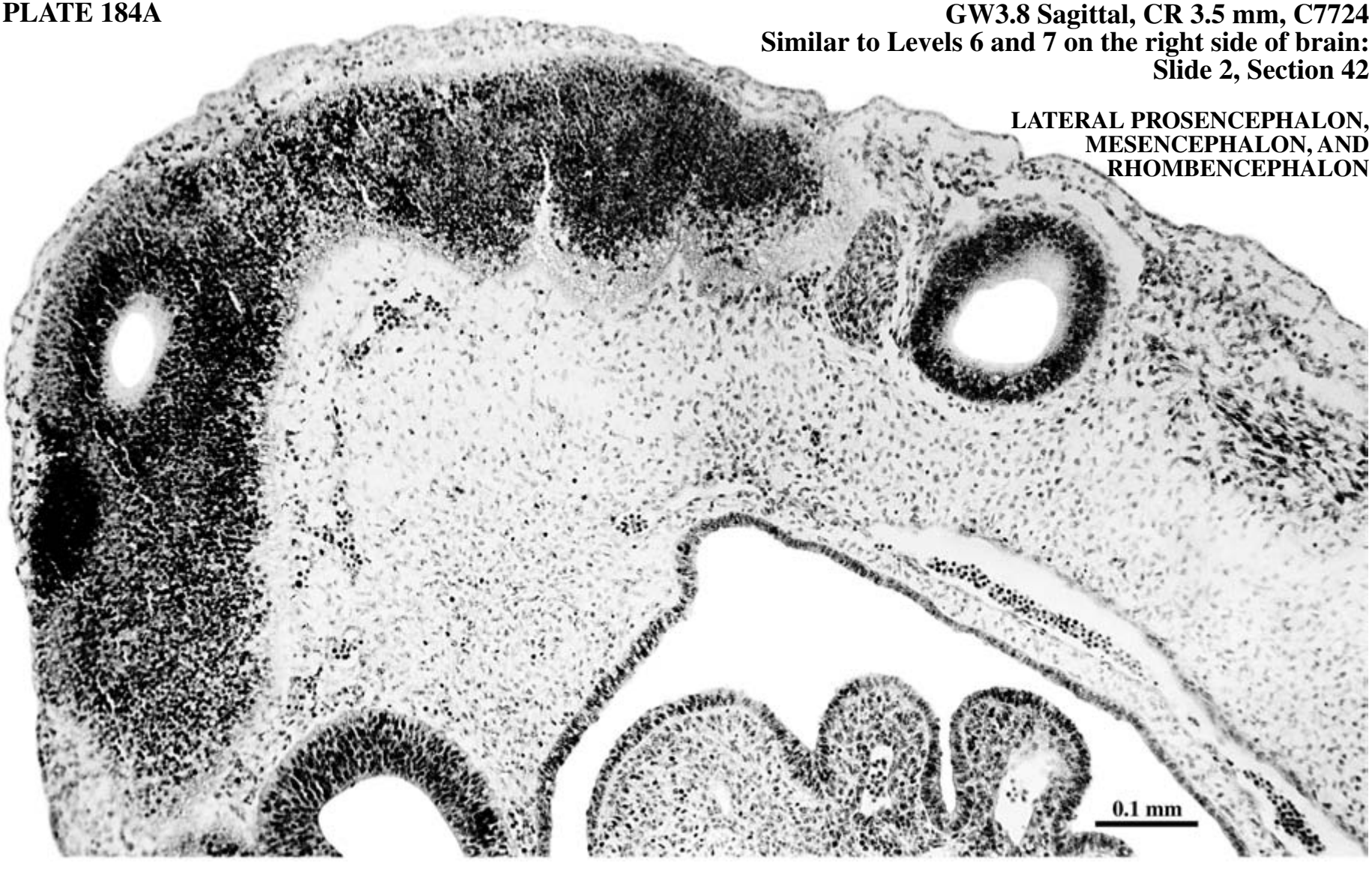

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or Bold
NEP - Neuroepithelium
Arrows indicate the presumed direction of neuron migration from neuroepithelial sources.
Early cell migration from rhombomeric NEPs
RHOMBENCEPHALON
MESENCEPHALON
Primordial mesenchymal brain case (skin, bone, and meninges)
Upper rhombic lip
Lower rhombic lip
Cochlear nuclear NEP?
Precerebellar NEP?
Gracile and cuneate nuclear NEP?
RHOMBENCEPHALIC PROTOVENTRICLE
(FUTURE FOURTH VENTRICLE)
Cerebellar NEP?
Medullary NEP
Pontine NEP
Migrating isthmal neurons
Isthmal NEP?
R2 (trigeminal NEP)
R3 (facial NEP)
R4 (vestibulo-auditory NEP)
R5 (vestibulo-auditory NEP)
R6 (glosso-pharyngeal NEP)
R7 (vagal NEP)
Dorsal lower medullary NEP
Brain surface (heavier line)
Migrating trigeminal nuclear complex (V) neurons from R2 NEP
Migrating facial (VII) neurons from R3 NEP
Migrating vestibular and auditory (VIII) neurons from R4 and R5 NEPs
Migrating solitary nucleus neurons (IX, glossopharyngeal receptors) from R6 NEP
Migrating vagal sensory (X) neurons from R7 NEP
Migrating medullary neurons
Migrating tectal neurons
Migrating pretectal neurons
Expanding superarachnoid reticulum
Oral preplacodes
Oral-pharyngeal cavity
Branchial preplacodes
Cephalic preplacodes
Pharyngeal preplacodes
Hyoid arch (II)
Arch III
Mandibular arch (I)

PLATE 184A

GW3.8 Sagittal, CR 3.5 mm, C7724
Similar to Levels 6 and 7 on the right side of brain:
Slide 2, Section 42

LATERAL PROSENCEPHALON, MESENCEPHALON, AND RHOMBENCEPHALON



PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.

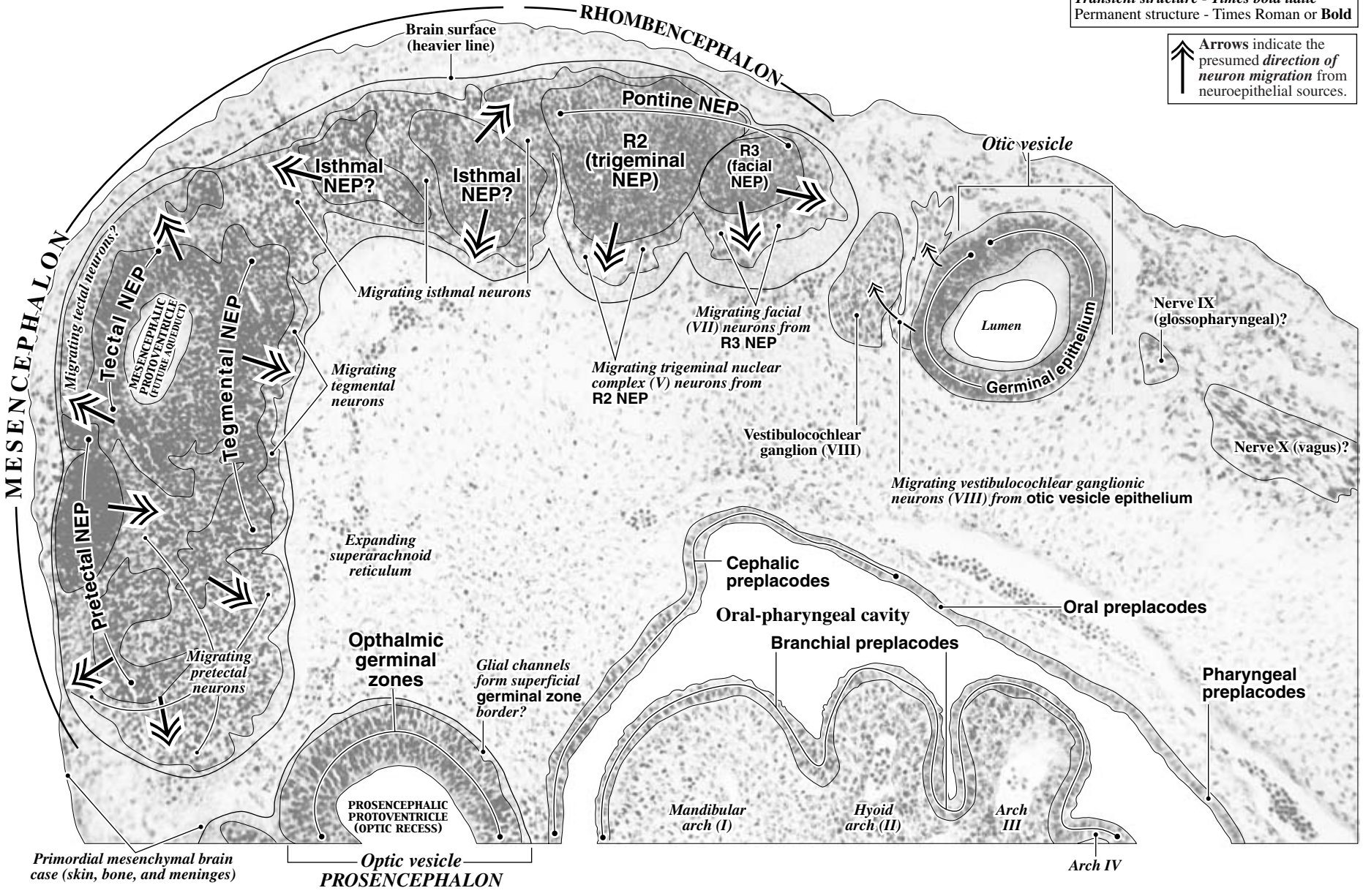
See Level 6 in Plates 177A and B, Level 7 in Plates 178A and B.

PLATE 184B

NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

Arrows indicate the presumed ***direction of neuron migration*** from neuroepithelial sources.



PART XV: GW3.2 CORONAL

This specimen is embryo #714 in the Minot Collection, designated here as M714. The crown-rump length (CR) is 4-mm. CR length is an unreliable measure to estimate gestational age because this specimen is much less mature than C7724, which also has a 4-mm CR. Since the number of somites could not be counted accurately in transverse sections, age determination is based on the degree of maturation of the central nervous system. The anterior neuropore closes at the 20-somite stage (Patten, 1953; Hamilton et al., 1959); M714 has a large open anterior neuropore. Using the timetables in Patten (1953) and Hamilton et al. (1959), we estimate that M714 has approximately 17 to 18 somites and is at gestational week (GW) 3.2. M714's prosencephalic and anterior mesencephalic sections are cut (8 μm) in the coronal plane, but the plane shifts to predominantly horizontal in the posterior mesencephalon, pons, and medulla. We photographed 21 sections at low magnification from the first section containing the head to the posterior tips of the rhombencephalon. Fifteen of these sections are illustrated in **Plates 185AB to 197AB**. All photographs were used to produce computer-aided 3-D reconstructions of the external features of M714's brain and optic vesicle (**Figure 14**), and to show each illustrated section *in situ* (*insets,* **Plates 185A to 197A**). Each illustrated section shows the brain with all surrounding tissues. Labels in **A Plates** (normal-contrast images) identify non-neural and peripheral neural structures; labels in **B Plates** (low-contrast images) identify central neural structures.

The prosencephalon is small and incomplete with a slit-like protoventricle. In front of the optic vesicles, the anterior neuropore is broadly open ventrally, and narrows dorsally. The most anterior sections have a continuum between the neuroepithelium (presumptively future telencephalic) and the cephalic preplacodal epithelium. The dorsal part of the anterior neuropore is closed in sections of the optic vesicle; these neuroepithelia are more clearly identified as future diencephalic. The preplacodal epithelium lines the lateral and ventral surfaces of the head and roof of the oral cavity. The evaginated optic vesicle is nearly touching part of the preplacodal epithelium that may have something to do with induction of the lens placode later on. An olfactory placode is very difficult to identify.

The mesencephalon contains a stockbuilding neuroepithelium surrounding a narrow keyhole-shaped protoventricle. Future tectal neuroepithelium is a small arch over the top, while the future tegmental and isthmal neuroepithelia form the slite-shaped bottom. There is a very thin cell-free primordial plexiform layer in future tegmental and isthmal areas.

The most prominent neuroepithelial structures in the rhombencephalon are the rhombomeric evaginations. In this specimen, several sections show how closely rhombomeres are associated with sensory cranial ganglia. The trigeminal ganglion (source of V sensory axons) is nearly attached to the brain surface at rhombomere 2. The vestibulocochlear ganglion (source of VIII axons) is attached to the rhombomere 4 brain surface. The otic vesicle touches the rhombomere 5 brain surface. The presumptive glossopharyngeal ganglion (source of IX sensory axons) is lateral to rhombomere 6. The short nerve extending from the large vagal ganglion (source of X sensory axons) touches the rhombomere 7 brain surface. The presumptive facial ganglion (source of sensory VII axons) is near a placode in the hyoid arch, slightly posterior and ventrolateral to rhombomere 3. A very thin layer of migrating neurons lines the superficial border of some rhombomeres; for the most part, cell migration has not yet started. The small cerebellar neuroepithelium is barely identifiable in the most posterior sections where the dorsal rhombencephalic neuroepithelium blends with tectal/isthmal neuroepithelia.

M714 Computer-aided 3-D Brain Reconstructions

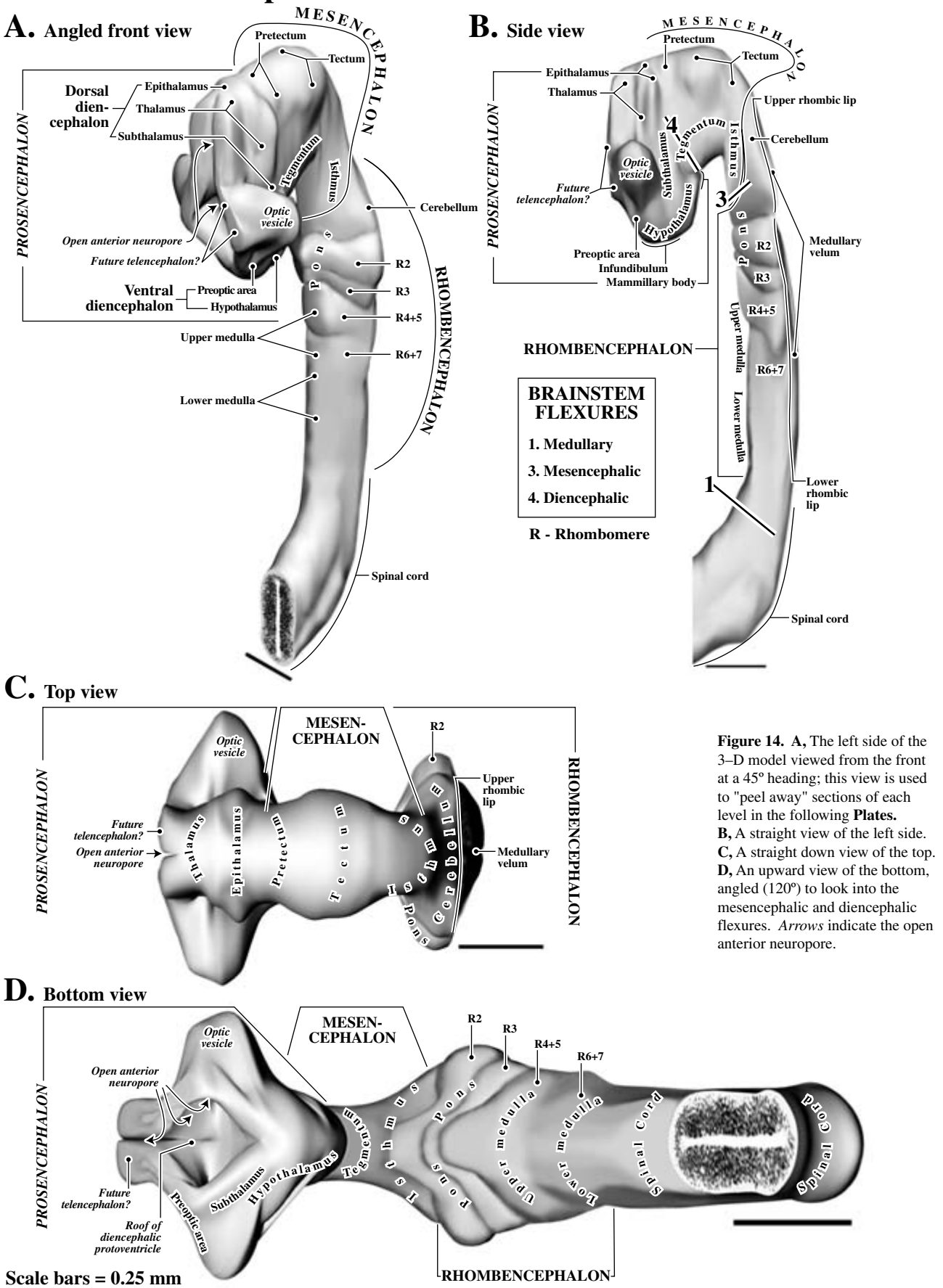


Figure 14. A, The left side of the 3–D model viewed from the front at a 45º heading; this view is used to "peel away" sections of each level in the following **Plates.** **B,** A straight view of the left side. **C,** A straight down view of the top. **D,** An upward view of the bottom, angled (120º) to look into the mesencephalic and diencephalic flexures. *Arrows* indicate the open anterior neuropore.

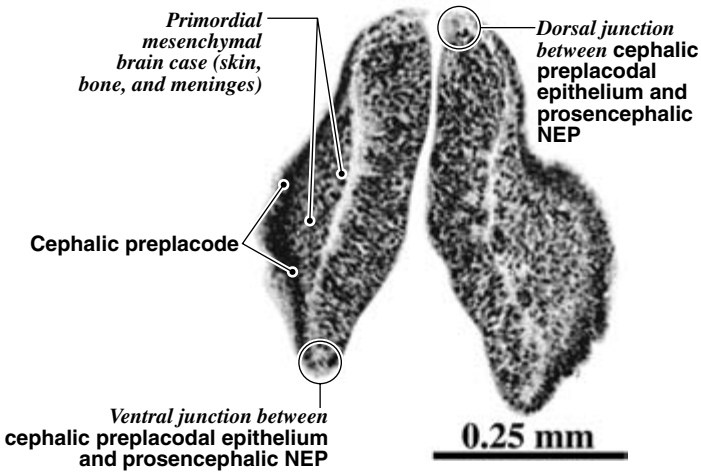
PLATE 185A

Peripheral neural and non-neural structures labeled

GW3.2 Coronal
17-18 Somites?
M714

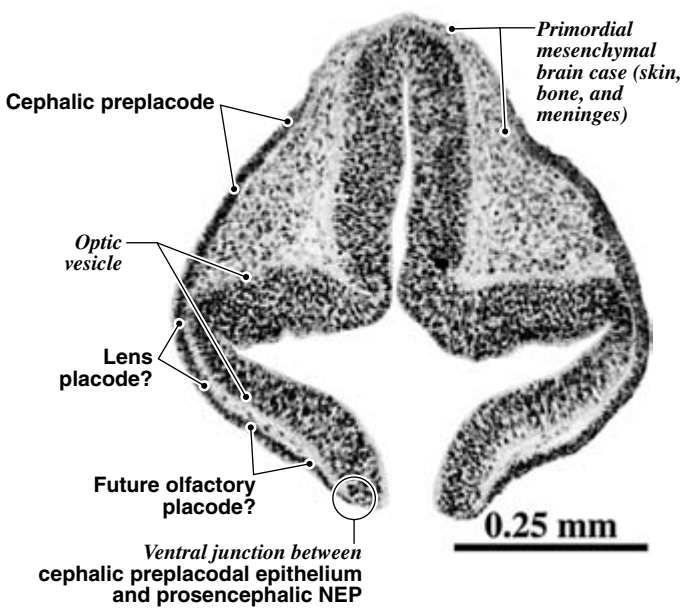
Level 1: Computer-aided 3-D Brain Reconstruction

Level 1: Section 3



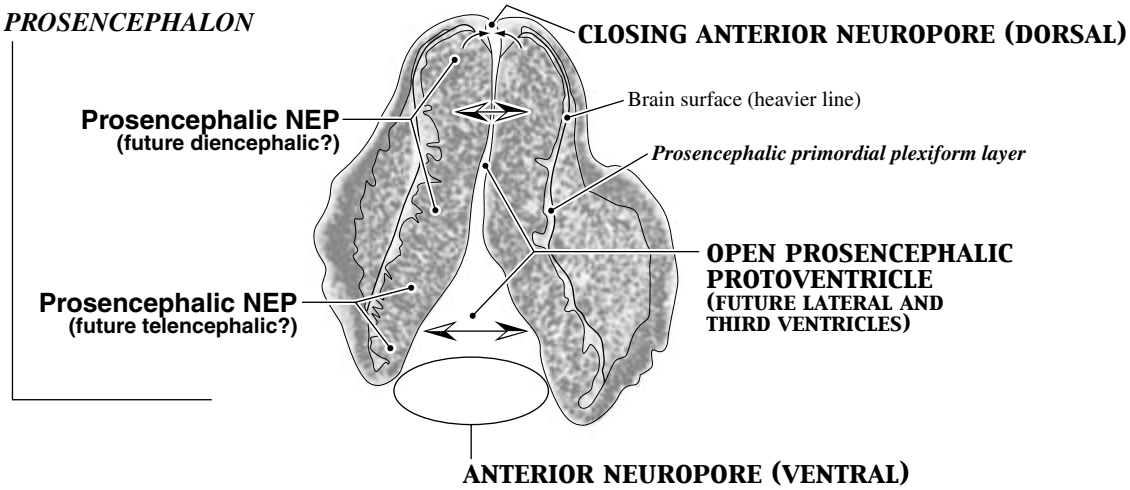
Level 2: Computer-aided 3-D Brain Reconstruction

Level 2: Section 13

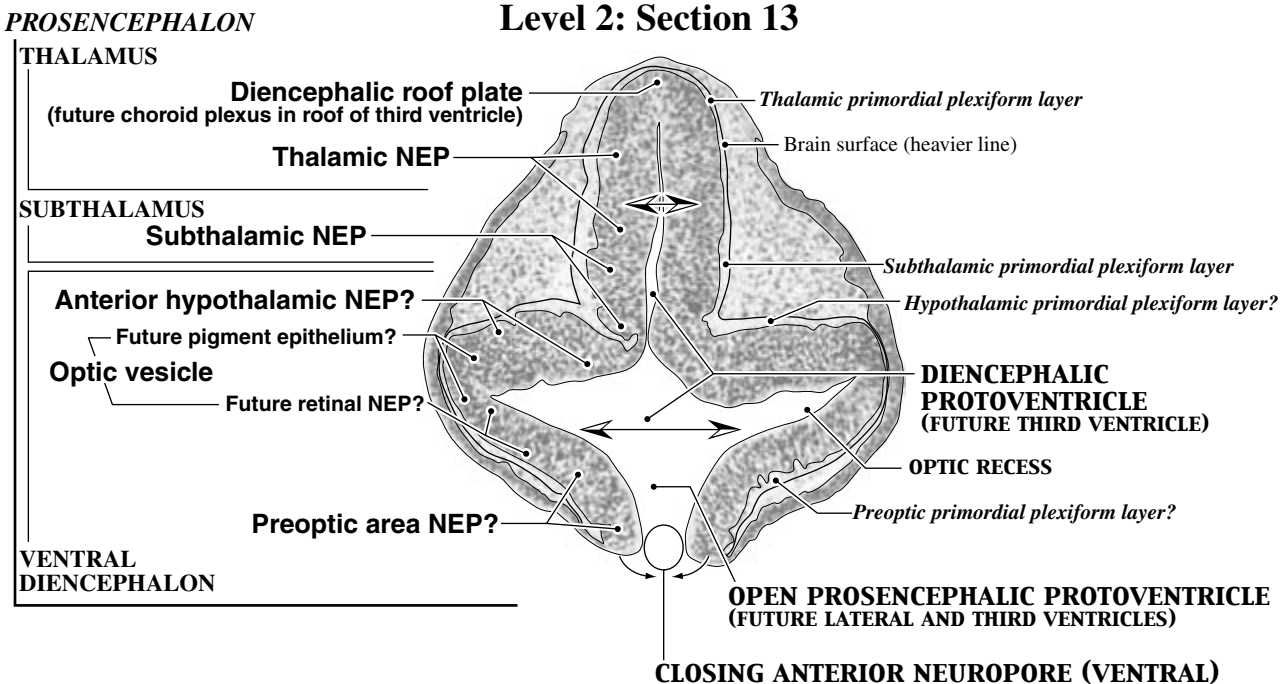


Central neural structures labeled **PLATE 185B**

Level 1: Section 3



Level 2: Section 13



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

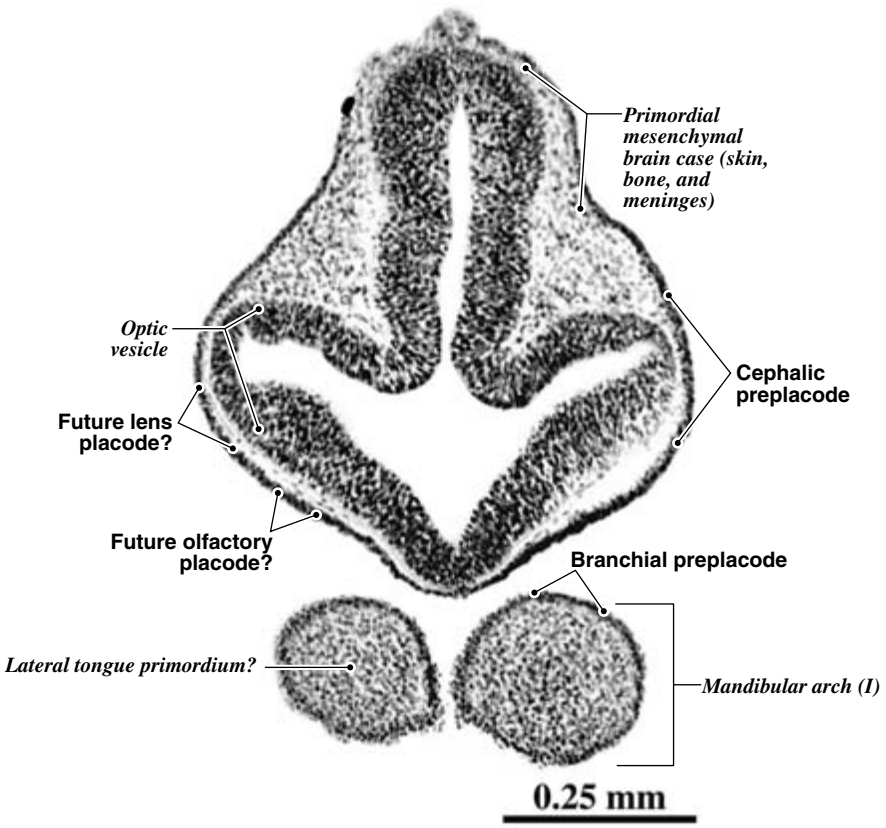
NEP - neuroepithelium

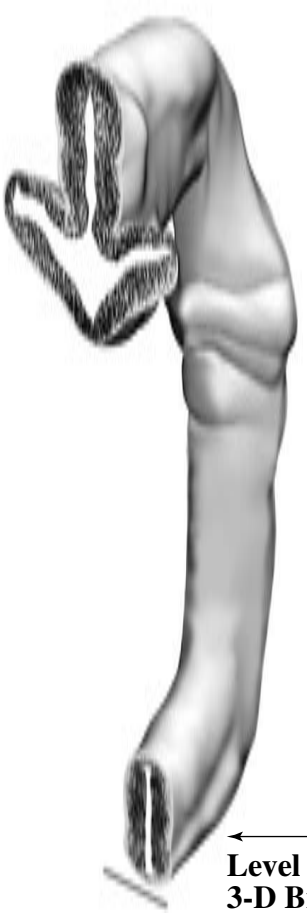
Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

PLATE 186A

Peripheral neural and non-neural structures labeled

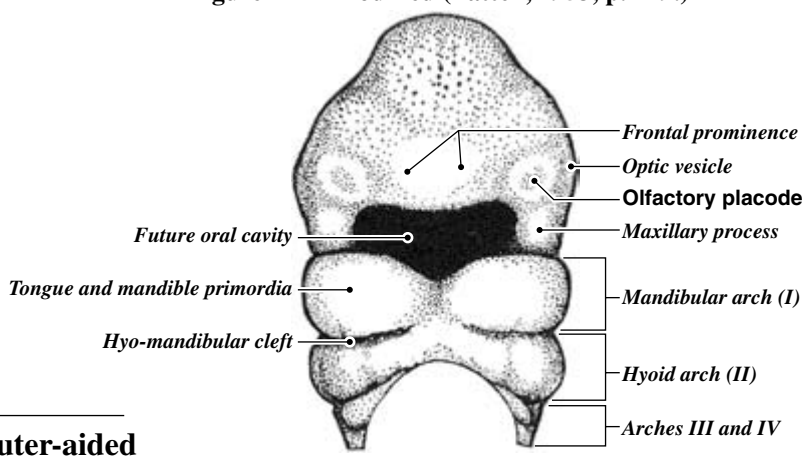
GW3.2 Coronal
17-18 Somites?
M714
Level 3: Section 18





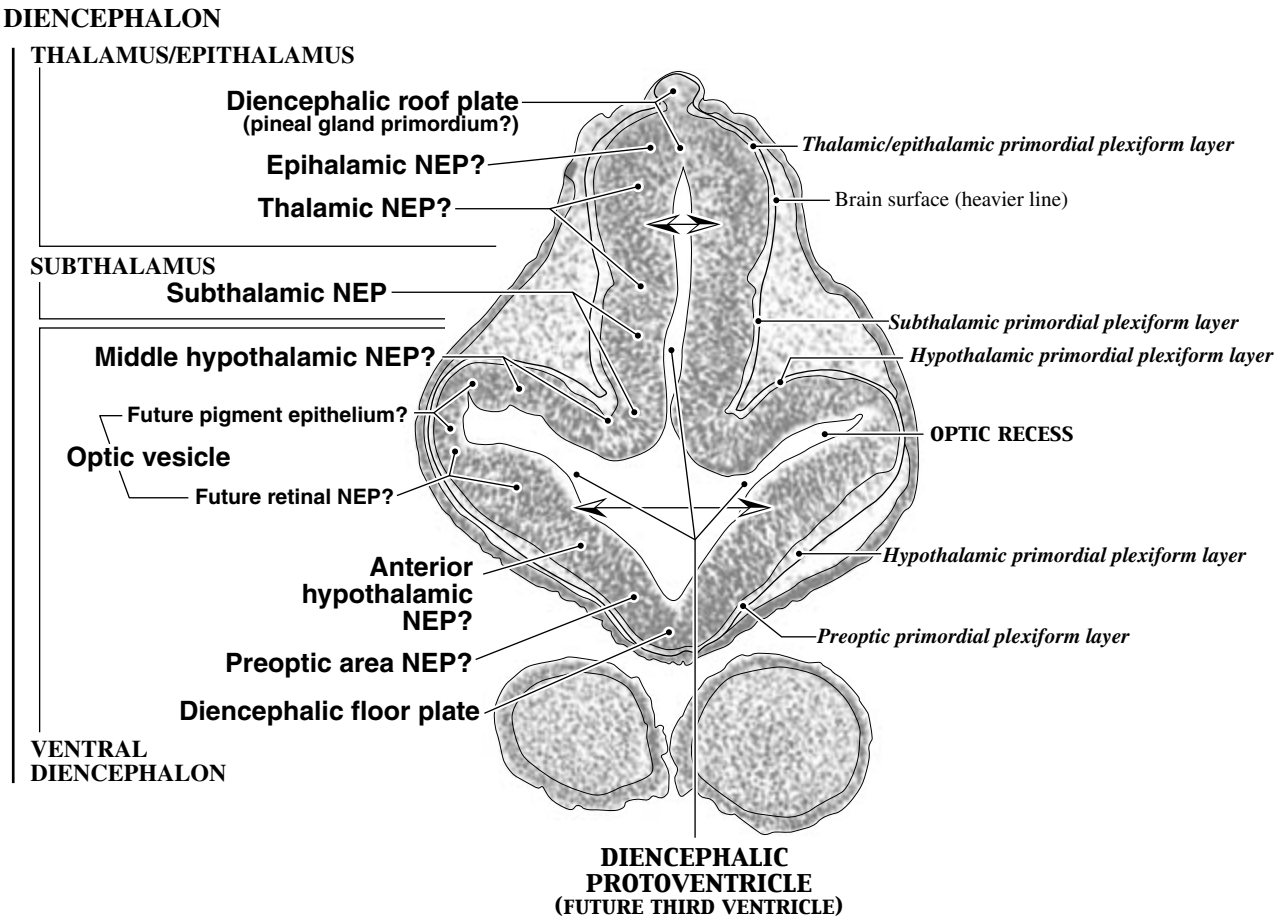
Level 3: Computer-aided 3-D Brain Reconstruction

The GW4 Face and Neck
Figure 247A modified (Patten, 1953, p. 429.)



Central neural structures labeled

PLATE 186B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

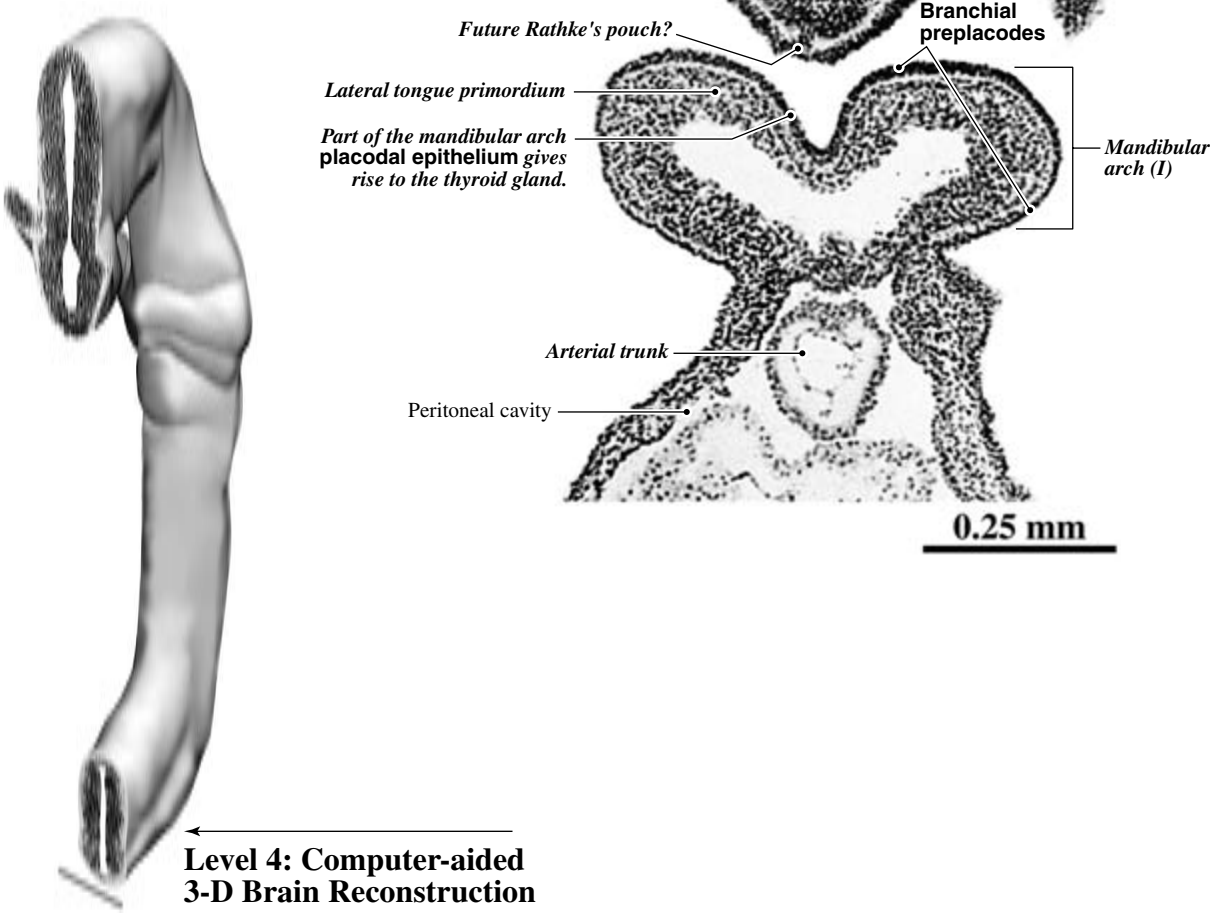
NEP - neuroepithelium

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

PLATE 187A

Peripheral neural and non-neural structures labeled

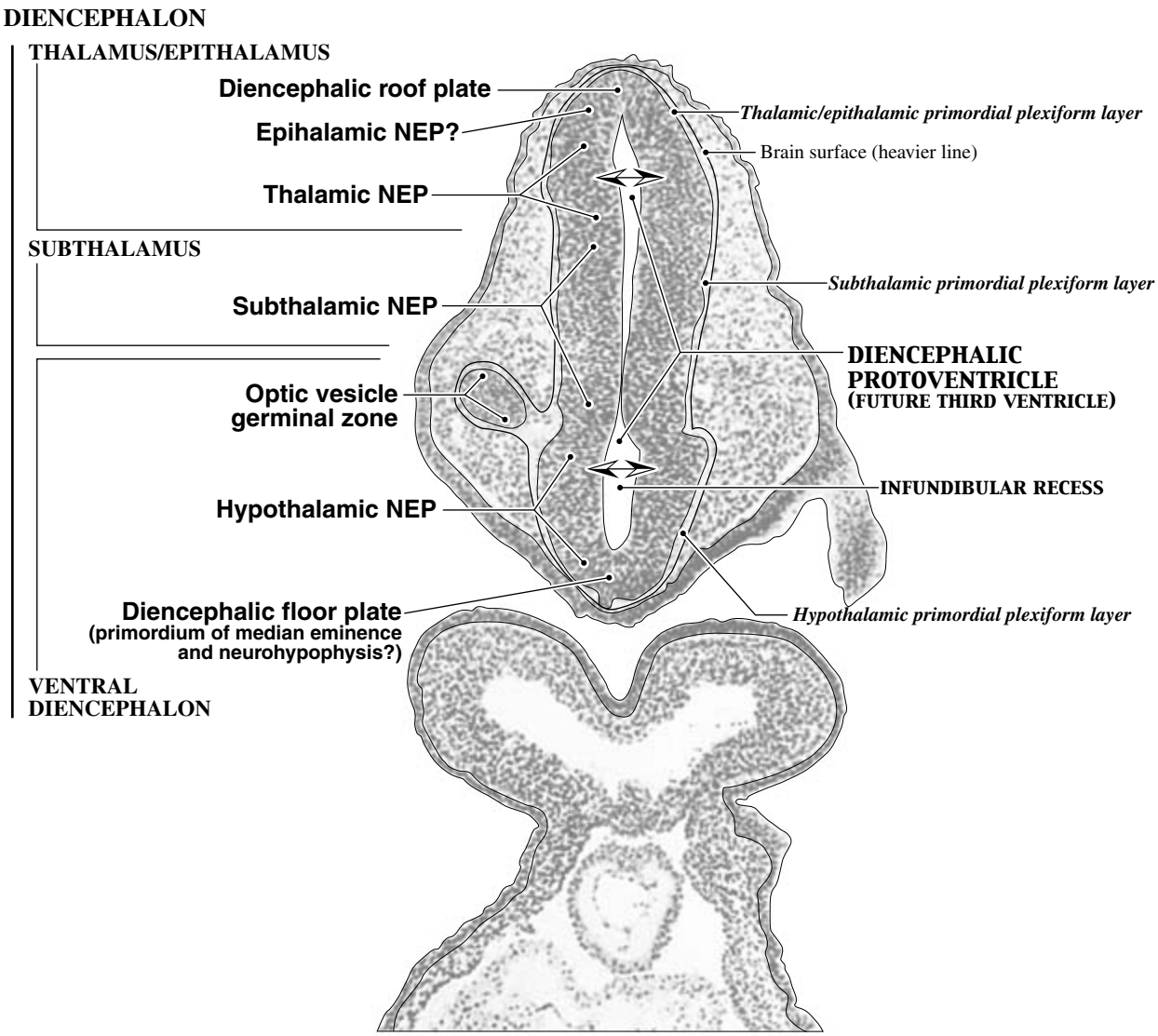
GW3.2 Coronal
17-18 Somites?
M714
Level 4: Section 28



Level 4: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 187B



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

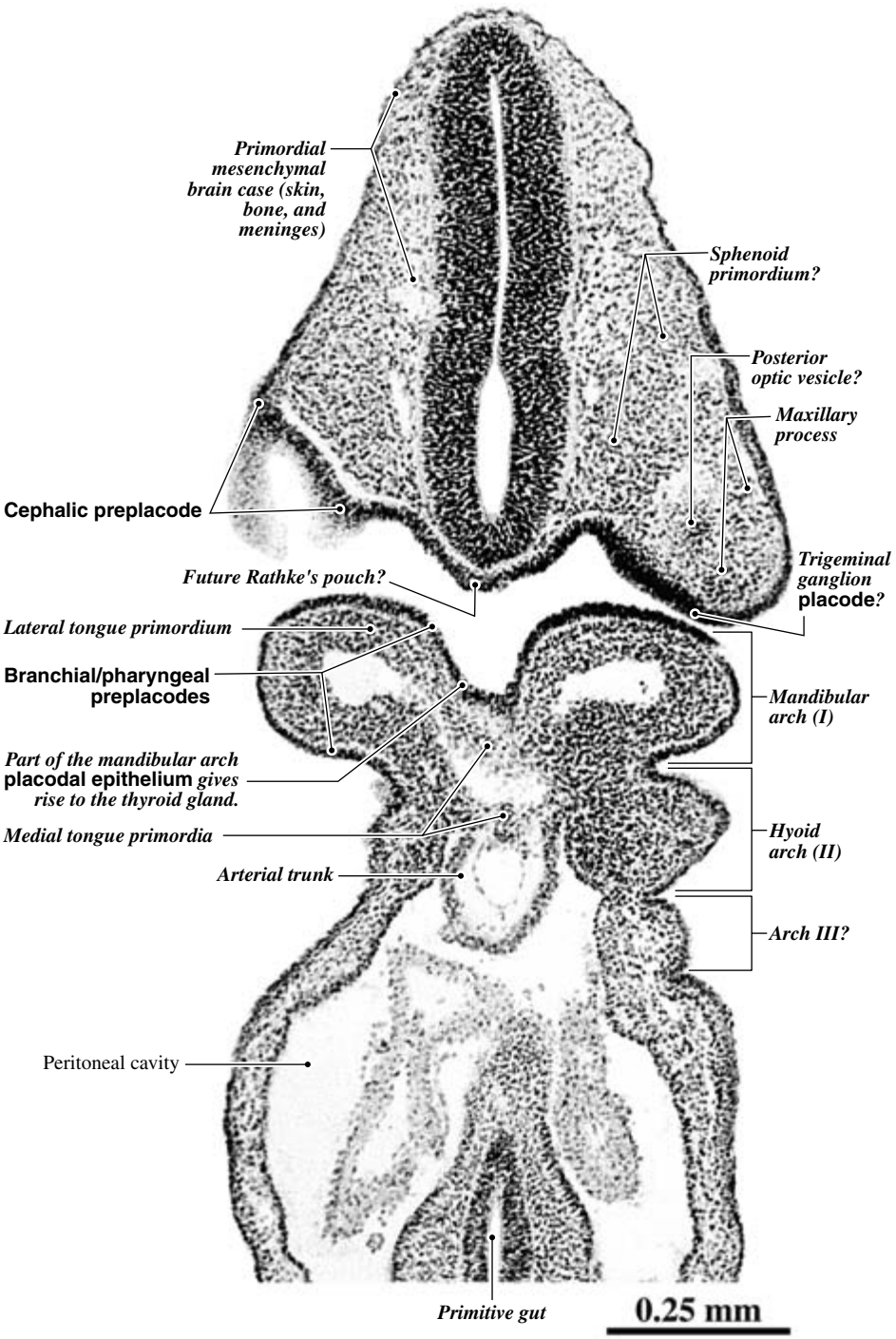
NEP - neuroepithelium

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

PLATE 188A

Peripheral neural and non-neural structures labeled

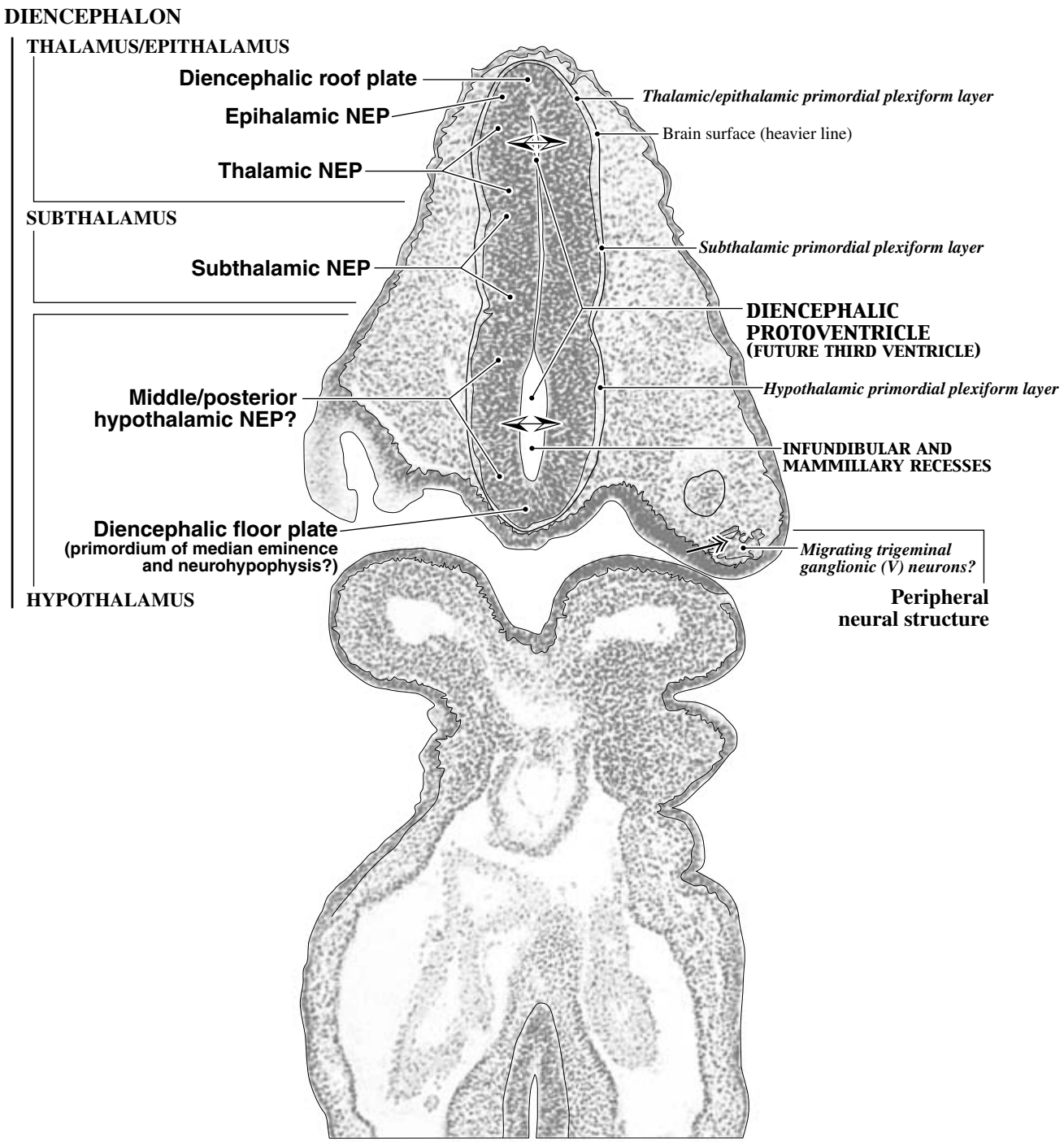
GW3.2 Coronal
17-18 Somites?
M714
Level 5: Section 33



Level 5: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 188B



Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

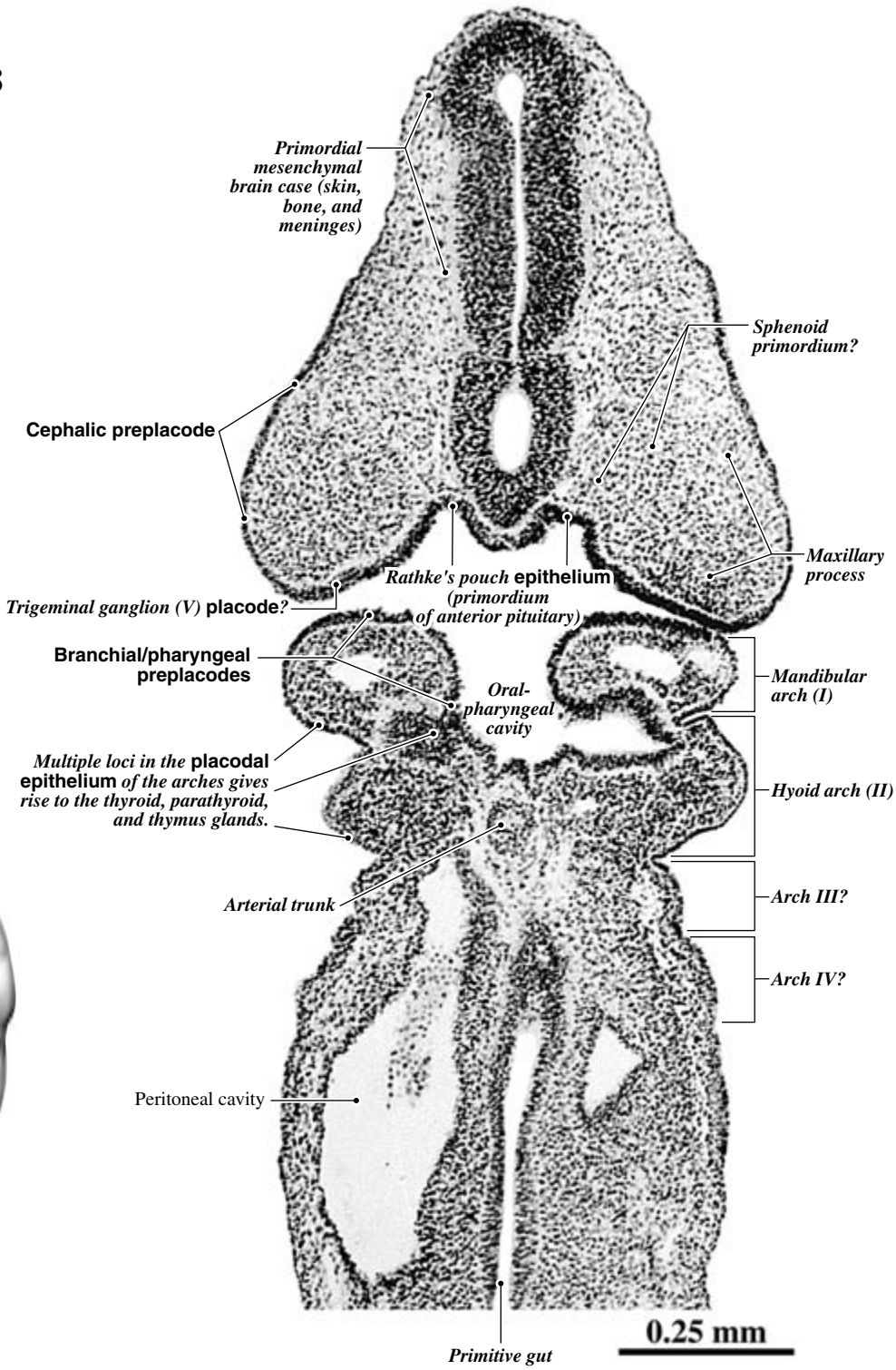
FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - neuroepithelium

PLATE 189A

Peripheral neural and non-neural structures labeled

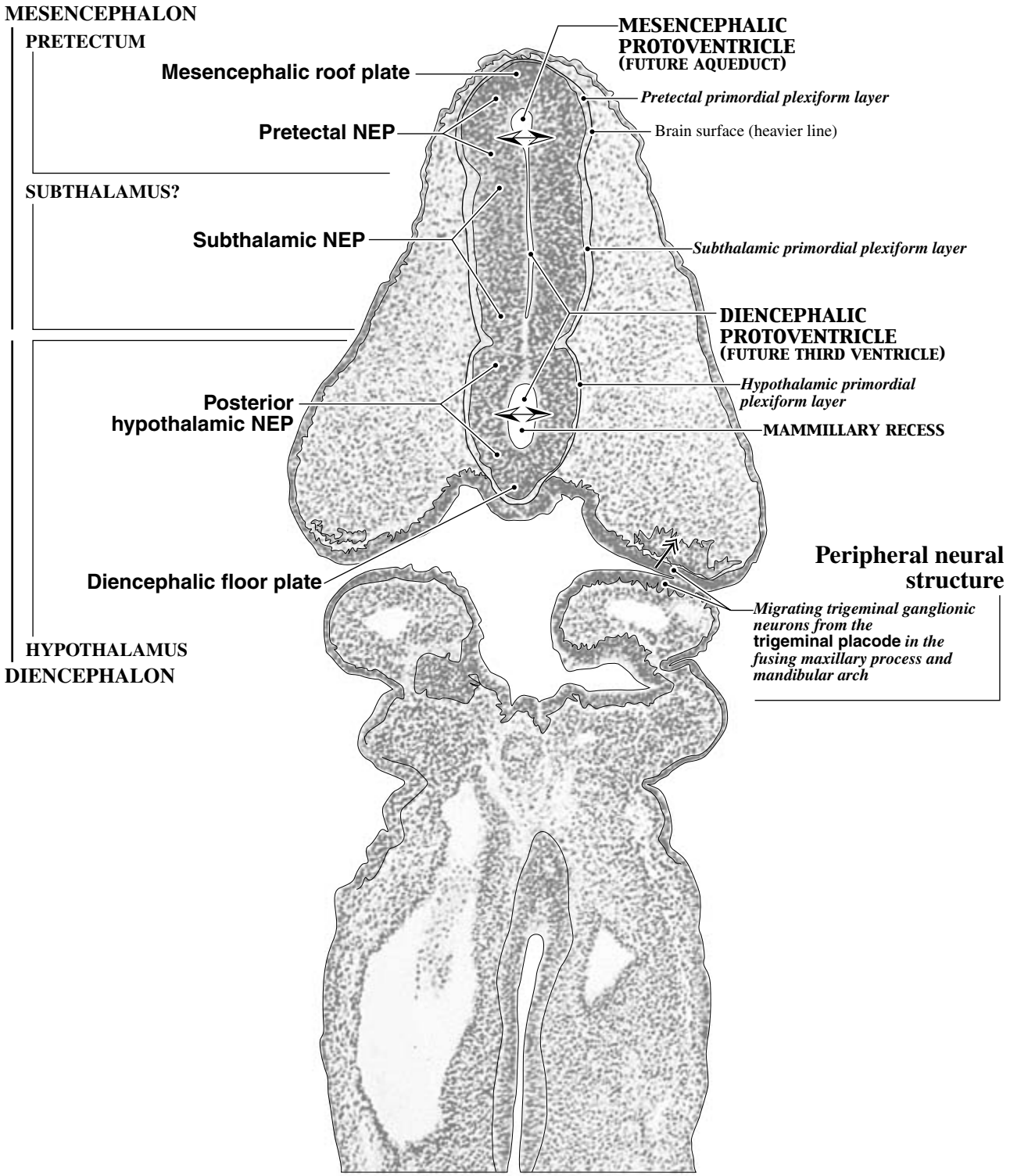
GW3.2 Coronal
17-18 Somites?
M714
Level 6: Section 38



Level 6: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 189B



Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

NEP - neuroepithelium

PLATE 190A

GW3.2 Coronal
17-18 Somites?
M714
Level 7: Section 43

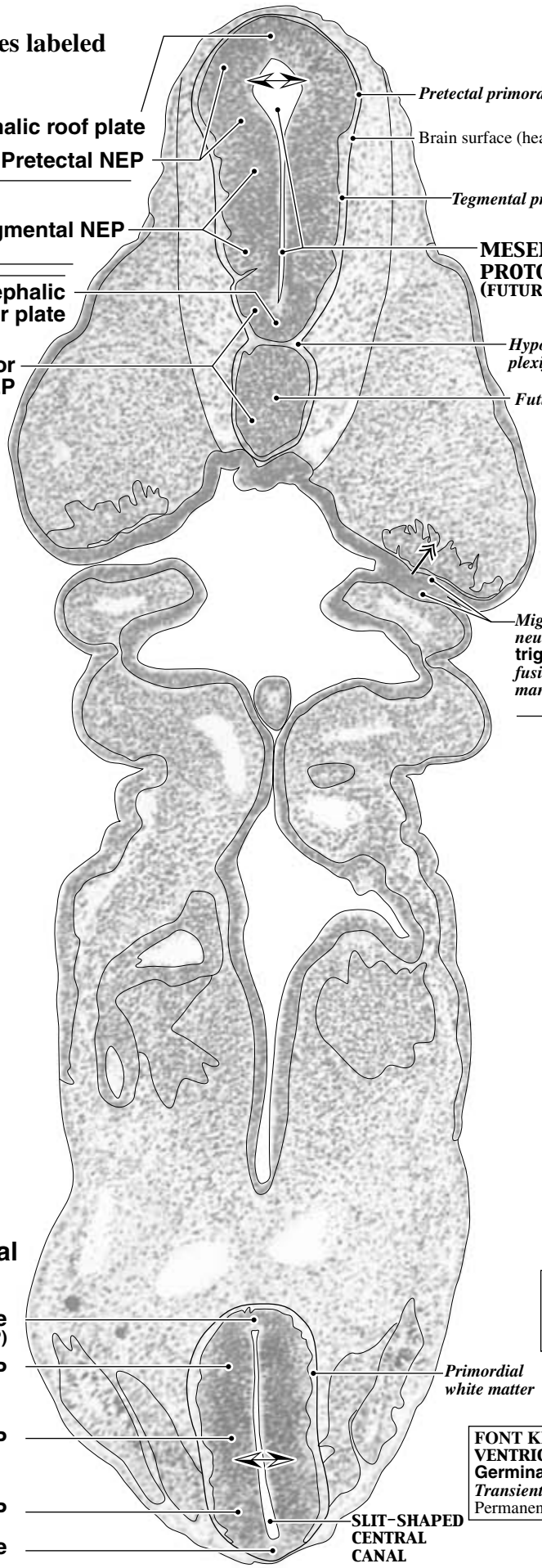
Peripheral neural and non-neural structures labeled

Level 7: Computer-aided 3-D Brain Reconstruction

Primordial mesenchymal brain case (skin, bone, and meninges)
Formative superarachnoid reticulum
Sphenoid primordium?
Cephalic preplacode
Maxillary process
Migrating trigeminal ganglionic neurons?
Rathke's pouch **epithelium** *(primordium of anterior pituitary)*
Trigeminal ganglion (V) **placode***?*
Branchial/pharyngeal preplacodes
Oral-pharyngeal cavity
Mandibular arch (I)
Hyoid arch (II)
Multiple loci in the **placodal epithelium** *of the arches gives rise to the thyroid, parathyroid, and thymus glands.*
Arch III?
Arch IV?
Anterior cardinal vein?
Primitive gut
Ganglion X?
Anterior cardinal vein
Dorsal aorta
Notochord
Somites
Dorsal root ganglion

0.25 mm

PLATE 190B



Central neural structures labeled

MESENCEPHALON

PRETECTUM

Mesencephalic roof plate

Pretectal NEP

TEGMENTUM

Tegmental NEP

Diencephalic floor plate

Posterior hypothalamic NEP

HYPOTHALAMUS

DIENCEPHALON

Pretectal primordial plexiform layer

Brain surface (heavier line)

Tegmental primordial plexiform layer

MESENCEPHALIC PROTOVENTRICLE (FUTURE AQUEDUCT)

Hypothalamic primordial plexiform layer

Future mammillary body

Peripheral neural structure

Migrating trigeminal ganglionic neurons from the* trigeminal placode *in the fusing maxillary process and mandibular arch

SPINAL CORD

Spinal germinal zones

Spinal floor plate (ventral commissural GEP)

Ventral NEP

Intermediate NEP

Dorsal NEP

Spinal roof plate

Primordial white matter

SLIT-SHAPED CENTRAL CANAL

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

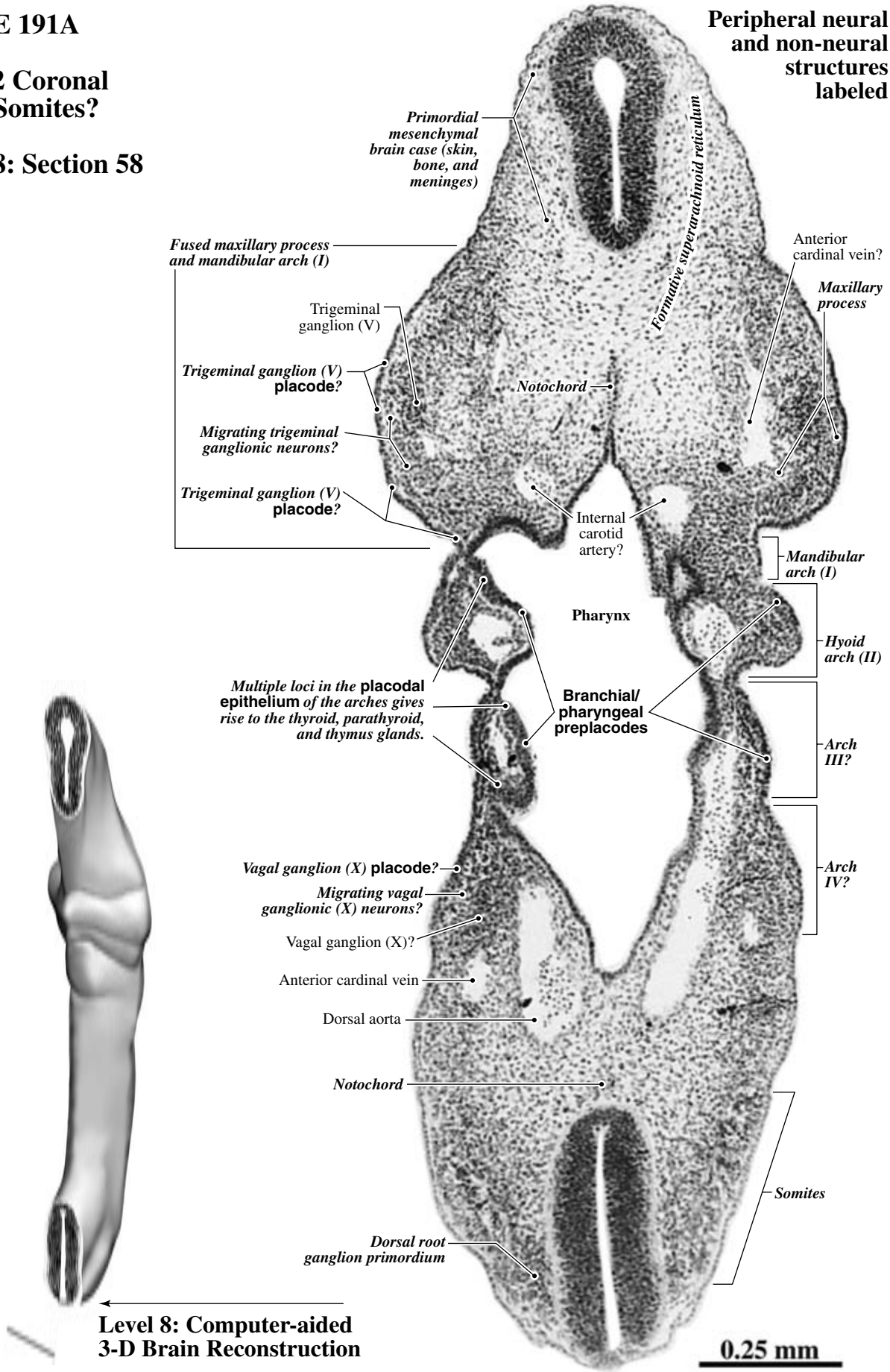
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS - CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 191A

GW3.2 Coronal
17-18 Somites?
M714
Level 8: Section 58

Peripheral neural and non-neural structures labeled



Level 8: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 191B

MESENCEPHALON

TECTUM

Mesencephalic roof plate

Tectal primordial plexiform layer

Brain surface (heavier line)

Tectal NEP

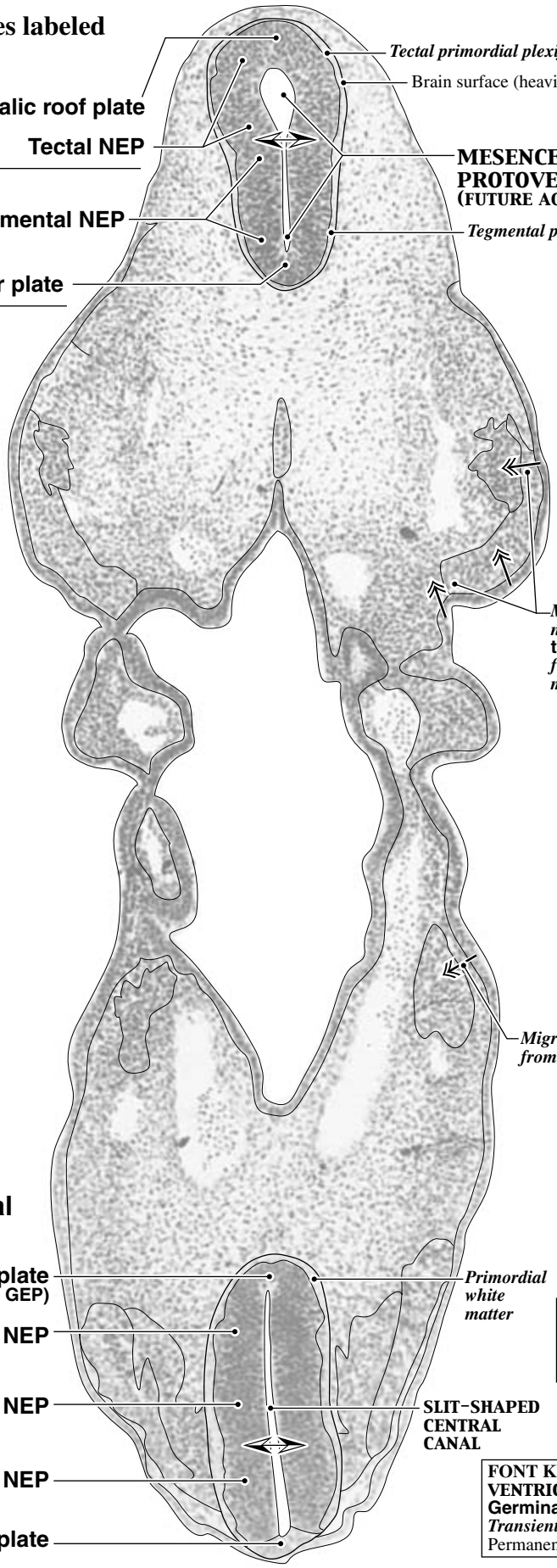
MESENCEPHALIC PROTOVENTRICLE (FUTURE AQUEDUCT)

TEGMENTUM

Tegmental NEP

Tegmental primordial plexiform layer

Mesencephalic floor plate



Peripheral neural structures

Migrating trigeminal ganglionic neurons from the* trigeminal placode *in the fused maxillary process and mandibular arch

Migrating vagal ganglionic neurons from the* vagal placode *in arch IV

SPINAL CORD

Spinal germinal zones

Spinal floor plate (ventral commissural GEP)

Primordial white matter

Ventral NEP

Intermediate NEP

SLIT-SHAPED CENTRAL CANAL

Dorsal NEP

Spinal roof plate

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

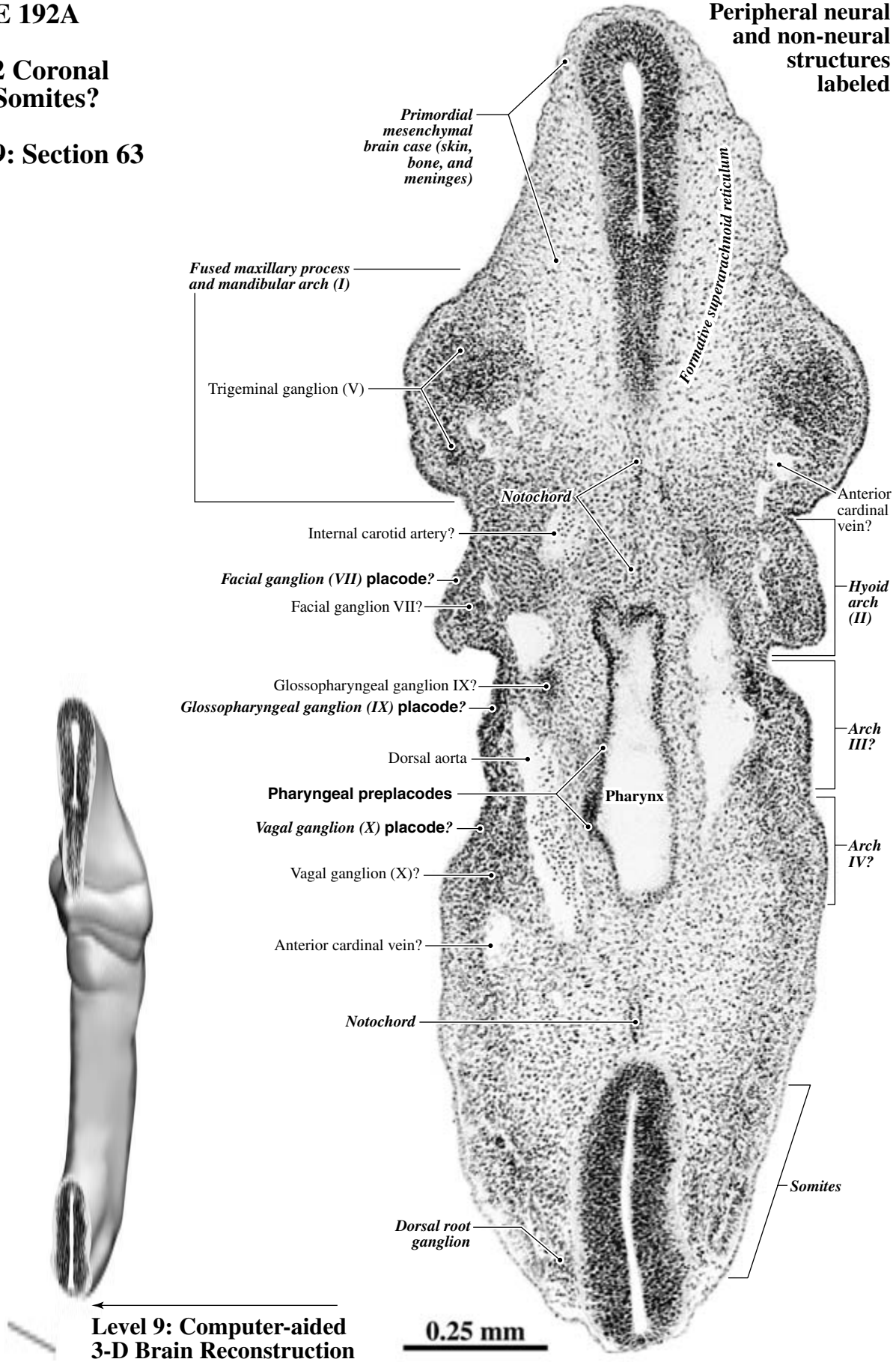
ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium

FONT KEY:
VENTRICULAR DIVISIONS - CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 192A

GW3.2 Coronal
17-18 Somites?
M714
Level 9: Section 63

Peripheral neural and non-neural structures labeled



Level 9: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 192B

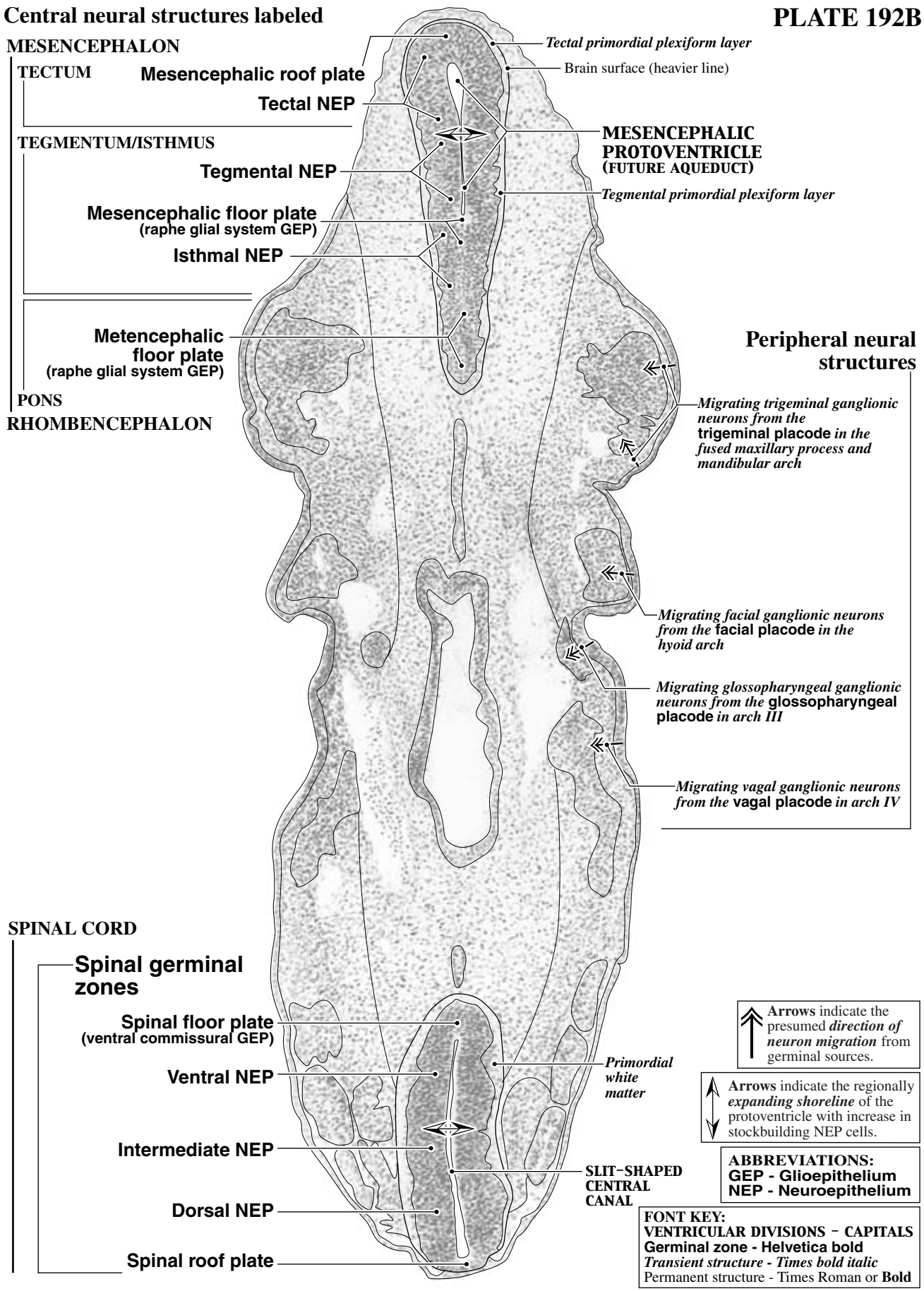
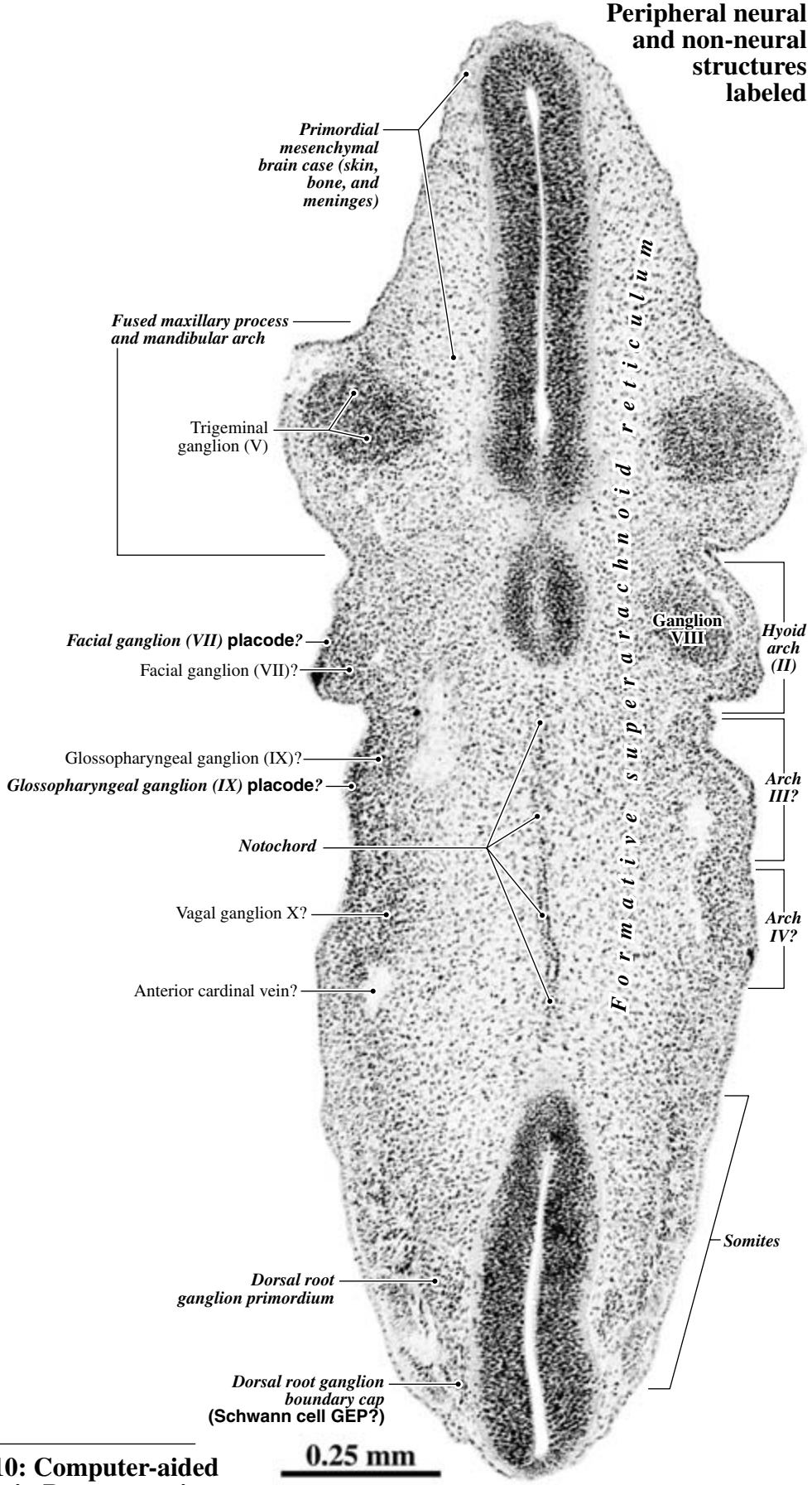


PLATE 193A

GW3.2 Coronal
17-18 Somites?
M714
Level 10: Section 68

Peripheral neural and non-neural structures labeled

Level 10: Computer-aided 3-D Brain Reconstruction



Central neural structures labeled

PLATE 193B

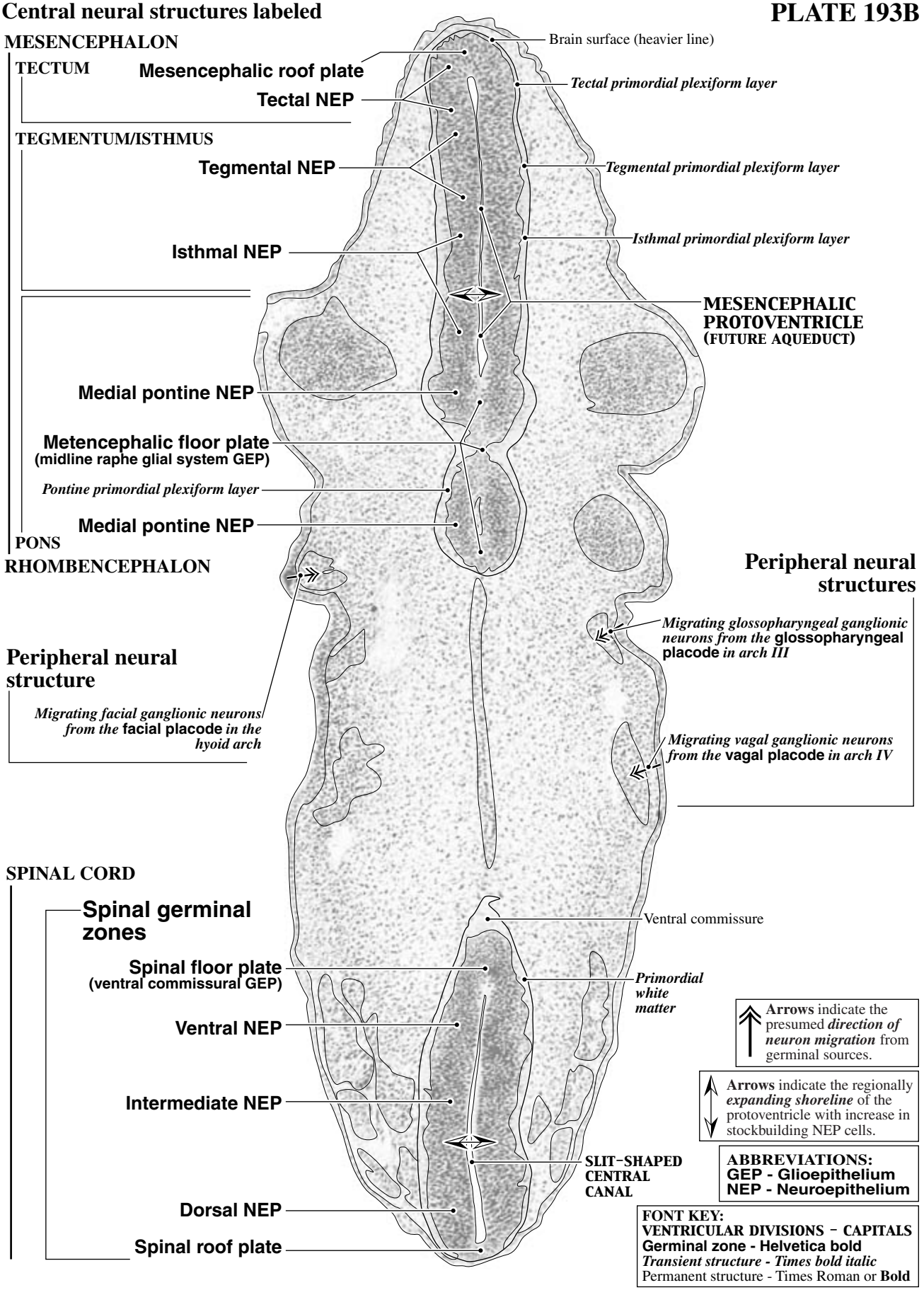
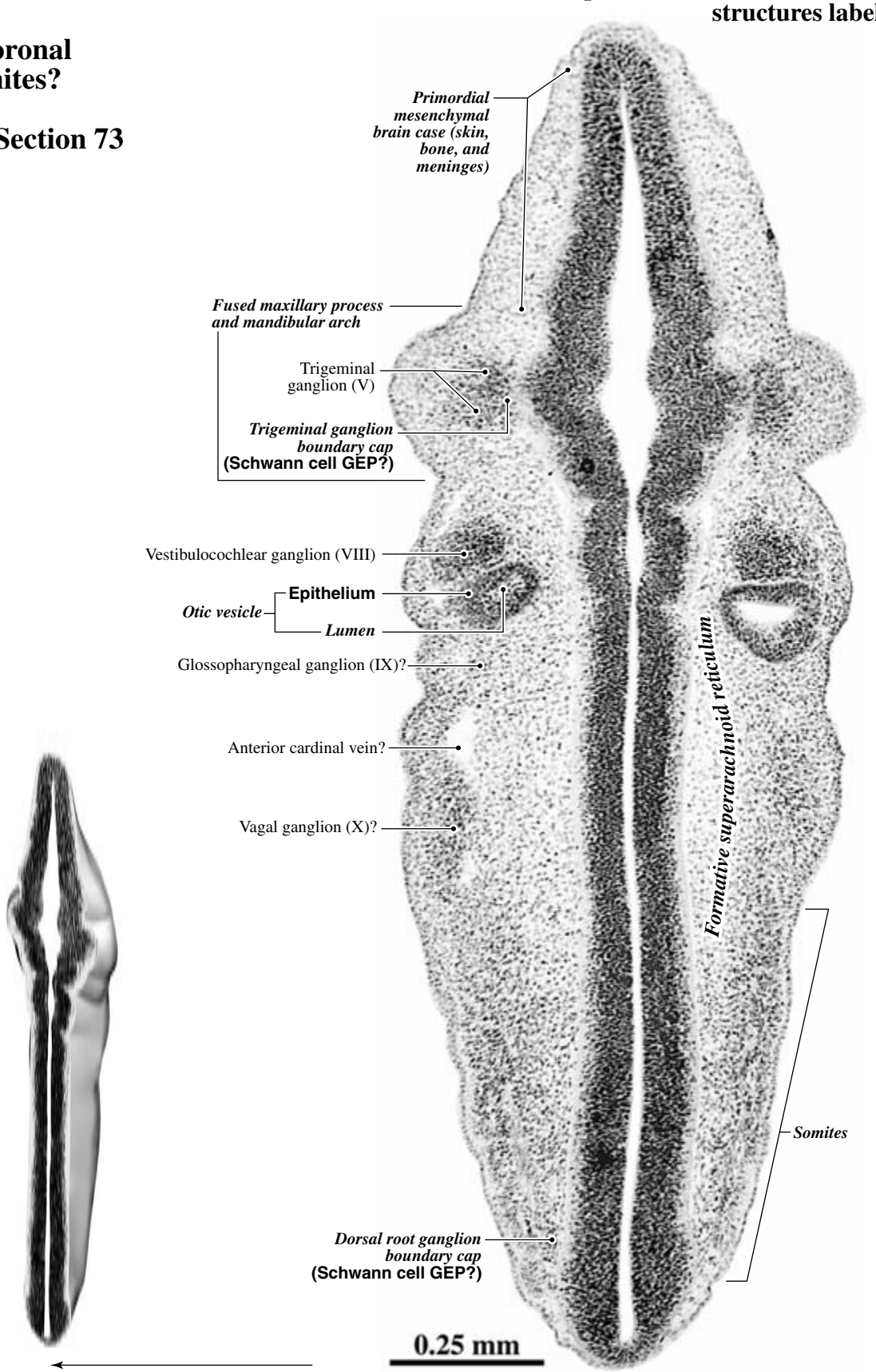


PLATE 194A

GW3.2 Coronal
17-18 Somites?
M714
Level 11: Section 73

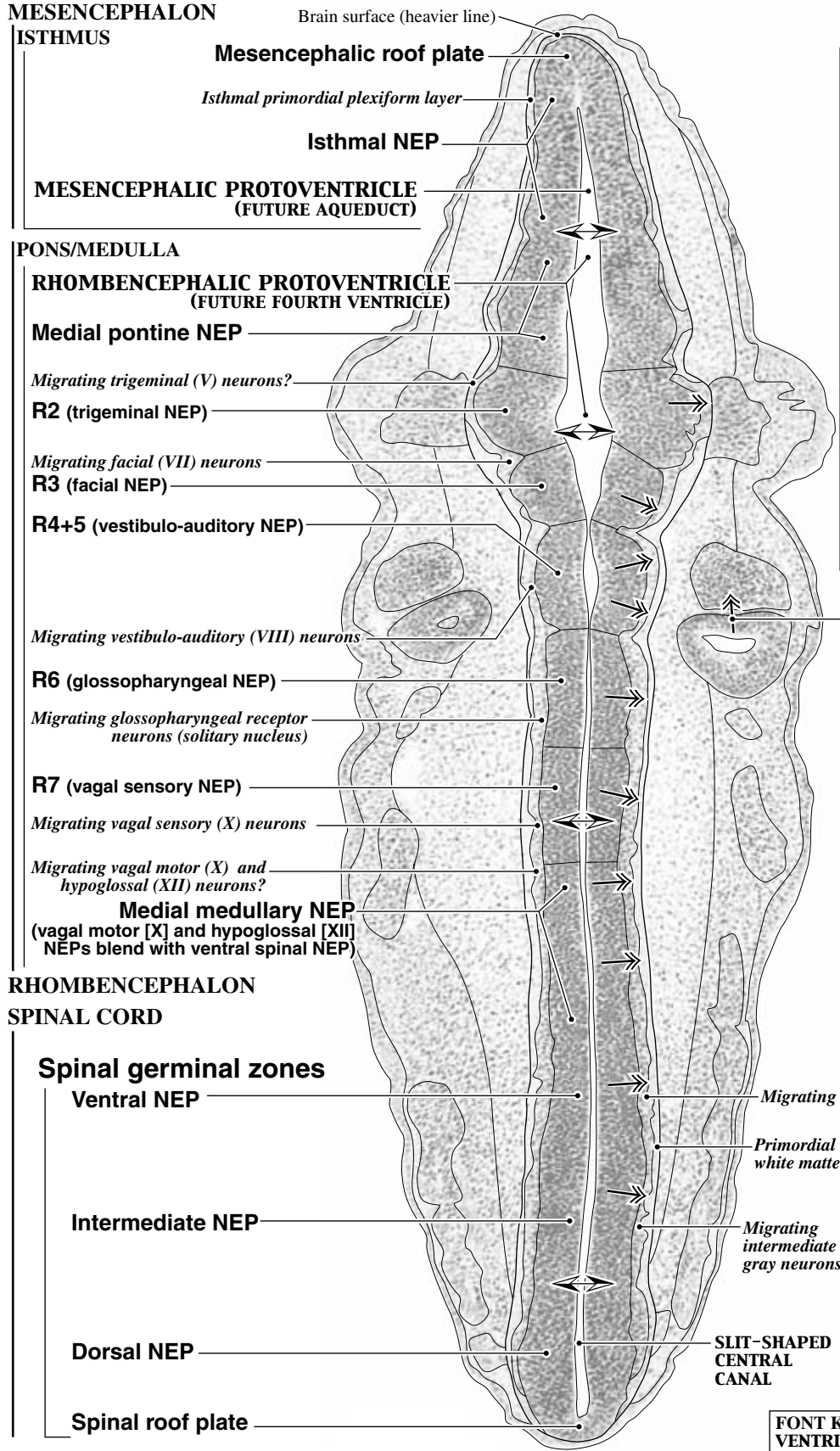
Peripheral neural and non-neural structures labeled



Level 11: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 194B



PROPOSED RHOMBOMERE IDENTITIES

- **R2** Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
- **R3** Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
- **R4** Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
- **R5** Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
- **R6** Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
- **R7** Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

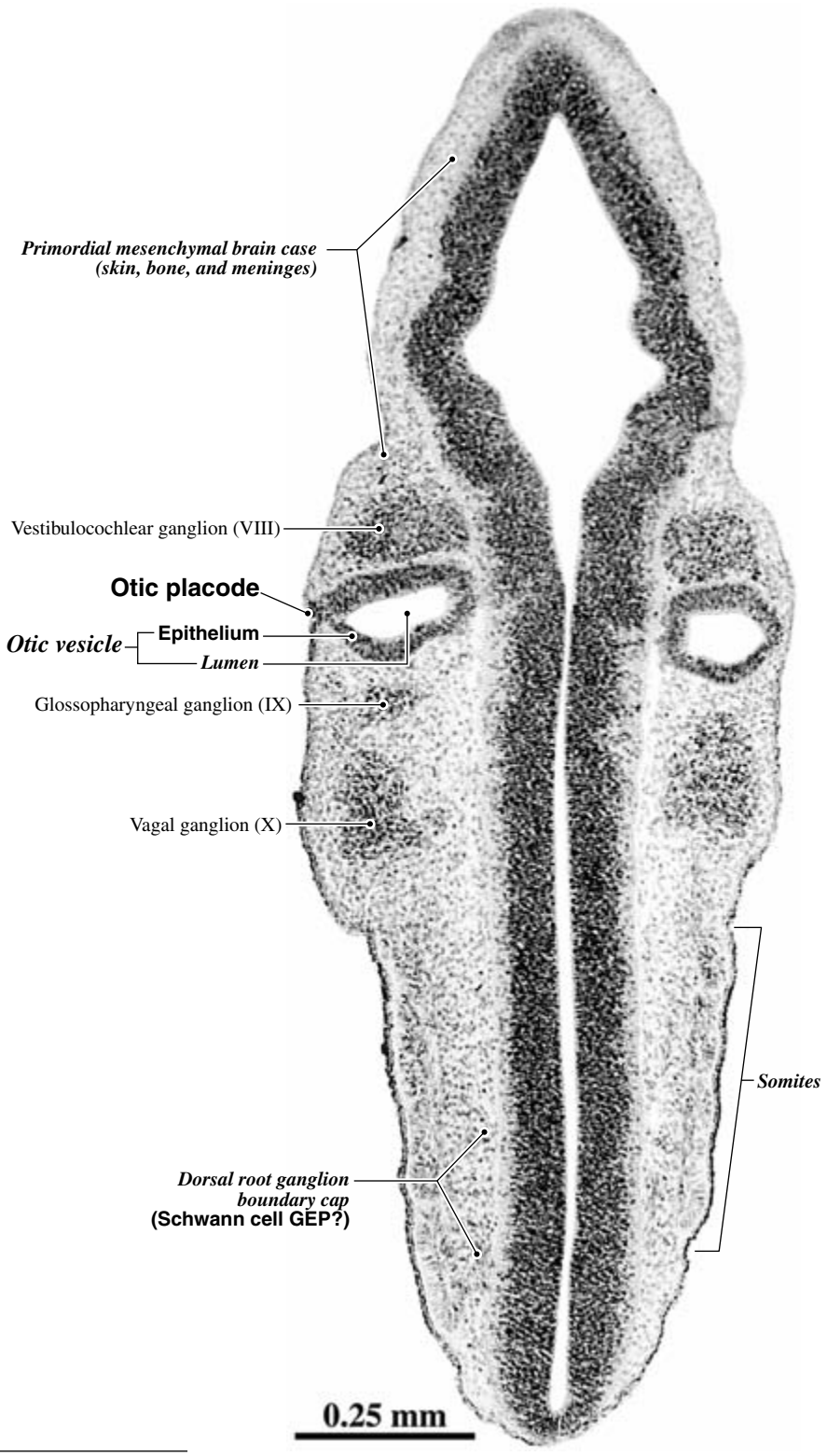
Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS - CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PLATE 195A

Peripheral neural and non-neural structures labeled

GW3.2 Coronal
17-18 Somites?
M714
Level 12: Section 78



Level 12: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 195B

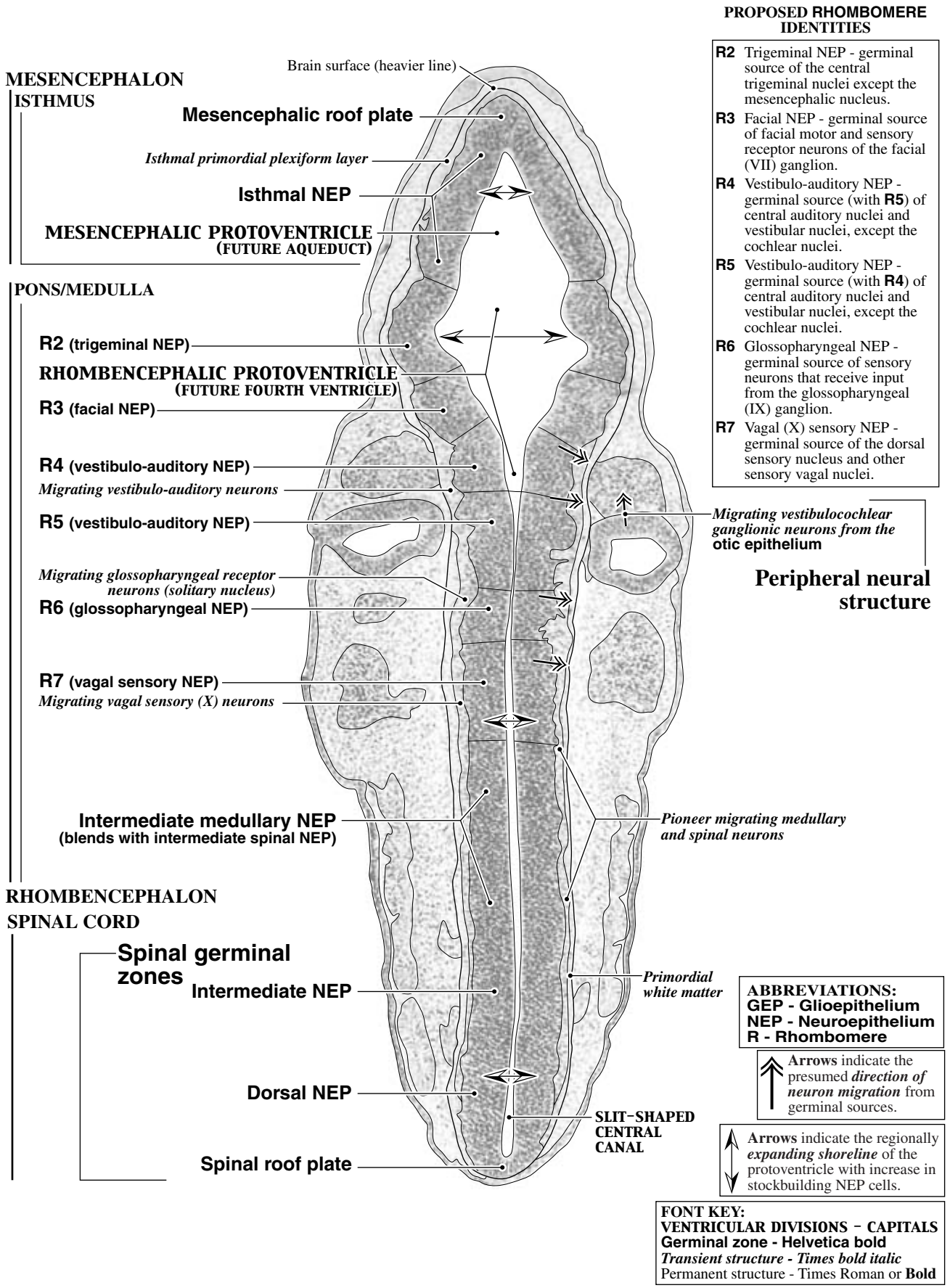
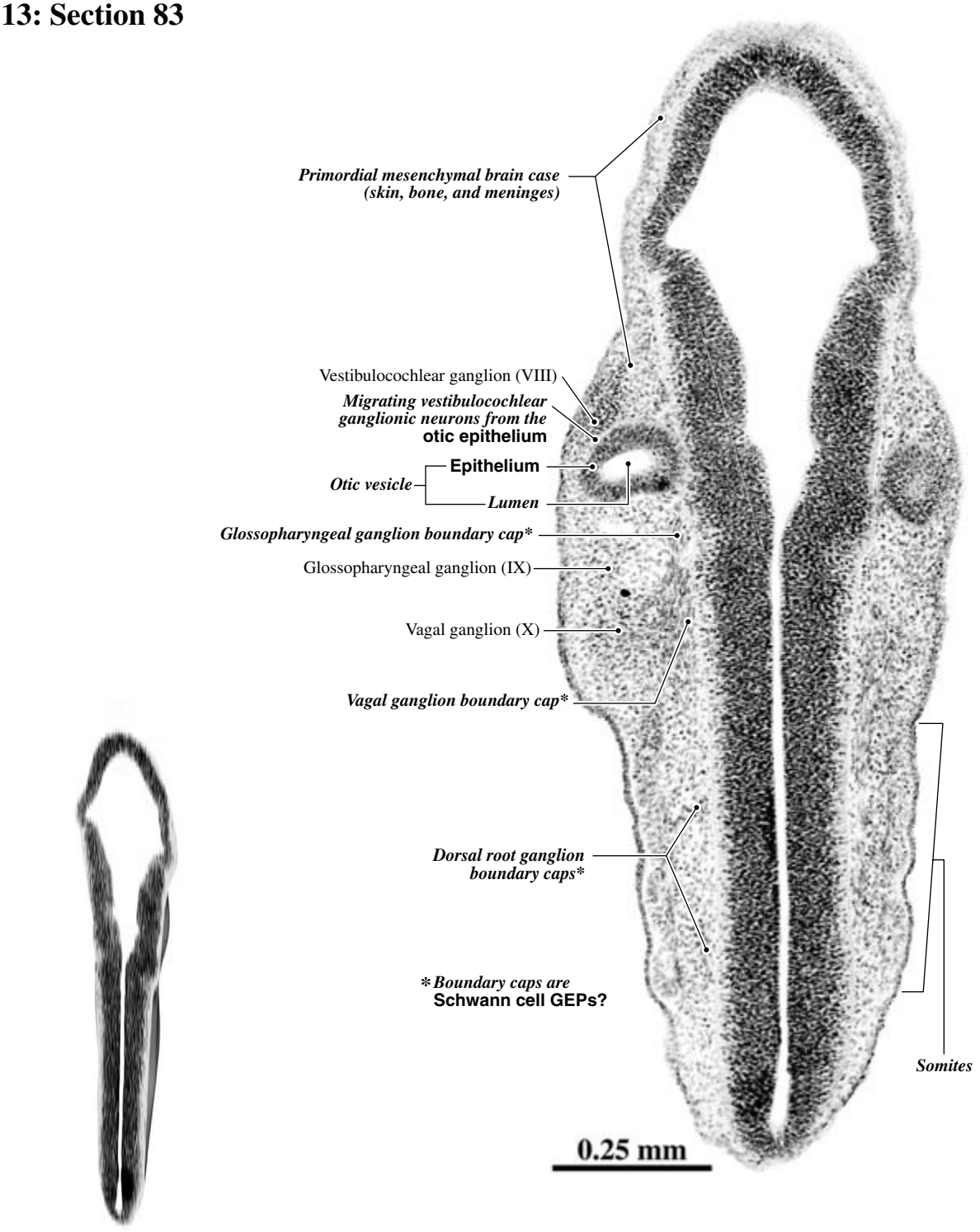


PLATE 196A

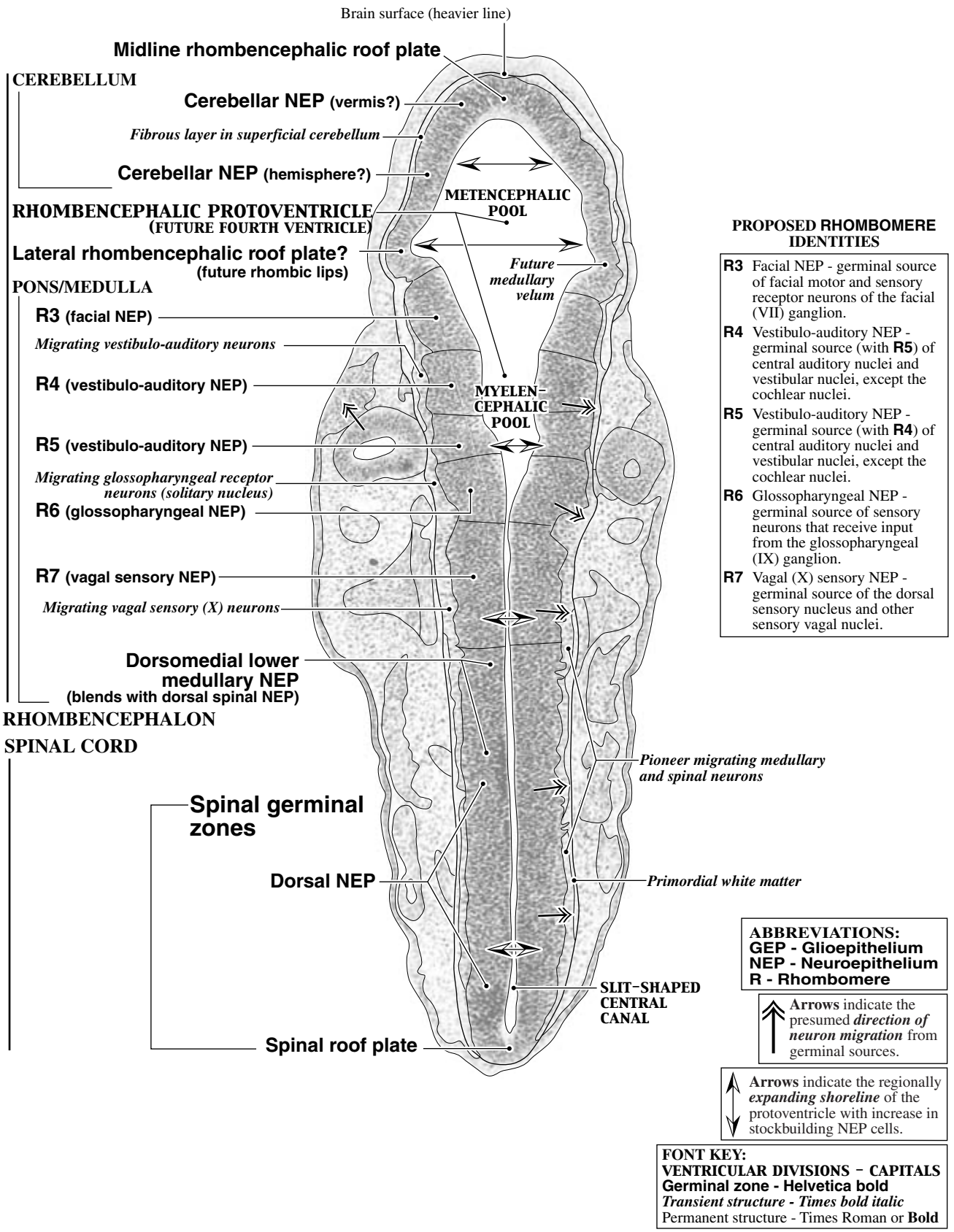
Peripheral neural and non-neural structures labeled

GW3.2 Coronal
17-18 Somites?
M714
Level 13: Section 83



Level 13: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled **PLATE 196B**



PROPOSED RHOMBOMERE IDENTITIES

R3 Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.

R4 Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

R5 Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.

R6 Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.

R7 Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

ABBREVIATIONS:
GEP - Glioepithelium
NEP - Neuroepithelium
R - Rhombomere

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS - CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

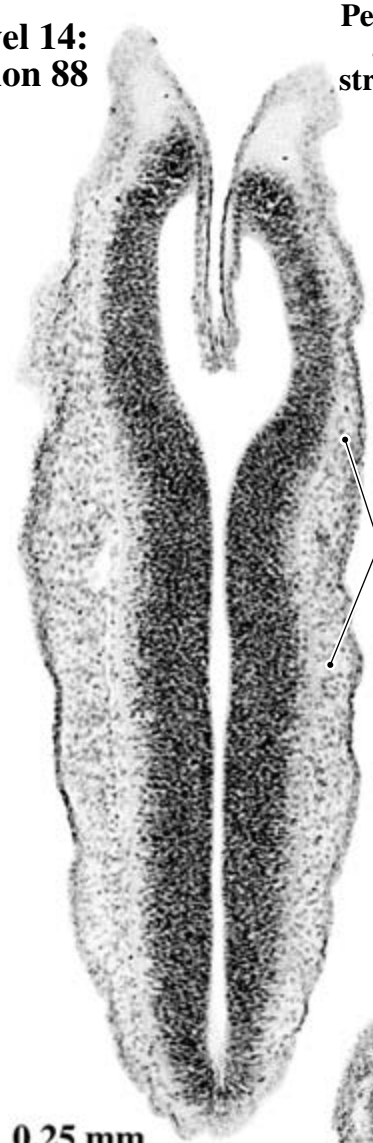
PLATE 197A

GW3.2 Coronal
17-18 Somites?
M714

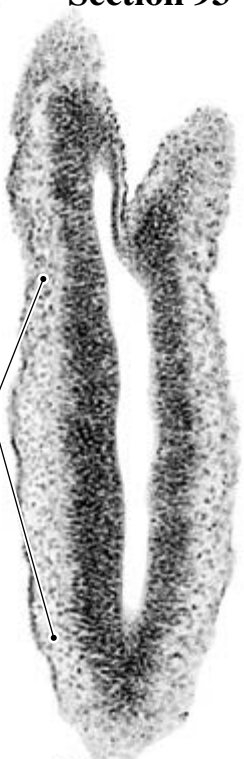
Level 14: Computer-aided 3-D Brain Reconstruction

Level 14: Section 88

Peripheral neural and non-neural structures labeled



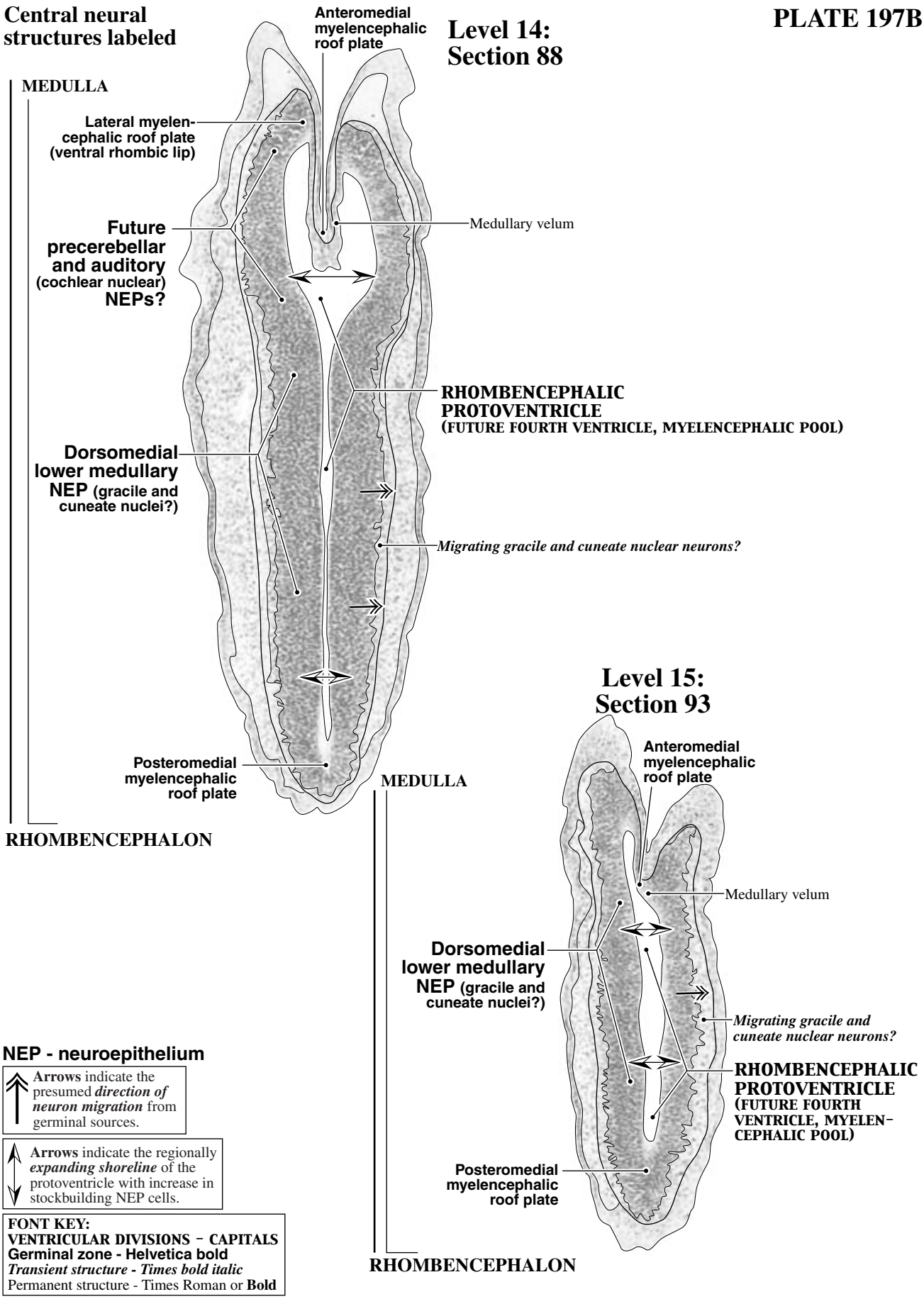
Level 15: Section 93



Level 15: Computer-aided 3-D Brain Reconstruction

Central neural structures labeled

PLATE 197B



NEP - neuroepithelium

Arrows indicate the presumed ***direction of neuron migration*** from germinal sources.

Arrows indicate the regionally ***expanding shoreline*** of the protoventricle with increase in stockbuilding NEP cells.

FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

PART XVI
CONCLUDING ESSAY

JOSEPH ALTMAN and SHIRLEY A. BAYER

We began to work on this project over a decade ago to produce a comprehensive, multi-volume *Atlas of Human Central Nervous System Development* (CNS). Our aim in starting this project was to try to interpret normal human CNS development in light of the understanding we have gained in the preceding three decades from an experimental analysis of the prenatal and postnatal development of the rat CNS. In that extensive work, we injected ^{3}H-thymidine at daily intervals to groups of pregnant rats. Those injections labeled DNA in the proliferating progenitors of neurons and neuroglia in the rat embryos and fetuses. We also injected ^{3}H-thymidine at varied intervals to groups of infant, juvenile, and adult rats to study the postnatal course of cell proliferation during late CNS development. By varying survival times after administration of the radiochemical from hours, to days and months, we used the techniques of short-survival, sequential-survival, and long-survival autoradiography to achieve the following. (1) Determine the proliferation dynamics of progenitor cells in the various compartments (mosaics) of the primary neuroepithelium (NEP) and in the various secondary germinal matrices—cortical and striatal subventricular zones (SVZ), cerebellar external germinal layer (EGL), hippocampal subgranular zone (SGZ)—as a function of prenatal and postnatal age. (2) Track the migratory routes of different populations of young neurons, their sojourn in transitional fields, and their final settling in the developing CNS. (3) Construct quantitative timetables of the birth dates of different classes of mature neurons in different components of the adult rat CNS. The results of these studies were published in a series of journal articles (*see* **Introduction, Part ID**), and were reviewed in chapters contributed to edited books (Altman, 1992; Altman and Bayer, 1975, 2004; Bayer and Altman, 1995a, 1995b, 2004b).

We embarked on this ambitious project for two reasons. First, to fill a gaping void in the literature on this important subject. There is currently no comprehensive atlas available that covers the entire time span of prenatal human CNS development from the time when the neural tube and the brain vesicles close (approximately GW3) until birth at the end of the third trimester (approximately GW37). Although there are many published accounts of certain facets of the early development of the human CNS (mostly in volumes of the *Carnegie Institution of Washington, Contributions to Embryology*), and a few published overviews of human brain development (e.g., Sidman and Rakic, 1982), as well as books on its early phases (*e.g.*, Gasser, 1975; O'Rahilly and Müller, 1994), this five-volume atlas is the first comprehensive source that provides a detailed description of the entire course of this momentous morphogenetic event. There are obvious needs for a detailed description of the prenatal development of the human brain and spinal cord: (i) as an aid to medical practitioners, (ii) as a reference work for molecular, physiological, and behavioral neurobiologists, and (iii) as an empirical foundation for the ethical, legal, and psychological assessments of the putative mental status of the human embryo and fetus. Second, we hoped that by extrapolating from the experimental data obtained in animals, we could go beyond a mere narrative account of developmental landmarks in human CNS development to a dynamic analysis of some of the morphogenetic processes involved. What we were surprised to find is that our detailed examination of the full course of CNS development in normal human embryos and fetuses has come to shed new light on some of the basic mechanisms involved in the production, migration, differentiation, and assembly of CNS neurons, and some aspects of its afferent and efferent wiring and circuitry formation. We begin here with a brief overview of these insights and provide some of the details with summary illustrations and documentation in the succeeding sections.

A. Overview

The Beginning of CNS Development: Stockbuilding NEP Cells and the NEP Matrix. An examination of the CNS of an older embryo or fetus may give the impression that the germinal matrix lining the ventricle (the ependymal layer of classical neuroanatomists and the ventricular zone of modern ones) is merely one of its laminar constituents, one that generates neurons and neuroglia for its more mature strata. In fact, for several weeks after closure of the neural tube, the human CNS consists only of a proliferative matrix of NEP cells and is devoid of differentiating neurons and neuroglia. The proliferating pluripotent or fate-restricted stockbuilding progenitor cells that compose the mosaic compartments of the NEP matrix are the sole constituents of the early-embryonic CNS. As development proceeds, the stockbuilding NEP cells give rise, at different rates in different NEP compartments, to differentiating (postmitotic) daughter cells. The latter exit the proliferative NEP matrix and start to form the differentiating elements of the brain parenchyma.

The Superventricles and their Variegated Shorelines. We offer evidence that, after closure of the neural tube, the mitotic division of stockbuilding NEP cells is promoted by the hypertrophied telencephalic, diencephalic, mesencephalic, and rhombencephalic superventricles. Because stem cell nuclei of the pseudostratified NEP matrix have to shuttle to the ventricular lumen to undergo mitosis, the areal extent and configuration (protuberances, eminences, invaginations, etc.) of the variegated superventricular shorelines, and their persistence over time, are a limiting factor in determining the population size of the neurons generated at different NEP locations. For instance, the immense growth of the cerebral and cerebellar cortices in the human CNS is dependent upon the immense expansion and long endurance of the telencephalic and rhombencephalic superventricles, respectively. Moreover, the cerebrospinal fluid of the superventricles and the hypertrophied embryonic telencephalic and rhombencephalic choroid plexuses may contain trophic factors that promote NEP cell proliferation.

The Superarachnoid Reticulum as a Parenchymal Expansion Field. As first identified in the present volume, the developing human brain is encased during the first trimester in the superarachnoid reticulum, a transiently inflated and spongy meningeal tissue sandwiched between the pial membrane, adjacent to the brain, and the formative dural membrane, adjacent to the mesenchymal tissue that will form the skull. The initial enlargement of the superarachnoid reticulum antedates the onset of neuronal migration and differentiation, providing expansion space for the settling neurons, their afferent and efferent fibers, and other differentiating components that form the developing brain parenchyma. Accordingly, we propose that during the embryonic and early fetal periods, components of the hypertrophied superarachnoid reticulum serve as regional parenchymal expansion fields. The superarachnoid fluids may contain trophic factors that promote NEP cell differentiation.

Metamerism versus Functional Mosaicism as Principles of CNS Development. According to the popular metameric hypothesis, the mammalian neuraxis is composed of a large number of reiterated transverse blocks or segments. However, the evidence we present indicates that the diverse NEP components of the dorsal and ventral mesencephalon, diencephalon, and telencephalon give no hint of a metameric organization at any phase of their development. While the trunk region and the spinal cord are distinguished by *peripheral segmentation* (the reiterated somites and the dorsal and ventral roots), the central gray matter of the spinal cord has a longitudinal (columnar) rather than a segmental organization. And while the rhombencephalon shows distinctive *central neuromerism* at a certain stage of its development, the different rhombomeres are not reiterated units but highly diversified NEP mosaics (see below). Although peripheral metamerism probably played an important role in the early evolution of the invertebrate and protochordate CNS, the overriding principle of CNS development in lower and higher vertebrates (including humans) is NEP mosaicism, the progressive diversification of progenitor compartments to generate neural systems with distinctive functions.

The Rhombomeres as NEP Mosaics. Contrary to the widely held view that the head-related rhombomeres are reiterated segmental units, analogous to the trunk-related peripheral somites and spinal ganglia, we present morphogenetic evidence that rhombomeres 2 to 7, are transient NEP mosaics that are directly linked with different cranial ganglia—the trigeminal, facial, vestibulocochlear, glossopharyngeal, and vagal ganglia—and morphogenetically related to the branchial and epibranchial placodes that, together with neural crest cells and some mesenchymal elements, give rise to such diverse structures as the face, the jaws, the palate, the inner ear, the upper gut, and several visceral organs.

Neuronal Migration, Sojourning, and Transitional Fields. Although the fate-specification of neurons begins before they leave their NEP compartments, their ongoing diversification is dependent on subsequent events, beginning with their migration, sojourning, and interactions with other neural elements along their trajectory. Instead of a uniform principle of cell migration, the available evidence suggests great diversity in the patterns and mechanisms used by different translocating neuronal populations and their dependence on different guideposts and signaling agents. Some classes of neurons migrate a short-distance, others follow a long course; some neurons migrate singly or in small groups, others form chains or large streams; some neurons move radially, others take a tangential or a tortuous path; some neurons move directly to their final destination, others sojourn for a shorter or longer period in transitional fields where they are subjected to different influences and where they may establish transient or enduring connections with other neuronal systems.

The Secondary Germinal Matrices. Proliferative NEP cells in some regions of the CNS generate not only differentiating neurons but also fate-restricted cells that retain their proliferative potency after they have left the ventricular lumen. These secondary matrices include the SVZ of the neocortex and the basal ganglia, the interstitial subgranular zone (SGZ) of the hippocampal dentate gyrus, and the subpial EGL of the cerebellar cortex and the cochlear nuclei. The secondary germinal matrices persist in many regions for a long time after the primary NEP matrix has disappeared. The neurogenic secondary matrices produce microneurons (like granule cells) with locally arborizing axons that become interdigitated with the earlier-generated larger neurons with long axons. Dispersed, fate-restricted glial progenitor cells in the CNS produce neuroglia that support neuronal growth and repair throughout life.

Periphero-Central Induction and Signaling. Functional mosaicism is a product of reciprocal induction and signaling between diversifying NEP matrix compartments and the peripheral or central structures with which they are fated to interact. At the beginning of development, NEP matrix compartmentation has to be coordinated with different peripheral structures: the sensory neurons of the spinal and cranial ganglia, the sense organs they serve, and the different peripheral muscle groups they will innervate. In the trunk region, this periphero-central coordination is accomplished by reciprocal induction and signaling between the spinal NEP and regional neural crest cell populations, the somites, the notochord, and their derivatives (the spinal ganglia, the cutaneous receptors, the developing axial and limb muscles, etc.). In the head region, this coordination is accomplished by reciprocal induction and signaling between the cephalic NEP and the peripheral cranial, branchial, and epibranchial placodes and their derivatives (the olfactory epithelium, the lens, the cranial sensory ganglia, the inner ear, etc.). This coordination occurs during the early first trimester in humans. Current research in experimental animals, which we will briefly review, implicates specific genes, transcription factors, and signaling molecules are involved in this morphogenetic transaction.

Centro-Central Induction and Signaling. The higher-order components of the CNS—such as the thalamic relay nuclei, the neocortical sensory and motor projection areas, the feedback loops of the cerebellum and the basal ganglia—have no direct connections with peripheral sense organs and effectors. However, they are intimately associated with one another through large fiber tracts and elaborate regional networks of axon terminals, dendrites and synaptic junctions. The establishment of topographically organized projection systems, and the development of serial or hierarchic interconnections among them, is dependent on centro-central induction and signaling. Current research in animals focuses on the identification of signaling mechanisms involved in the guided pathfinding of axons and the choreographed migration of neurons. In the human CNS, long-range axonal connections are established by the late first trimester but the establishment of the fine circuitry of many brain regions through interdigitation of interneurons and microneurons is a lengthy process that extends beyond the second and third trimesters and continues through the postnatal period of brain development.

B. The NEP Matrix: Stockbuilding NEP Cells, and Differentiating NEP Cells

The NEP Matrix. For weeks after uterine implantation, the human embryo lacks a functional CNS with differentiated neurons furnished with dendrites, axons, and intercellular connections that make possible the gathering, conveying, processing, and storing of sensory information and the generation of responses to them by overt movements and actions. It is only about one month following conception (approximately GW4-4.5) that differentiating neurons start to aggregate in the earliest-maturing regions of the spinal cord (Altman and Bayer, 2001). In the late-developing cerebral cortex, the rudiment of the gray matter, the cortical plate, does not begin to form until approximately GW8-8.5 (Volume 4 of this Atlas). Instead of differentiating neurons, the early embryonic CNS consists of an expanding proliferative matrix of neural stem cells and precursor cells, the neuroepithelium (NEP). The life-career of the NEP matrix begins in the form of a superficial, flat ectodermal sheet, the neural plate, which is recognizable in the human embryo by approximately GW2.5 (O'Rahilly and Müller, 1994). This open NEP matrix is devoid of its own distinctive fluid environment. The ventricular system filled with cerebrospinal fluid (CSF) begins to form at approximately GW3-3.5 when the open neural plate changes into a closed vessel. This takes place as two other ectodermal derivatives, the neural crest and the placodes, differentiate lateral to the folding neural plate. The highly motile neural crest cells give rise to the PNS of the trunk region, including the neurons of the dorsal root ganglia, the sympathetic and parasympathetic ganglia, and enteric nervous system, as well as some non-neuronal elements (Weston, 1970; LeDouarin, 1982). In the head region, neural crest cells are believed to produce some neuronal elements and the facial skeleton, but the peripheral cranial nerve ganglia and components of the head sensors (olfactory, visual, auditory) originate from a distinctive ectodermal matrix, the placodes (Knouff, 1935; Jacobson, 1963; Noden 1993). After separation of the neural crest and the placodes, the neural folds fuse dorsally and that leads, in the trunk region, to the formation of the closed NEP matrix of the neural tube (future spinal cord) and, in the head region, to the formation of the cranial vesicles (future brain). There are initially three cranial vesicles: the prosencephalic NEP (forebrain primordium), the mesencephalic NEP (midbrain primordium), and the rhombencephalic NEP (hindbrain primordium). Then, as a portion of the prosencephalic NEP evaginates and expands laterally, the forebrain rudiment is transformed into a medial diencephalic NEP (future thalamus, subthalamus, and hypothalamus) and a bilateral telencephalic NEP (future cerebral cortex, basal ganglia, and olfactory bulb).

Stockbuilding and Differentiating NEP Cells. There are several controversial issues regarding the features and properties of NEP cells that constitute the NEP matrix. One concerns the differences in the cleavage orientation and fate of NEP cells that undergo mitosis near the lumen, another concerns the variable morphology of NEP cells, and still another the typology of NEP cells. It has been noted in the past (e.g., Bayer and Altman, 1991a) that the cleavage plane of NEP cells varies from vertical (perpendicular to the ventricular lining) to horizontal (parallel to the ventricular lining). It has been hypothesized that vertical cleavage results in symmetrical cell division, and hori-

zontal cleavage in asymmetric cell division (e.g., Chenn and McConnell, 1995). Symmetric NEP cell division is assumed to produce two neural precursor cells, or what we call *stockbuilding* cells. Asymmetric cell division is presumed to produce at least one *differentiating* (postmitotic) neural cell. Presumably the cell located farther from the ventricular lumen withdraws from the mitotic cell cycle, leaves the NEP matrix, and starts the long process of differentiation. From the perspective of the areal extent of the ventricular shoreline, vertically cleaving cells take up twice as much NEP/CSF interface space as the horizontally cleaving cells. Hence, a high rate of symmetric divisions should result in expansion of the ventricular shoreline whereas high rate of asymmetric divisions should result in its shrinkage. Indeed, some evidence has been presented that there is an increase in the asymmetric division of cortical NEP cells in mice as a function of increasing fetal age (Estivill-Torrus et al., 2002). Currently there is considerable interest in the molecular mechanisms that affect the switch from stockbuilding to neurogenic NEP cell division. *Notch* signaling has been reported to foster expansionary (stockbuilding) symmetric division of NEP cells (Ishibashi et al., 1994; Artavanis-Tsakonas et al., 1999; Alexson et al., 2006). In the absence of repressor type-bHLH (basic helix-loop-helix) genes, which are essential for *Notch* signaling, NEP cells prematurely differentiate into neurons and neuroglia (Nakamura et al., 2000; Hatakeyama et al., 2004). Transient misexpression in mice of the repressor -type bHLH genes, *Hes1* and *Hes5*, known *Notch* effectors, results in the expansion of the stockbuilding population of telencephalic NEP cells, but once *Hes* expression starts to decrease, the NEP cells differentiate into neurons and neuroglia (Ohtsuka et al., 2001). Another consequence of the depletion of repressor type *Hes* genes is that the premature differentiation of NEP cells prevents the formation of late-generated astrocytes and ependymal cells (Kageyama et al., 2005). Other molecular factors that appear to promote stockbuilding cortical NEP cell division include *C3G*, a guanine nucleotide exchange factor (Voss et al., 2006), and ß-Catenin, a protein enriched in adherens junctions at the ventricular lining, since its over-expression produces enlarged cortices in transgenic mice (Chenn and Walsh, 2003). Some stockbuilding genes and factors antagonize genes, while other factors promote cell differentiation. Among the latter are the activator type bHLH genes, *Mash1*, *Math*, and neurogenin (Kageyama et al., 2005). Another factor, *Aspm*, a protein whose mutation is associated with microcephaly (reduced neuron populations) in humans, is down-regulated in NEP cells as they switch from stockbuilding to neurogenic cell division (Fish et al., 2006).

It is important to emphasize that the NEP cells which line the ventricles have neither the morphological nor the physiological features of their progeny, the distinctive neurons, neuroglia, ependymal cells, tanycytes, and a few other neural elements of the developing and mature CNS. Differentiated neurons reside outside the NEP matrix, have axons, dendrites and synaptic vesicles, and conduct generator and action potentials. In higher vertebrates and humans, the NEP matrix does not contain differentiated neurons. Differentiated neuroglia, likewise, have clear distinguishing anatomical and physiological characteristics. For instance, oligodendrocyte lamellae produce the myelin sheath of axons, astrocyte processes nourish neurons, and the radial glia (like the Bergmann glia of the cerebellar cortex) form compartmental palisades. However, we cannot flatly assert that the NEP matrix does not contain neuroglia because that contradicts the popular current view that some of the cells of the ventricular matrix are "radial glia" (e.g., Malatesta et al., 2000; Hartfuss et al., 2001). However, that designation is not justified and has only led to conceptual confusion. Observations made over a century with the Golgi technique has revealed three types of NEP cells: (1) a round *globular cell* with its endfoot attached to the ventricular lumen; (2) an oval *fibrous cell* with its endfoot contacting the ventricle and its thin radial fiber reaching the pial surface; and (3) a *detached cell* with its leading fiber approaching or reaching the pial surface. (Illustrations of these cell types were provided by Morest, 1970, and Morest and Silver, 2003.) Most (though not all) anatomists have assumed that these NEP cells are neural progenitor cells but differed in viewing them as either different types of precursor cells or different stages of the same cell. The popular notion that the fibrous NEP cells are "radial glia," a separate cell lineage that guides migrating young cortical neurons toward their targets, was advocated by Rakic (1971). The subsequent demonstration that many of these ventricular cells express the glial marker *GFAP* (Levitt et al., 1981) reinforced this identification. However, the expression of a marker that in the mature nervous system specifically reacts with glial filaments, does not rule out the possibility that the same marker reacts with transient filamentous elements in non-glial embryonic cells (Bennett, 1987). Indeed, the current demonstration that the majority of mitotic NEP cells with radial fibers are neuron progenitors (Malatesta et al., 2000; Miyata et al., 2001; Tamamaki et al., 2001; Noctor et al., 2002) definitively establishes that the fibrous NEP cells are not specialized glia (like the Bergmann radial glia) but are prototypical NEP cells. In addition to neurons, the fibrous NEP cells may also generate other neural elements, such as astrocytes (Misson et al., 1991). Whether there is any direct relationship between symmetrically and asymmetrically dividing NEP cells, on the one hand, and the globular and fibrous NEP cells, on the other, remains to be determined. In light of our observations in the developing human brain, the fibrous NEP cell may be viewed as a neural progenitor that is in contact with the aqueous medium of the superventricle with its endfoot, and approximates the spongy medium of the pia and superarachnoid reticulum with its radial fiber.

C. The Superventricles and the Superarachnoid Reticulum

The Superventricles. While the telencephalic, diencephalic, mesencephalic and rhombencephalic ventricles are quite narrow and quasi-tubular at GW3.5 (**Figure 15A**), they expand considerably during the rest of the first trimester (**Figure 15B to 15G**). We have named these ballooning embryonic cisterns superventricles (Volume 4: Bayer and Altman, 2006). There is a caudal-to-rostral gradient in the time course of superventricular expansion and shrinkage, with the rhombencephalic superventricle leading and the telencephalic superventricle trailing. There are also differences in the magnitude of superventricular expansion, being less pronounced for the mesencephalic and diencephalic superventricles associated with midline nuclear structures (midbrain, thalamus, hypothalamus) and the rhombencephalic and telencephalic superventricles associated with hemispheric cortical structures (cerebellum and cerebrum). We attribute great significance to the expansion, configurational changes, and shrinkage of the superventricles because the ventricular shorelines provide the substratum for NEP cell mitotic division and because proximity to the ventricular CSF appears essential for that division. In our earlier study of human spinal cord development (Altman and Bayer, 2001; Volume 1: Bayer and Altman, 2002), we documented the relationship between ventral-to-dorsal expansion and shrinkage of the central canal with ventral-to-dorsal thickening and thinning of the NEP matrix. That relationship resulted in early-to-late neurogenetic gradients between ventral horn motor neurons and dorsal horn sensory-relay neurons. We inferred that increased proliferation in a NEP compartment is associated with the expansion of its shoreline in the ventricular lumen. As a NEP compartment produces neurons that leave the matrix, it thins and its ventricular shoreline shrinks. Supporting that inference is the relationship we document in this Atlas between the temporal order in the expansion and shrinkage of different components of the NEP matrix—the lengthening and shortening of their shorelines in the superventricles—and the rise and fall in the number of neurons they generate.

The first ventricle that commences to expand to form a cavernous cistern is the rhombencephalic superventricle. As seen in sagittal sections, the rhombencephalic superventricle first forms a dome dorsally as the medullary velum expands (**Figure 15A, B**). Then, as the medullary flexure forms ventrally it also expands in that direction to form a triangular cavity (**Figure 15C, D**). The medullary velum then invaginates to produce the expanding rhombencephalic choroid plexus, and the superventricle becomes divided into a metencephalic (cerebello-pontine) pool and a myelencephalic (medullary) pool. Thereafter, the rhombencephalic superventricle begins its gradual shrinkage and eventually assumes the size and form of the familiar fouth ventricle. The expansion of the mesencephalic superventricle (the future aqueduct) and that of the diencephalic superventricle (the future third ventricle) is not as pronounced as that of the rhombencephalic superventricle but is evident when the parenchyma of the mesencephalic tectum and tegmentum, and the diencephalic thalamus and hypothalamus, start to expand. The expansion of the telencephalic superventricles does not commence until approximately GW5.5, when two symmetrical, balloon-like fluid compartments start their lateral outpouching from the midline prosencephalic ventricle. The great expansion of the telencephalic superventricles continues up to approximately GW11. Then, in correlation with expansion of the cerebral cortex and the basal ganglia, the telencephalic superventricles begin to shrink during the second and third trimesters and are eventually transformed into the enduring lateral ventricles. The initial expansion, of the midline prosencephalic superventricle, and then of the bilateral telencephalic superventricles are illustrated in coronal sections in **Figure 16A to 16I**.

How is overall superventricular expansion, in general, and regional differences in the configuration and magnitude of that expansion, in particular, related to neurogenesis? We propose that the area of the variegated ventricular NEP lining, in combination with such important factors as cell cycle speed and the number of mitotic divisions prior to differentiation, determines the size of the neuron population generated at a particular site. This is so because the nuclei of the pseudostratified NEP cells have to undergo "interkinetic nuclear migration" (Sauer, 1936), i.e., shuttle to the ventricular lumen, to undergo mitotic division. That is, the number of NEP cells produced is limited by the surface area (length and width) of the ventricular shoreline because the elongated cells inside the NEP matrix cannot undergo mitosis unless there is room for them to descend to the NEP/CSF interface. The overall extent of the shoreline of a particular superventricle provides the required space for the shuttling NEP cells to continue their cycle of divisions until a specified number of neurons are generated for that brain system; the variegated regional size or configuration of the shoreline—in the form of expanding and shrinking eminences, protuberances, evaginations and invaginations into the ventricle—provide the required space for the production of the right number of neurons for a specific brain region or structure within that brain system. In general, NEPs lining ventricular surfaces that produce large cortical structures composed of similar neuronal populations (e.g., the neocortical, tectal, and cerebellar NEPs) tend to be extensive and smooth, whereas the NEPs lining ventricular surfaces that produce a multitude of distinctive but smaller neuronal populations (e.g., the NEP mosaics that produce the various thalamic and hypothalamic nuclei) tend to be small and corrugated. The correlation between ventricular size and the magnitude of the generated neuronal population is illustrated in a comparison of the area of the telencephalic superventricle (specifically, its cortical pool) between the rat that develops a small neo-

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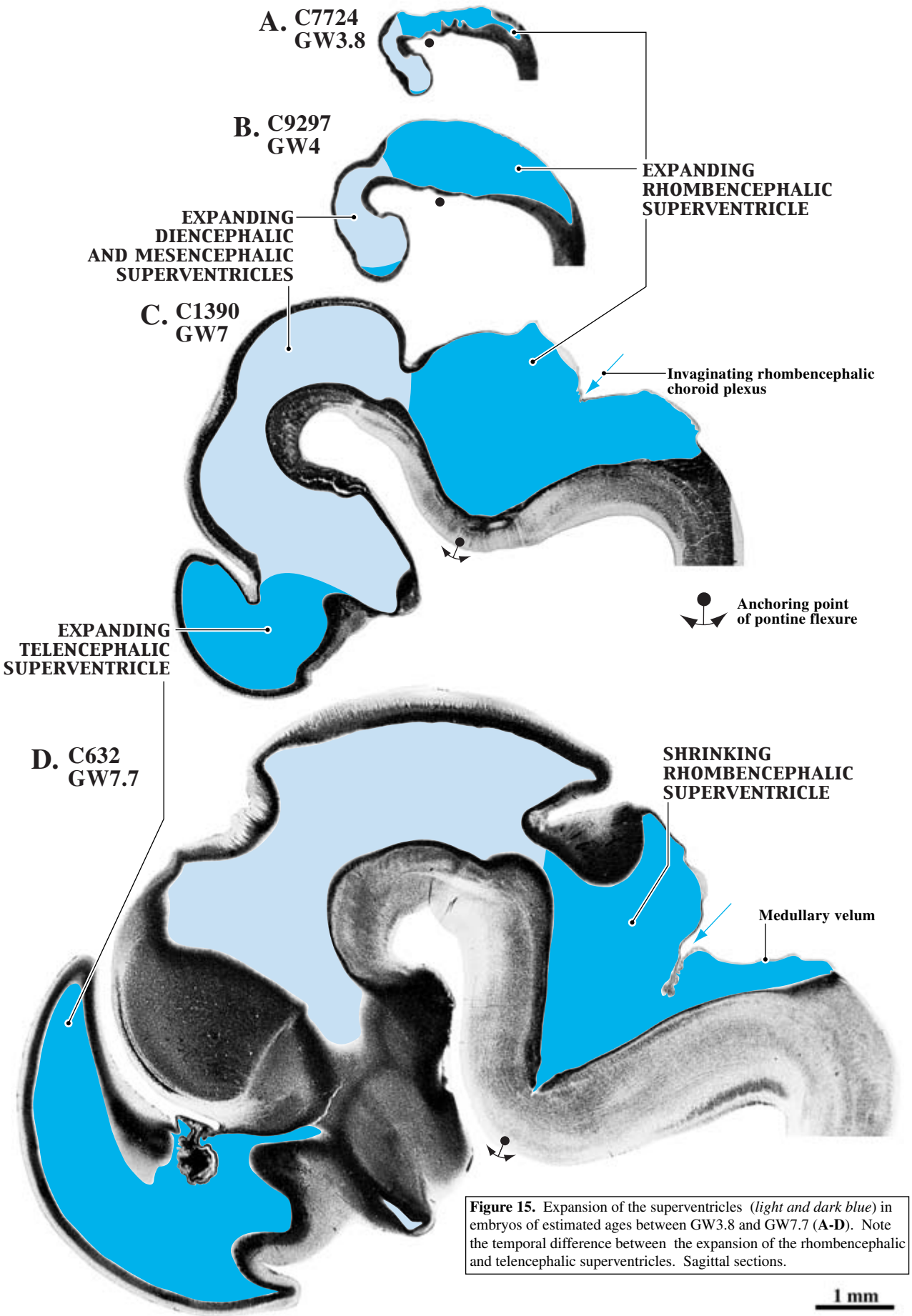


Figure 15. Expansion of the superventricles (*light and dark blue*) in embryos of estimated ages between GW3.8 and GW7.7 (**A-D**). Note the temporal difference between the expansion of the rhombencephalic and telencephalic superventricles. Sagittal sections.

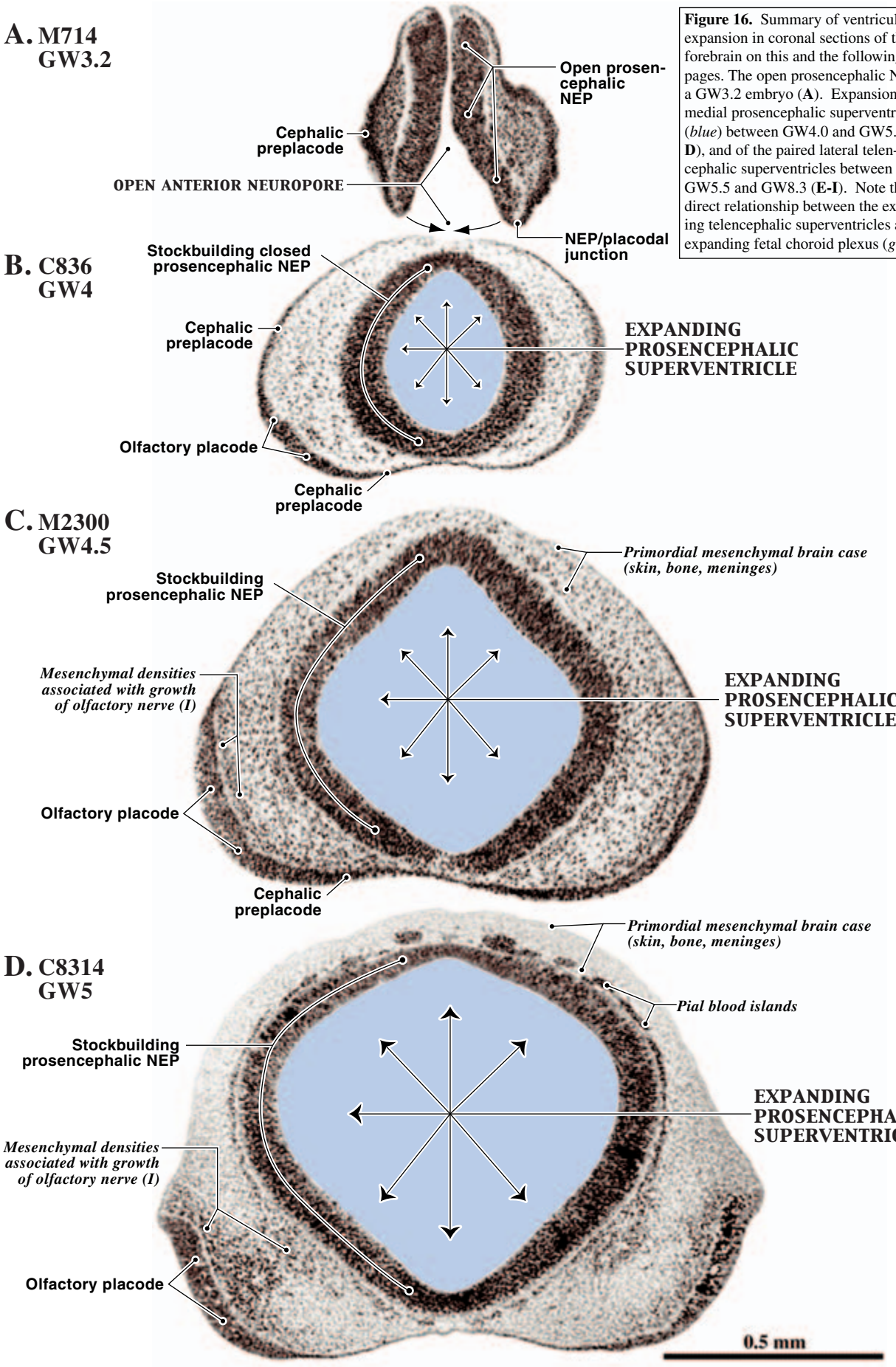


Figure 16. Summary of ventricular expansion in coronal sections of the forebrain on this and the following two pages. The open prosencephalic NEP in a GW3.2 embryo (**A**). Expansion of the medial prosencephalic superventricle (*blue*) between GW4.0 and GW5.0 (**B-D**), and of the paired lateral telencephalic superventricles between GW5.5 and GW8.3 (**E-I**). Note the direct relationship between the expanding telencephalic superventricles and the expanding fetal choroid plexus (*green*).

Figure 16 continued.

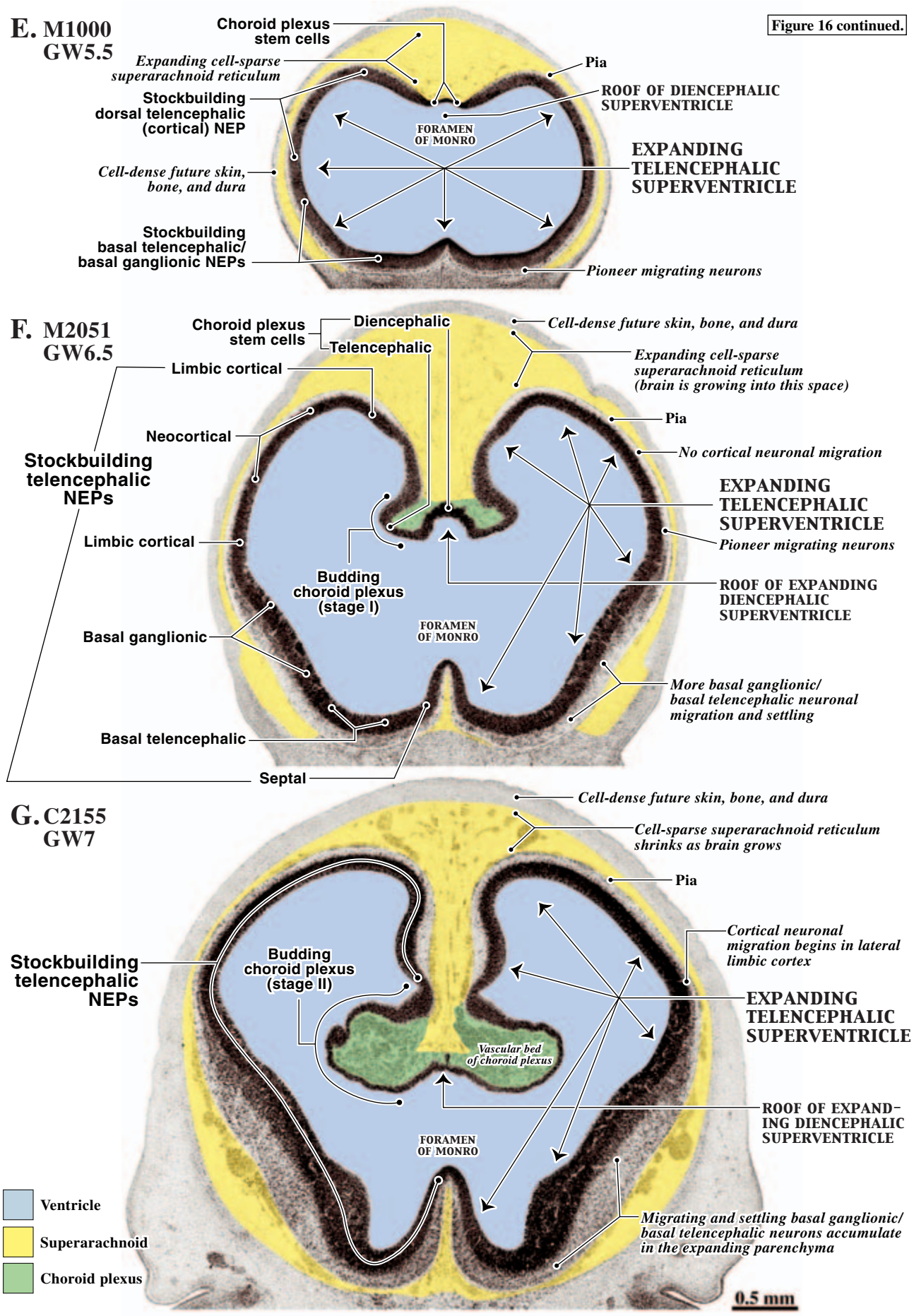
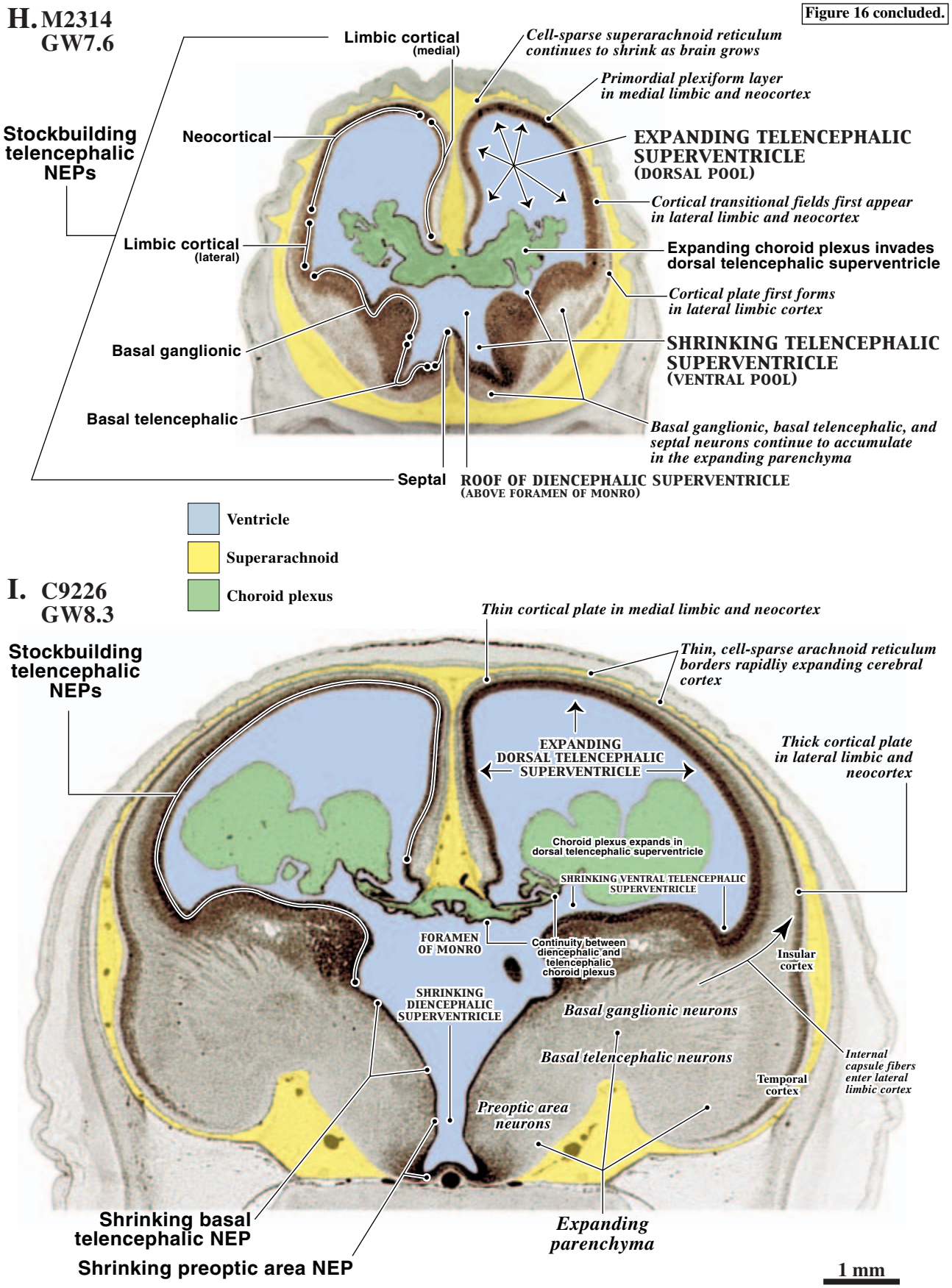


Figure 16 concluded.



cortex and the human that develops a very large neocortex (**Figure 17**).

In addition to the ventricular shoreline providing the space for the mitotic division of NEP cells, there is emerging evidence that the embryonic CSF contains trophic molecules that promote NEP cell division. Since we know that the fate-restricted progenitor cells of the secondary germinal matrices—like those of the subpial external germinal layer of the cerebellum (Altman and Bayer, 1982a) and the interstitial subgranular zone of the hippocampus (Altman and Bayer, 1975)—undergo mitosis some distance from the ventricles, the presence of CSF is obviously not required for the proliferation of late-generated microneuronal progenitors (Altman and Das, 1965b). However, proximity to the embryonic CSF may be a prerequisite for the production of the early, pluripotent NEP cells that generate the large projection neurons. This assumption is supported by reports that the embryonic CSF contains a variety of gene products, proteins, and growth factors (Parada et al., 2006), some of which promote NEP cell proliferation and neurogenesis in experimental animals (Gato et al., 2005; Martin et al., 2006; Mashayekhi and Salehi, 2006). What is the origin of the embryonic CSF? In light of the fact that in the mature brain CSF production is dependent on the choroid plexus (CP), it is important to note that the initial great expansion of both the rhombencephalic and telencephalic superventricles antedates by several weeks the formation of the CP (**Figure 15 and Figure 16**). Moreover, the great flowering of the fetal CP is limited to two sites, the anterior (cerebellar) pool of the rhombencephalic superventricle and the dorsal (neocortical) pool of the telencephalic superventricle. It is significant that in humans, an immensely enlarged CP fills the ballooning telencephalic superventricle as the neocortical NEP vastly expands to produce a large neocortex; compare that to rats where a small CP is in the more flattened telencephalic ventricle as the rat neocortical NEP minimally expands to produce a small neocortex (**Figure 17**). This suggests that there may be two phases in CSF production in the human CNS: an early phase that depends on a "budding" CP, and a late phase that depends on a "blooming" CP, one that sustains the prolonged production of cortical and cerebellar NEP cells. It should be noted finally that the fetal CP has a different cellular organization than the mature CP (Kappers, 1958; Tennyson and Pappas, 1964; Shuangshoti and Netsky, 1966; Dohrmann, 1970; Dziegielewska et al., 2001; Johansson et al., 2005). The adult CP is a distinctive frond-like tissue composed of a monolayer of differentiated cuboidal cells that surround a capillary core. The exposed surface of these cuboidal cells is covered by a rich meshwork of microvilli and some cilia, and the cell interior is filled with mitochondria. In contrast, the fetal CP is a smooth, multilayered (pseudostratified) epithelium composed of spindle-shaped cells that have a simple exposed surface and contain few mitochondria. Unlike the mature CP cells, these fetal CP cells are full of glycogen. Hence, it may be that one of the functions of the embryonic CP is the glycolytic (anaerobic) support of NEP cell proliferation and neurogenesis.

The Superarachnoid Reticulum. The mature brain is surrounded by a tripartite membranous envelope, the meninges, composed of the fine pia mater abutting the brain parenchyma, the tough dura in contact with the bony skull, and the spongy arachnoid sandwiched between the two. The pia is composed of a network of reticular and elastic fibers that adhere to the underlying neural tissue. The dura is formed of connective tissue that serves both as a protective envelope of the brain and as a periosteum of the skull. The interlacing cobweb-like processes of the arachnoid form the spongy subarachnoid space filled with CSF, containing granulations, villi, septa and other regional modifications in relation to the local distribution of blood vessels, perivascular spaces, and venous sinuses. Little information is currently available about the features and properties of the embryonic meninges (Angelov and Vasilev, 1989; Kamiryo et al., 1990; Sturrock, 1990). A study of the development of the human optic nerve emphasized the presence of glycogen-rich cells in the dura and arachnoid (Sturrock, 1987). Observations we present in this Volume indicate that of the three components of the meninges, the pia emerges early during human brain development but the dura much later. Before differentiating neurons start to leave the NEP matrix, a thin tissue layer separates the brain primordium from the surrounding cell-dense (darkly staining) mesenchymal tissue that will later form the skin and bone of the skull. Associated with the development of this formative pia, a cell-sparse (lightly staining) field emerges between it and the cell-dense mesenchyme. This cell-sparse field expands enormously as the brain parenchyma grows through the first trimester, and has variably sized divisions in relation to the different developmental dynamics of components of the telencephalon, diencephalon, mesencephalon and rhombencephalon. We call this embryonic meningeal field the superarachnoid reticulum (**Figure 18A to 18D**). (We must note here that we have failed to recognize this unique feature of the developing brain in the GW7.5 specimen illustrated in Plates 186 to 206 in Volume 4 of the Atlas [Bayer and Altman, 2006], where we simply referred to the region as the "meninges.") As the dura gradually becomes recognizable, the superarachnoid reticulum is seen to become enclosed by an internal and external network of blood vessels associated with the pia and the dura, respectively. By about GW9, the superarachnoid greatly diminishes in size (**Figure 18E**) and the meninges gradually assume their mature form. Because the expansion of the superarachnoid reticulum antedates the growth of the brain parenchyma (**Figure 18A to 18C**), and the brain parenchyma subsequently expands into the space formed by it (**Figure 18D, E**), we postulate that the superarachnoid reticulum constitutes a parenchymal expansion field, a site that is being readied for (and possibly promoting) the entry of differenti-

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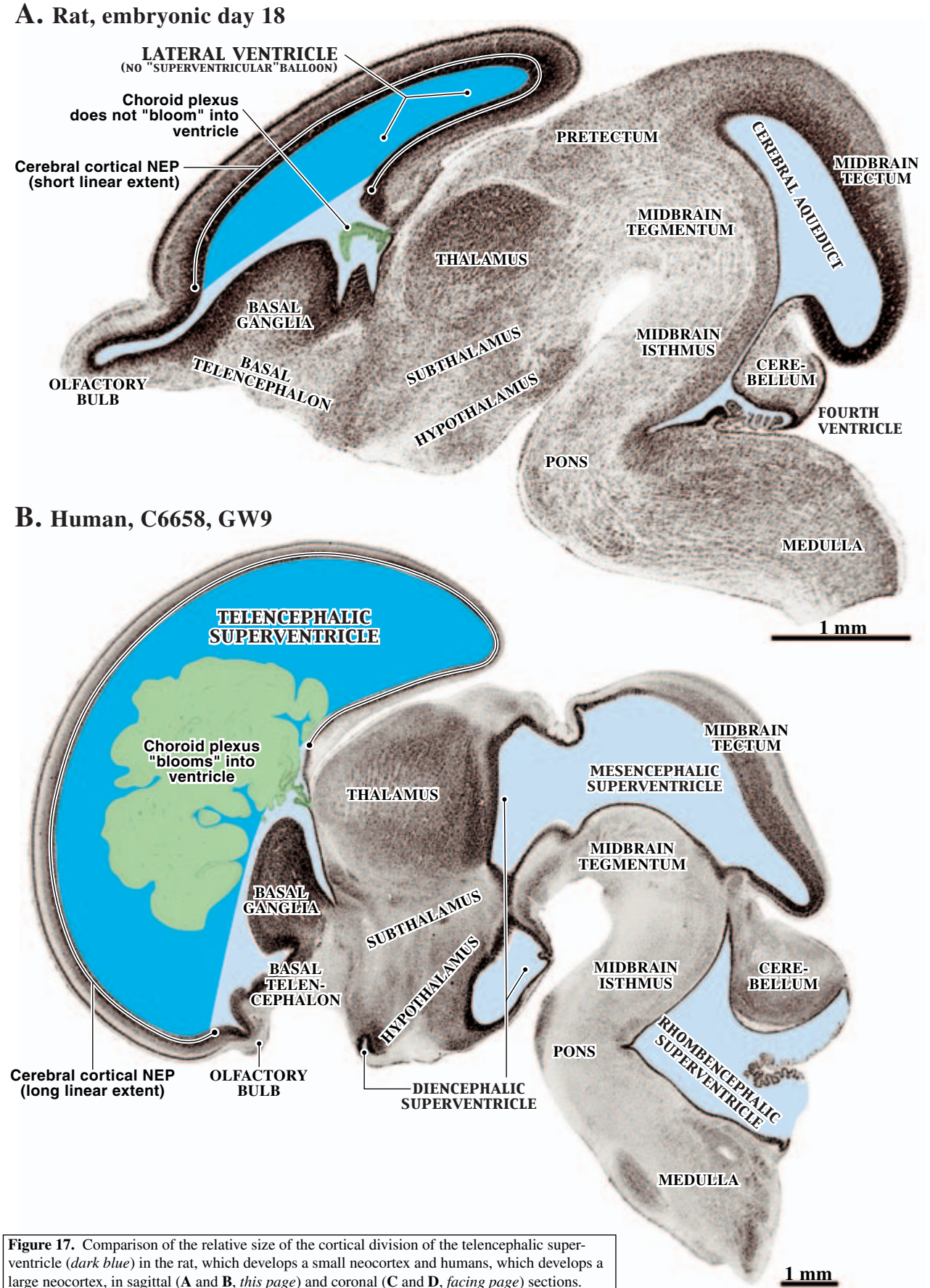
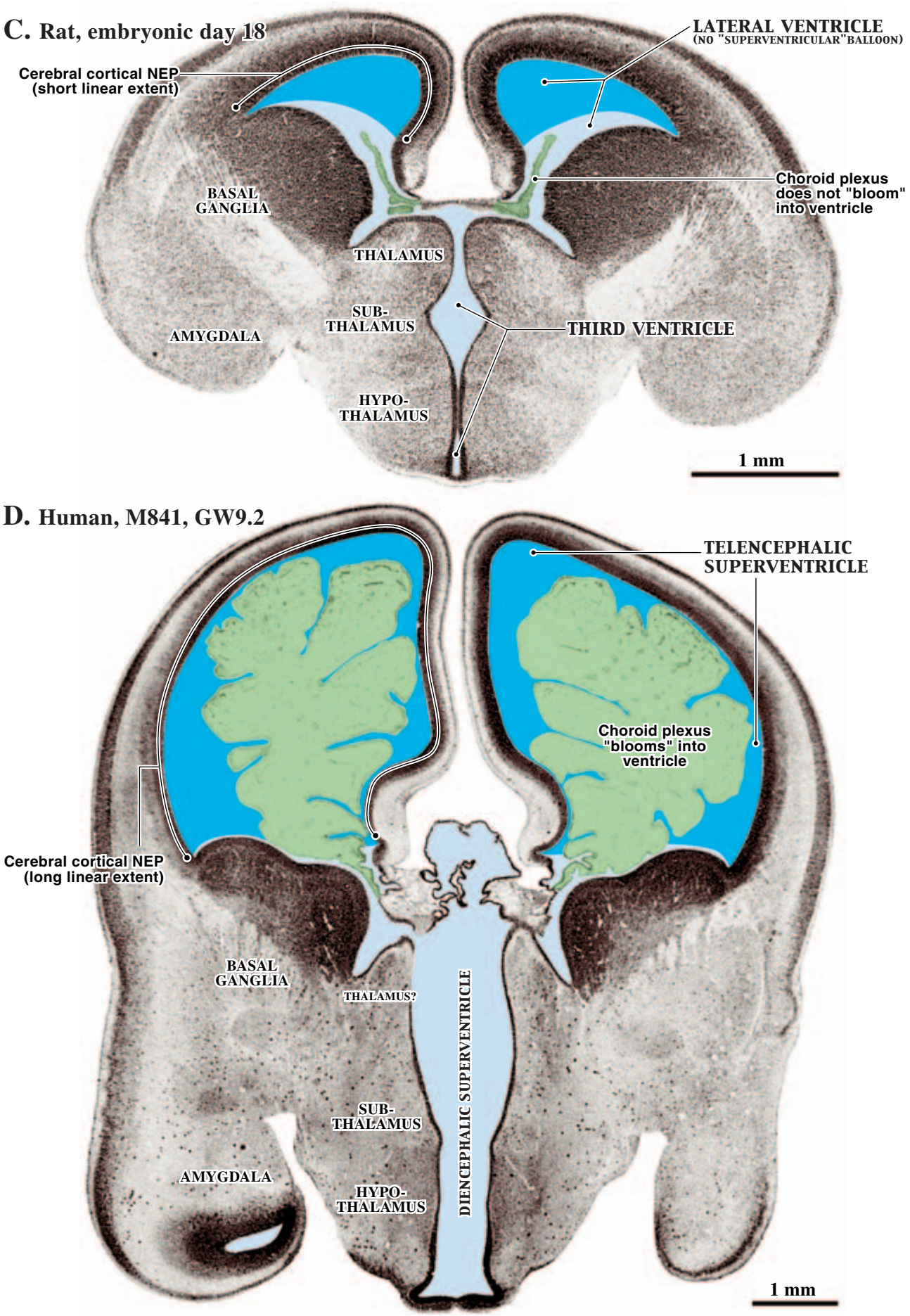


Figure 17. Comparison of the relative size of the cortical division of the telencephalic superventricle (*dark blue*) in the rat, which develops a small neocortex and humans, which develops a large neocortex, in sagittal (**A** and **B**, *this page*) and coronal (**C** and **D**, *facing page*) sections. Note the correlated difference in the size of the choroid plexus (*green*) in the two species.


C. Rat, embryonic day 18
LATERAL VENTRICLE
(NO "SUPERVENTRICULAR" BALLOON)
Cerebral cortical NEP
(short linear extent)
Choroid plexus
does not "bloom"
into ventricle
BASAL
GANGLIA
THALAMUS
SUB-
THALAMUS
THIRD VENTRICLE
AMYGDALA
HYPO-
THALAMUS
1 mm
D. Human, M841, GW9.2
TELENCEPHALIC
SUPERVENTRICLE
Choroid plexus
"blooms" into
ventricle
Cerebral cortical NEP
(long linear extent)
BASAL
GANGLIA
THALAMUS?
DIENCEPHALIC SUPERVENTRICLE
SUB-
THALAMUS
AMYGDALA
HYPO-
THALAMUS
1 mm

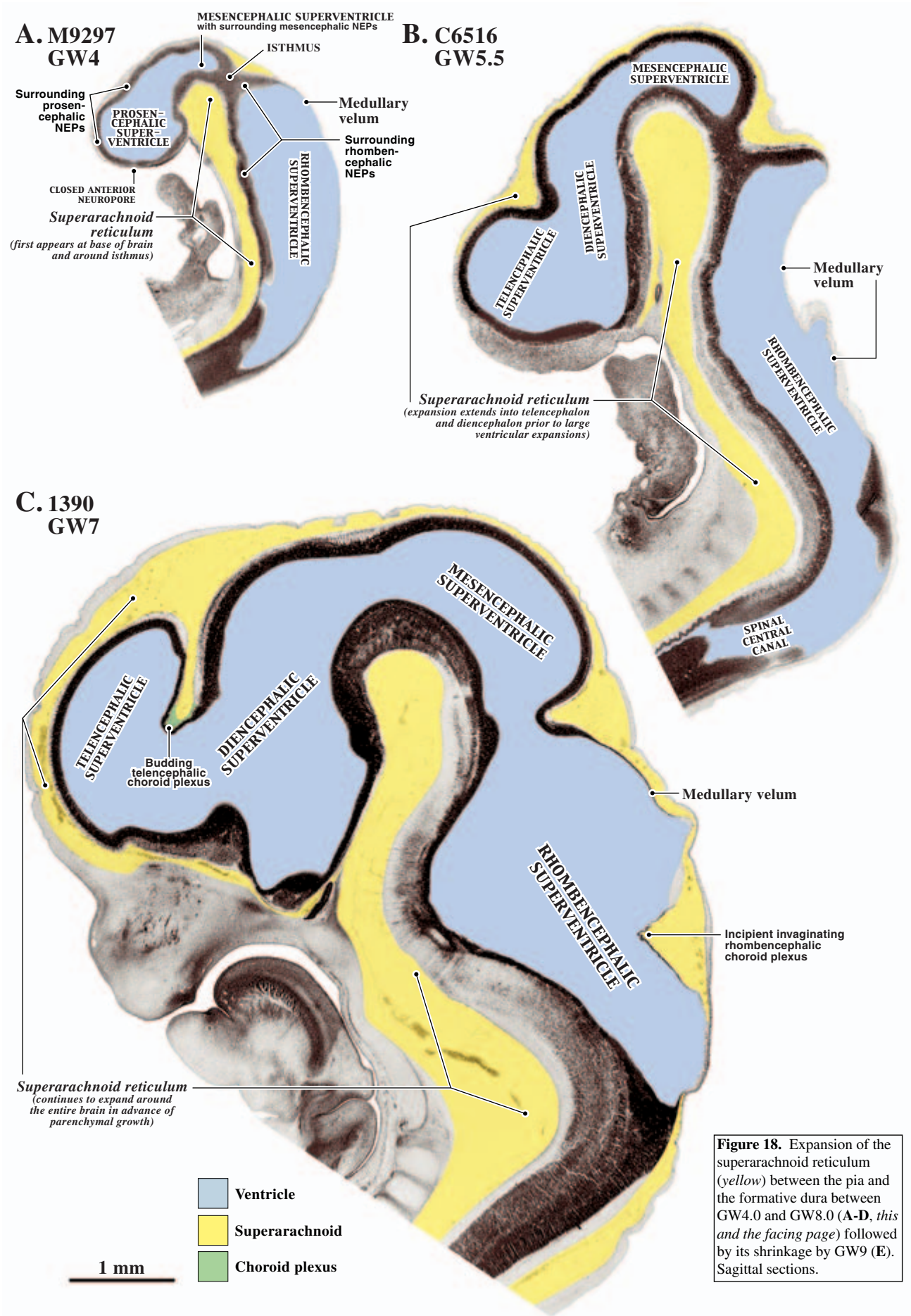
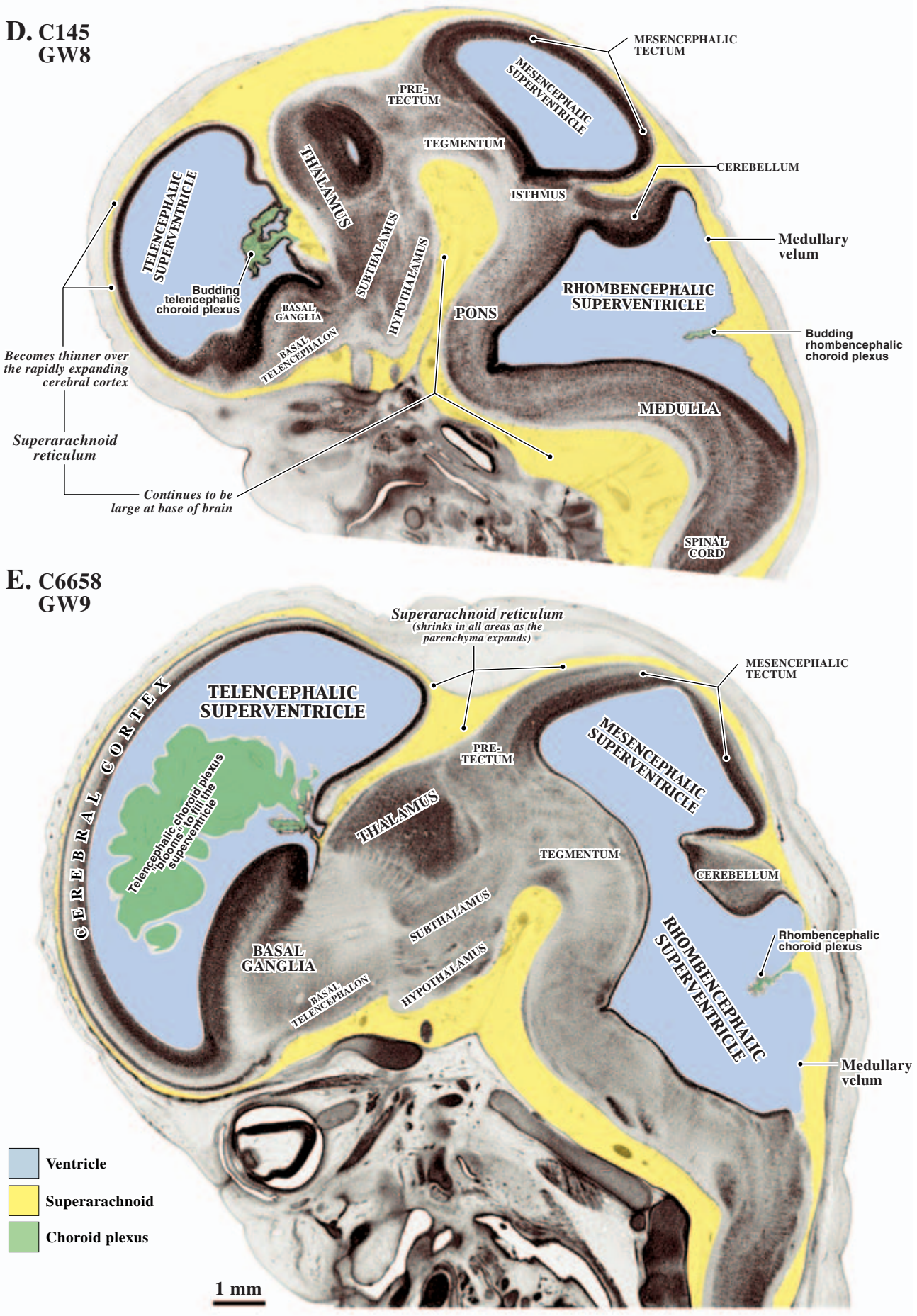


Figure 18. Expansion of the superarachnoid reticulum (*yellow*) between the pia and the formative dura between GW4.0 and GW8.0 (**A-D**, *this and the facing page*) followed by its shrinkage by GW9 (**E**). Sagittal sections.


D. C145
GW8
MESENCEPHALIC TECTUM
MESENCEPHALIC SUPERVENTRICLE
PRE-TECTUM
TEGMENTUM
CEREBELLUM
ISTHMUS
THALAMUS
TELENCEPHALIC SUPERVENTRICLE
SUBTHALAMUS
HYPOTHALAMUS
Medullary velum
Budding telencephalic choroid plexus
BASAL GANGLIA
PONS
RHOMBENCEPHALIC SUPERVENTRICLE
BASAL TELENCEPHALON
Budding rhombencephalic choroid plexus
Becomes thinner over the rapidly expanding cerebral cortex
MEDULLA
Superarachnoid reticulum
Continues to be large at base of brain
SPINAL CORD
E. C6658
GW9
Superarachnoid reticulum
(shrinks in all areas as the parenchyma expands)
MESENCEPHALIC TECTUM
TELENCEPHALIC SUPERVENTRICLE
CEREBRAL CORTEX
PRE-TECTUM
MESENCEPHALIC SUPERVENTRICLE
Telencephalic choroid plexus blooms to fill the superventricle
THALAMUS
TEGMENTUM
CEREBELLUM
SUBTHALAMUS
Rhombencephalic choroid plexus
BASAL GANGLIA
RHOMBENCEPHALIC SUPERVENTRICLE
HYPOTHALAMUS
BASAL TELENCEPHALON
Medullary velum
Ventricle
Superarachnoid
Choroid plexus
1 mm

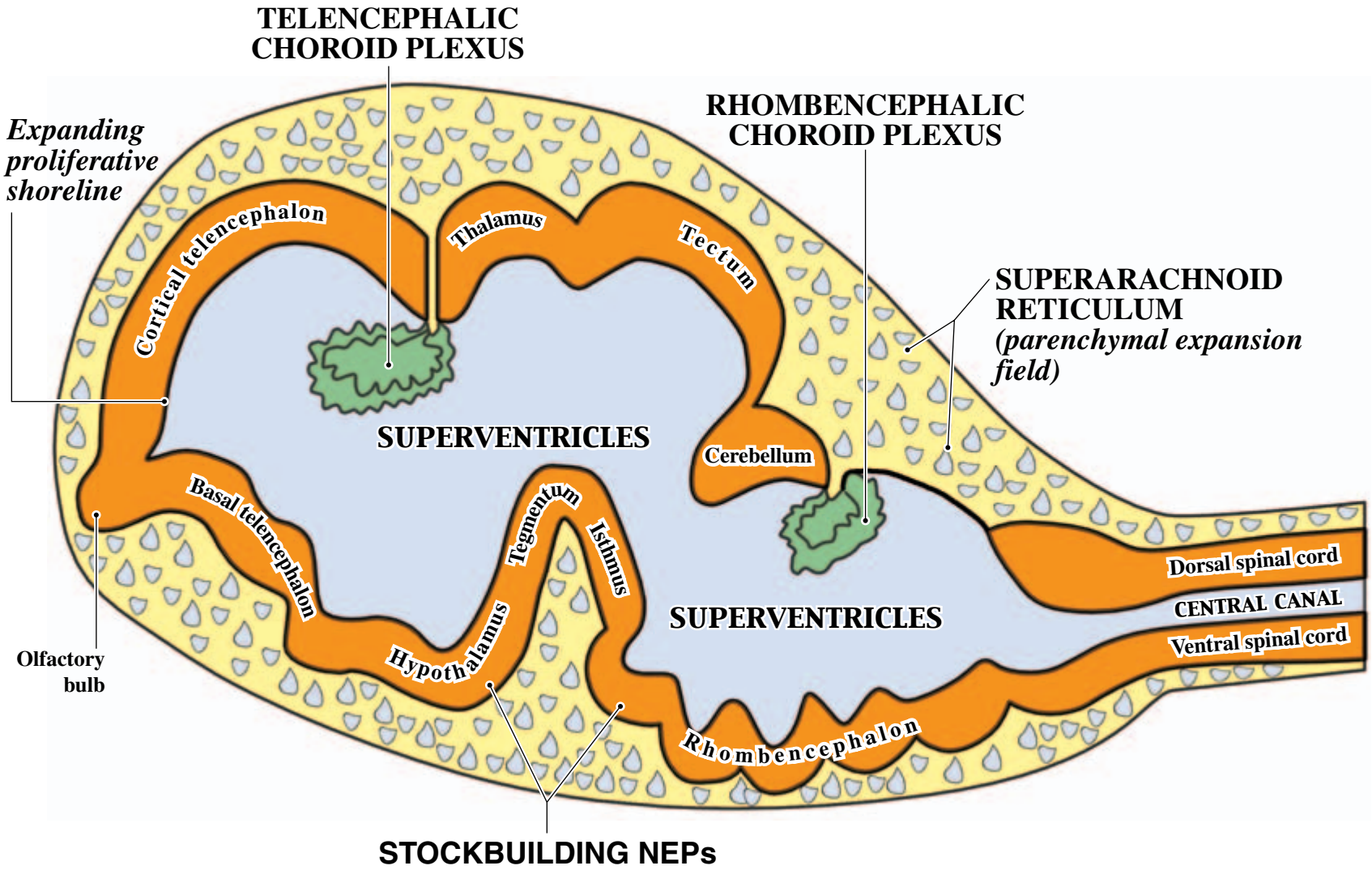


Figure 19. Schematic drawing of the embryonic human CNS with the expanding superventricles (*blue*) that provide the extended shoreline for the mitotic division of stockbuilding NEP cells, and the expanding superarachnoid reticulum (*yellow with blue*) that serves as the parenchymal expansion field for the migrating and settling neurons.

ating neurons and their processes into the developing brain tissue. We speculate that the two fluid-filled spaces, the expanding superventricles and the superarachnoid reticulum—interconnected by the rhombencephalic and telencephalic tela choroidea (**Figure 19**)—play a complementary role in CNS development, trophic factors in the superventricular CSF promoting expansion of the stockbuilding NEP cell population, and trophic factors in the superarachnoid CSF promoting neuronal differentiation and migration.

D. Metamerism or Mosaicism as Principles of CNS Development

From Metamerism to Functional Compartmentation. It is a popular current hypothesis that the neuraxis that extends from the caudal spinal cord to the rostral forebrain develops from a series of reiterated segments or metameric units. This idea goes back to pre-Darwinian evolutionary speculations of early 19th-century thinkers, such as Oken and Goethe, who argued that the vertebrate skull is composed of a number of transformed vertebrae (de Beer, 1937; Starck, 1963). That is, the head is but a modified rostral portion of the trunk. An extension of this idea was that, much as the axial spinal cord is divided into so many transverse segments by the entering and exiting dorsal and ventral spinal nerves, so also the brain is built from a series of transverse units, the neuromeres. This view was supported by the identification of a set of 7 or 8 protuberances, the rhombomeres, in the developing vertebrate hindbrain in association with some of the cranial nerves (Orr, 1887; Vaage, 1969). This view has currently found some support from studies that use genetic markers and mutants to analyze the features of the different rhombomeres (Lumsden and Krumlauf, 1994; Gavalas et al., 1998, 2003) and metamerism has been extended to the midbrain and forebrain by postulating the existence of the so-called prosomeres (Rubinstein and Puelles, 1994).

However, an analysis of what is meant by "segmentation" or "metamerism " when applied to different components of the body and the CNS reveals conceptual inconsistencies. Segmentation in the trunk (somitomerism) is principally a peripheral phenomenon. It is manifested during early development by the presence of reiterated morphogenic blocks, the somites, and as the PNS develops later, by the formation of the segmental dorsal root ganglia and dorsal and ventral spinal nerves in relation to reiterated dermatomal and myotomal compartments. This peripheral segmentation, which is an ancient chordate legacy (Romer, 1970) persists throughout life with profound topological transformations in all vertebrates, including humans. Significantly, however, there is no central segmentation (transverse partitioning) in the vertebrate spinal cord. On the contrary, the vertebrate spinal cord (unlike the neuraxis of many invertebrates) is a longitudinally organized morphogenetic and functional system. The spinal NEP is a continuous proliferative matrix through its entire length. And as differentiation begins and progresses, the motor neurons of the ventral horn form longitudinal columns, and the sensory neurons of the dorsal horn extend from lower lumbar levels to upper cervical levels without any transverse partitioning (e.g., Altman and Bayer, 2001). In contrast to the enduring peripheral metamerism in the spinal cord, the metamerism in the rhombencephalon, the reiterated NEP bulges known as rhombomeres, is an instance of transient central segmentation. Although there are indications for some peripheral metamerism here, too, in the form of vestigial gill arches (branchiomerism), these reiterated structures of ancestral protochordates have become transformed into structurally and functionally diversified cranial organs in vertebrates (Shimeld and Holland, 2000). In contrast to the reiterated trunk somites, the cranial primordia and placodes (see below) give rise to such diverse specialized structures as the jaws, various oro-facial organs, the inner ear, the pharynx, and certain viscera that are absent in the trunk region. Moreover, the cranial ganglia associated with these various organ systems—trigeminal, facial, vestibular, spiral, glossopharyngeal, and vagal ganglia—are not reiterated structures like the spinal ganglia but functionally diversified sensory systems.

There is no empirical evidence to support the idea of a metameric organization either in the skull or the rostral CNS (mesencephalon, diencephalon, telencephalon). Even in the most primitive extant vertebrate, the lamprey, the mesoderm is segmented along the trunk but not in the head region (Kuratani et al., 1999). Nor is there evidence that the different brain vesicles are reiterated metameric units. For instance, the two transverse "segments" of the tectum in the dorsal mesencephalon (the inferior and superior colliculi) are structurally and functionally quite dissimilar structures, one being the target of auditory fibers from the medulla, the other of optic fibers from the retina. The multifarious structures in the tegmentum of the ventral mesencephalon, the red nucleus, the oculomotor nuclear complex, the periaqueductal gray, the substantia nigra, the ventral tegmental area, the interpeduncular nucleus, etc. provide not even a hint of reiterated transverse organization. The same applies to the diencephalon and the telencephalon. Compartmentation in components of diencephalon (optic vesicle, thalamus, subthalamus, preoptic area, hypothalamus, etc.) and compartmentation in the telencephalon (olfactory bulb, neocortex, hippocampus, striatum, amygdala, etc.) cannot be fitted, by any stretch of the imagination, into a reductionistic metameric framework.

We do not deny metamerism is a facet in the early development of body and brain in vertebrates, man included, but we question its significance as an overriding morphogenetic principle of CNS development. Specifically, we look upon metamerism as a protochordate and protovertebrate legacy, a phylogenetic burden that was gradually overcome as the segmented, limbless, and headless worm-like ances-

tral lines acquired a far more complex body structure with a functionally integrated CNS in the course of vertebrate evolution. The story may have begun with an ancestral protochordate, not unlike the extant Amphioxus. Amphioxus spends most of its time buried in gravel or sand and uses its oral cilia and gills to filter nutrients suspended in the water (Buchsbaum, 1948). The mesoderm of Amphioxus is segmentally organized, with bilaterally arranged muscle blocks along its elongated body which resembles that of a fish. The wave of alternate contractions of these muscle blocks produces the undulatory swimming motion that allows Amphioxus to flee when disturbed. The spinal cord of Amphioxus is situated above the notochord (the phylogenetic and ontogenetic precursor of the vertebral column of vertebrates), and it shares many features with the spinal cord of vertebrates, such as the dorsal position of the sensory nerves and the ventral position of the motor nerves (Bone, 1960). However, the bipolar sensory neurons of Amphioxus are located in the spinal cord centrally rather than peripherally in the spinal ganglia (as in vertebrates), and its motor neurons are located near the spinal canal rather than in the ventral horn. Moreover, Amphioxus lacks a true brain. As a sedentary filter feeder, Amphioxus survives without having a head furnished with specialized sense organs and a specialized muscular oral apparatus. Instead of eyes, it has a few pigmented photosensitive cells near the anterior tip of the spinal cord, and its "cerebral vesicle," marked by *Otx* gene expression (Shimeld and Holland, 2000), is composed of little more than a few dopaminergic and serotoninergic cells (Lacalli, 2001; Ekhart et al., 2003; Moret et al., 2004). It has been argued that Amphioxus is a degenerate chordate. Another possibility is that a closely related filter-feeder species was the ancestor of more advanced chordates who, by acquiring cranial sense organs and a brain, became enabled to cruise freely in the open waters and turn into successful scavengers, grazers, or predators. The recent discovery of fossil chordates from 520 million-year-old Lower Cambrian beds, named Haikouella and Yunnanozoon, may bridge the gap between these two lines of chordates (Holland and Chen, 2001; Mallatt and Chen, 2003). Haikouella had a body similar to Amphioxus and a head furnished with some sense organs and a small bilobed brain. If this scenario is correct, the quasi-segmental spinal cord is a protochordate legacy, with the proviso that it became further elaborated as the notochord became transformed into an articulated cartilaginous or bony vertebral column and a rib cage, and as the neural crest-derived dorsal root ganglia became exteriorized in more advanced fish.

The transformation of sedentary chordates into mobile fish required the development of a head with specialized information-gathering sense organs—the olfactory, visual, auditory, vestibular, lateral line, and gustatory systems—and such specialized motor mechanisms as the muscular mouth of jawless fish and the skeletomuscular jaw of more advanced fish. The trunk also became modified as the segmentally mediated undulatory swimming was supplemented by fin action for better postural control and maneuverability. As the extremities evolved in tetrapods, body and head organization became more complex, requiring modification of existing neural systems and the formation of new ones. Contrary to the idea that the skull and face are modified vertebral segments, and the brain a modified spinal cord, it appears more likely that most cranial organs and the brain mechanisms serving them evolved *de novo*. This is supported by the accumulating evidence that different morphogenetic mechanisms are involved in the regulation of spinal cord development and brain development. The spinal NEP surrounding the slit-shaped spinal ventricle is initially uniform in its appearance both in rat (Altman and Bayer, 1984) and humans (Altman and Bayer, 2001; Volume 1 of this Atlas). But then the spinal ventricle changes its shape and a ventrodorsal compartmentation becomes apparent, with the ventral NEP starting to generate the motor neurons of the expanding ventral horn and, later, the dorsal NEP starting to generate the sensory neurons of the dorsal horn. The ventrodorsal compartmentation in the spinal cord is under the inductive influence of the neural crest and two peripheral structures, the somites and the notochord. The sheet of crest cells that spins off the dorsal neural fold and migrates toward the discrete somites, give rise to the neurons of the segmented dorsal root ganglia, and these exert a "dorsalizing" influence upon the dorsal spinal NEP. The unsegmented notochord, in contrast, exerts a "ventralizing" influence on the ventral spinal NEP to generate the motor neurons of the ventral horn. The early differentiation of motor neurons depends on *Shh* (sonic hedgehog) signaling that is transmitted from the notochord and the floor plate to the ventral NEP (Briscoe, 2000), and retinoids and *FGFs* (fibroblast growth factors) have been implicated in the rostrocaudal axial specification of spinal motor neurons (Liu et al., 2001). The morphogenesis of the brain obeys different principles than the spinal cord. The somites are absent and the notochord is often indistinct. There is no evidence for comparable dorsalizing and ventralizing influences upon the development of the rhombencephalic, mesencephalic, and telencephalic NEPs. Here the principal inductive influence emanates from two altogether different cranial structures that are absent in the trunk region, the gill arches and the cranial and branchial placodes.

The Rhombomeres as NEP Mosaics. As illustrated in this volume of the Atlas, the rhombencephalic NEP has several components. (i) The upper rhombic lip region and (ii) the lower rhombic lip region dorsally form the bridgeheads of the membranous medullary velum that covers the rhombencephalic superventricle. (iii) The less clearly defined ventromedial NEPs are the source of several pontine and medullary motor nuclei. (iv) The ventrolateral NEPs form distinct rhombomeres. The region of the upper rhombic lip NEP is the direct or indirect source of neurons of the cerebellum. The region of the lower rhombic lip

NEP is the source of the neurons of the precerebellar nuclei (inferior olive, basal pontine gray, etc.) and the cochlear nuclei. The rhombomeres, a set of conspicuous semicircular NEP evaginations, are the most often cited example of brain metamerism. The exact number of rhombomeres has been controversial (the old literature is reviewed by Vaage, 1969); in the currently popular numerical designation, there are seven rhombomeres (R1-R7), where R1 refers to the cerebellar NEP. This is unfortunate because the cerebellar NEP has little in common either structurally or functionally with rhombomeres R2-R7, which do share some common properties. As we shall describe later, the expanding and long-enduring cerebellar NEP is largely connected with second- and higher-order central afferent systems (some first-order vestibular input excepted), in contrast to the transient rhombomeres that are intimately associated with the first-order peripheral afferents of cranial sensory ganglia.

According to Bartelmez and Evans' (1925) observations in human embryos, R1 and R2 originate from prorhombomere A, R3 and R4 from prorhombomere B, and R5-R7 from prorhombomere C. A similar pattern has been described in mouse embryos (Osumi-Yamashita et al., 1996). According to the latter study, crest cells from prorhombomere A (R2?) migrate into the first branchial arch and produce the trigeminal (V) ganglion; crest cells from prorhombere B (R3 and R4) migrate into second arch and produce the facial and vestibulocochlear (VII-VIII) ganglia; crest cells from the anterior portion of prorhombomere C (R5 and R6) migrate into the third arch and produce the glossopharyngeal (IX) ganglia; and crest cells from the posterior portion of prorhombere C supply cells to the fourth arch and the vagal (X) ganglia. Our observations, which start at a later developmental stage (about 17 to 18 pairs of somites) than those described by Bartelmez and Evans (2 to 16 pairs of somites), indicate a close association between the rhombomeres and the branchial placodes, and the following developmental pattern. In the youngest embryo (estimated age GW3.2), in which the rhombencephalic superventricle is just beginning to expand, three evaginating bulges are evident caudal to the cerebellar NEP (**Figure 20A**). The first is contiguous with the condensing, small trigeminal ganglion inside the maxillary process. We designate this germinal mosaic as the trigeminal NEP (R2), the target of future cranial nerve V fibers. The affiliation of the second rhombomere (presumably R3) is unclear; we hypothesize that it is the facial (nerve VII) NEP. According to a recent study, R2-derived neuronal progeny contribute to the lower jaw somatosensory representation, and R3 progeny to whisker representation in the barrel fields of mice (Oury et al., 2006). It is possible that the facial NEP is mostly a source of efferents that start to sprout after the facial motor neurons leave R3. (The roundabout migration of facial motor neurons, whose trailing axons form the loop [genu] of the facial nerve, is well known [Altman and Bayer, 1982b]). The third evaginating early rhombomere is aligned with the condensing vestibulocochlear ganglion (nerve VIII) and the otic vesicle. We presume this rhombomere will become subdivided into R4-R5, as seen in a slightly older embryo (estimated age GW4.0) with a greatly expanded rhombencephalic superventricle (**Figure 20B**). As we documented over two decades ago in the rat (Altman and Bayer, 1982b), the otic vesicle is the source not only of the non-neural elements of the inner ear but also of a large contingent of delaminating neurons, either the neurons of the spiral ganglion and/or some components of the vestibular ganglion. R6 and R7 are not evident in the GW3.2 embryo (**Figure 20A**) but are beginning to evaginate in the GW4.0 embryo (**Figure 20B**) and are pronounced in a somewhat older embryo (**Figure 20C**). In the latter, R6 is aligned with and is in direct contact with afferents of superior glossopharyngeal ganglion, the source of the sensory fibers of cranial nerve IX, and R7 with superior vagal ganglion, the sensory component of nerve X. Accordingly, we designate R6 as the glossopharyngeal NEP, and R7 as the vagal NEP. If this interpretation is correct, the oro-facial peripheral and central systems innervated by the future cranial nerves V and VII, and the vestibulocochlear systems innervated by the future cranial nerve VIII are developing before the pharyngeal-visceral systems innervated by the future cranial nerves IX and X. By GW5, the rhombomeres begin to shrink (**Figure 21A**); by GW7, they are no longer recognizable in the developing pons and medulla (**Figure 21B**).

Although we stress here the sensory affiliations of the rhombomeres, there is ample evidence from animal studies that the rhombomeres are also a source of motor neurons (e.g., Lumsden and Keynes, 1989). According to a recent study in larval and adult frogs (Straka et al., 2006), trigeminal efferents are derived from R2-R3; facial and vestibular efferents from R4-R5; glossopharyngeal efferents from R6; and vagal efferents from R7 and the rostral medulla and the spinal cord. However, in the human specimens we have examined we find only cranial afferents entering the rhombomeres and no evidence of exiting motor fibers. This may be because either axonal outgrowth occurs after the transient NEP rhombomeres are no longer recognizable as such or axonal sprouting commences, as is well known in the case of facial nerve, after the migrating motor neurons have left the rhombomere NEPs.

Timetables of the Development of Placodes, Cranial Ganglia, and Rhombomeres. Whereas in the trunk region, crest cells generate the peripheral neurons of the spinal (dorsal root) ganglia (Weston, 1970; LeDouarin, 1982), the principal source of neurons of the cranial ganglia in the head region are the placodes (Knouff, 1935) or, more accurately, the cephalic and branchial preplacodes that later become divided into specialized placodes (Jacobson, 1963; Noden 1993). The cephalic and branchial preplacodes, formed by pluripotent stem cells, are thickened epithelia that extend from the vicinity of the forebrain NEP to the

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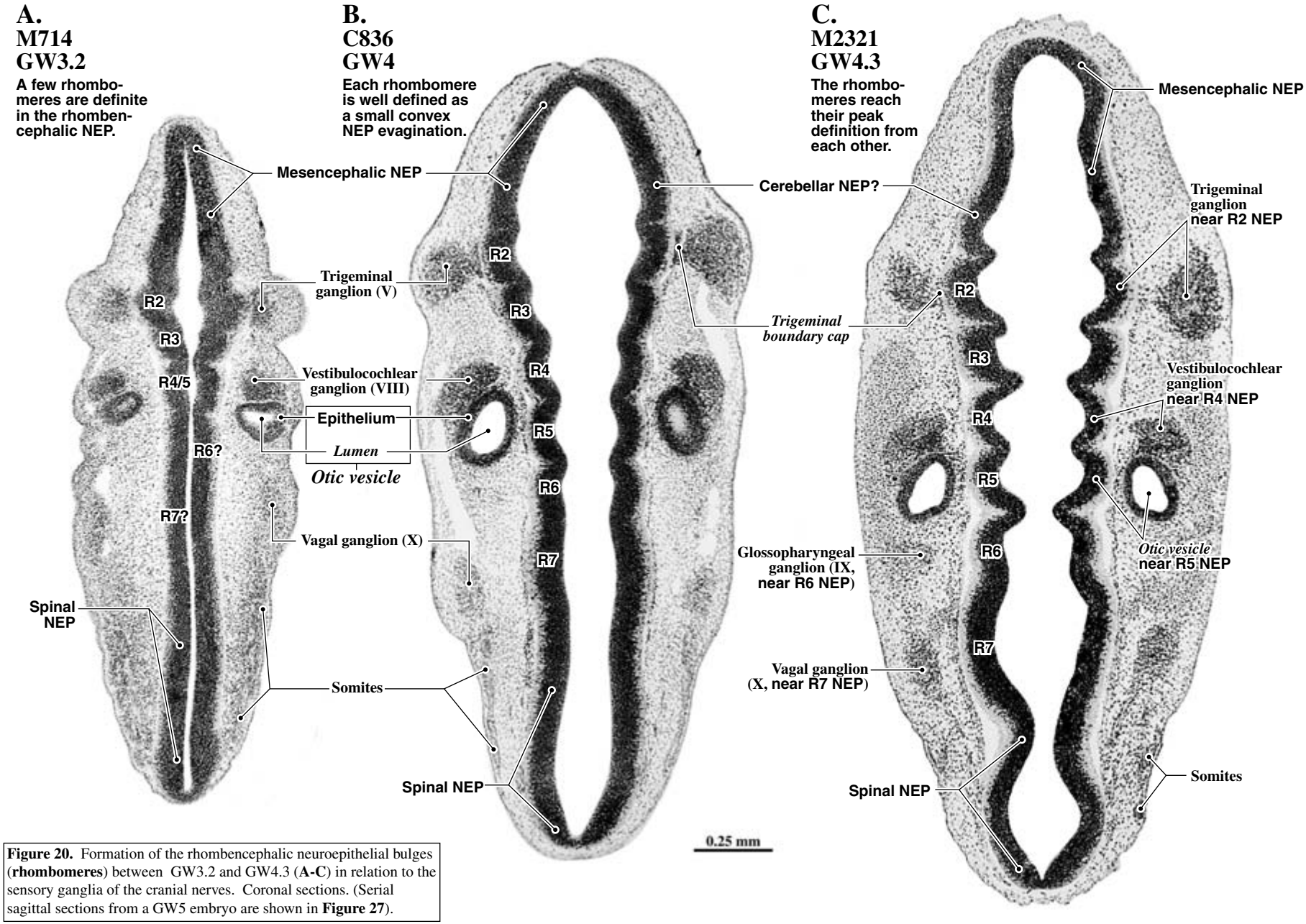

Figure 20. Formation of the rhombencephalic neuroepithelial bulges (**rhombomeres**) between GW3.2 and GW4.3 (**A-C**) in relation to the sensory ganglia of the cranial nerves. Coronal sections. (Serial sagittal sections from a GW5 embryo are shown in **Figure 27**).

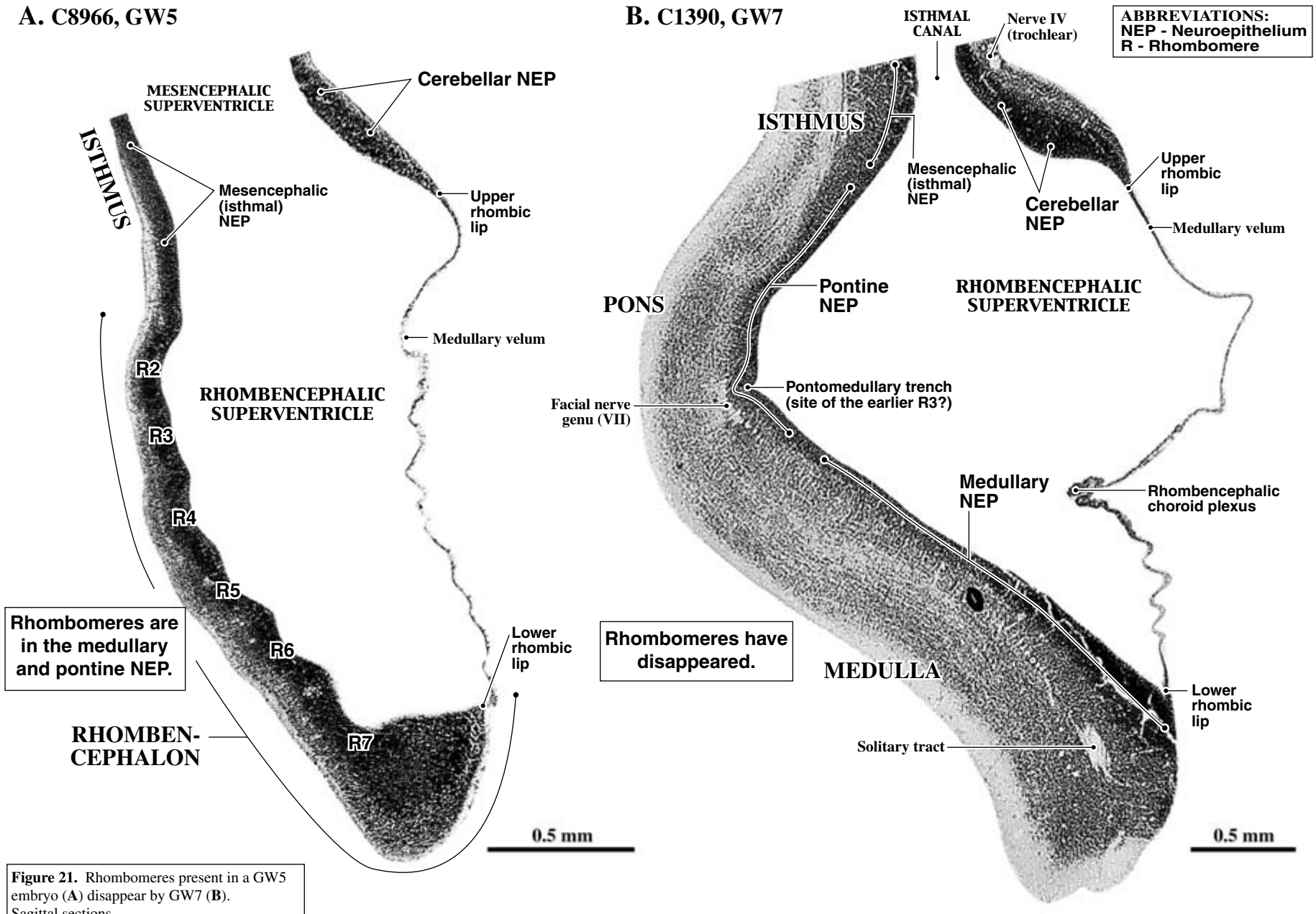

Figure 21. Rhombomeres present in a GW5 embryo (**A**) disappear by GW7 (**B**). Sagittal sections.

border of the trunk region. The different hypothetical origins of neurons of the spinal and cranial nerve ganglia, prior to fusion of the neural tube and the brain vesicles, is illustrated in **Figure 22**. As seen in a coronal section of a GW3.2 embryo, the cephalic preplacode is continuous with the prosencephalic NEP prior to the fusion of the anterior neuropore (**Figure 23A**). It abuts the ventral and ventrolateral prosencephalon but is notably absent over the dorsal prosencephalon and farther caudally (**Figure 23A, B**). The cephalic preplacode is continuous, by way of the oral epithelium, with the branchial preplacode that covers the brachial arches I-IV some distance from the rhombencephalon (**Figure 23B**). Experiments in animals have shown that, during early embryonic development, the cells of the pluripotent preplacodes are competent to form different special placodes (Jacobson, 1963; Groves and Bronner-Fraser, 2000). This pluripotency is lost when the preplacodes become partitioned into special placodes that acquire diverse structural and functional properties. The cephalic preplacode divides into the profoundly different olfactory, optic, and pituitary placodes; the branchial preplacode divides to form the diverse domains of the trigeminal, facial, vestibulocochlear, glossopharyngeal, and vagal ganglia.

The human embryos we have analyzed in this volume provide chronological information about the developmental course of the peripheral cephalic and branchial placodes, the cranial nerve ganglia they generate, and the emergence and dissolution of the rhombomere NEPs with which they are associated. Thickening of the olfactory placode anteromedially is evident in the GW3.8 and GW4.0 embryos (**Figure 24A, B**). The formation of the nasal olfactory epithelium and the outgrowth of olfactory nerve fibers is in progress in the GW5.0 and GW5.5 embryos (**Figure 24C, D**). The vesiculation of the olfactory placode (formation of the nasal cavity) is evident in the GW5.5 embryo (**Figure 24D**), which also shows the first hint of the evagination of the olfactory NEP. The evagination of the olfactory NEP becomes more and more pronounced between GW6.5 and GW7.5 (**Figure 24E to 24I**). The presumptive optic lens placode, which surrounds the bulging optic vesicle NEP in the GW3.2 and GW4.0 embryos (**Figure 25A, B**) thickens in the GW4.5 embryo (**Figure 25C**) as the invaginating optic vesicle NEP becomes partitioned into a thin pigment epithelium and a thicker retinal NEP. Contrary to the classical view that the evaginating optic vesicle NEP induces placodal lens formation (Spemann, 1938), it has recently been argued that an earlier interaction between the anterior neural plate NEP and a portion of the preplacode establishes a lens-forming bias in the latter (Grainger et al., 1997). The lens placode assumes a spherical configuration in the GW5.0 embryo (**Figure 25D**) and the onset of the cytological differentiation of the crystalline lens is evident in the GW6 embryo (**Figure 25E**). The exodus of ganglion cells from the retinal NEP and the sprouting of optic nerve fibers is in progress in the GW7 embryo (**Figure 25F**). Finally, the formation of the pituitary gland begins in GW3.8-GW5.0 embryos with the folding of the posterior tip of the cephalic preplacode (**Figure 26A to 26C**). The fusion of this placode between GW5.5-GW6.5 produces Rathke's pouch, the primordium of the anterior pituitary gland or adenohypophysis (**Figure 26D, E**). Contiguity between Rathke's pouch and the posterior pituitary GEP, the neurohypophysis derived from the hypothalamic NEP, is evident in the GW6.0-GW7.0 embryos (**Figure 26E to 26H**).

As noted earlier, the caudal branchial preplacode has two components: a thinner epithelium covering the roof of the oral cavity, which is continuous with the cephalic preplacode, and a thicker portion covering the oral cavity floor (**Figure 23B**). The latter has several components: the discrete placodes that surround the maxillary process, the mandibular and the hyoid arches (I, II), and visceral arches III and IV (**Figure 23B and Figure 27**). As it is currently understood, mesenchymal elements of the maxillary process and the mandibular arch are the source of various orofacial structures, such as the jaws, and the visceral arches generate components of the tongue, the pharynx, and the upper gut. The placodes surrounding these diverse structures, together with neural crest cells, are the precursors of sensory cells and of neurons in the cranial ganglia. The latter are the trigeminal (V), facial (VII), vestibulocochlear (VIII), glossopharyngeal (IX), and vagal (X) ganglia. The afferents of these ganglia link various orofacial, inner ear, and gut organs derived from the branchial arches with different divisions of the rhombencephalic NEP. The neurons of the trigeminal and facial ganglia link the orofacial region with rhombomeres R2-R3. As early as GW3.2, a small, spherical trigeminal ganglion is visible near R2 (**Figure 20A**), and by GW5.0 there is direct continuity between the large trigeminal ganglion and R2 (**Figure 27A, B**). By that age, three cell-dense arms of ganglion V are identifiable (**Figure 28A**), and by GW5.5 the ophthalmic, maxillary, and mandibular branches of the trigeminal nerve approximate the eye region and penetrate the maxillary process and the mandibular arch, respectively (**Figure 28B**). With respect to the central projections of the trigeminal nerve, by GW5.5 the penetrating fibers start to form a bulge at the knee of the pons (**Figure 29A, B**), and trigeminal fibers clearly intermingle with other fibers of the pontine white matter by GW6.5 (**Figure 30A**). As early as GW4.0, the vestibulocochlear ganglion is aligned with R4, and the otic vesicle with R5 (**Figure 20B**). The two are also aligned peripherally with the hyoid arch (**Figure 27**) but their association is problematic. The afferents of the vestibulocochlear ganglion reach R4 by GW5.0 (**Figure 27B**), and they penetrate the white matter of R4 and R5 between GW5.5 (**Figure 29A, B**) and GW6.5 (**Figure 30A**). The formation of the glossopharyngeal and vagal ganglia, and of R6 and R7 with which they are aligned, is not evident until about GW4.0-GW4.3 (**Figure 20B, C**). The two are aligned peripherally with the visceral arches III and

IV (**Figure 27A, B, Figure 29B**) but their exact relationship remains to be elucidated. Glossopharyngeal afferents approximate R6, and vagal fibers approximate R7 by GW5.0 (**Figure 27B, C**), and they penetrate the white matter of R6 and R7, respectively, by GW5.5 and GW6.5 (**Figure 25B, Figure 30A, B**).

E. Exogenous and Endogenous Mechanisms of NEP Cell Diversification

The Role of Periphero-Central Signaling in Placodal and NEP Cell Diversification. An important first step in mosaicism of the NEP matrix is synchronizing its diversification with both somatic and neural development in the body periphery, including the placodes and the peripheral nervous system (PNS). There is emerging experimental evidence that periphero-central coordination is aided by induction and signaling molecules (Baker and Bronner-Fraser, 2001; Streit, 2004). For instance, the rostral cephalic preplacode expresses *Six*, *Eya*, and *Dach* protein markers (Ikeda et al., 2002; Brugmann et al., 2004; Schlosser and Ahrens, 2004; Litsiou et al., 2005) and it has been found that in the presence of both cranial mesoderm and rostral neural plate NEP, excessive *Six1* expression expands the preplacode at the expense of the epidermis, whereas *Six1* depletion results in a reduction of the preplacodal domain (Brugmann et al., 2004; Ahrens and Schlosser, 2005). The next step in the diversification of the rostral cephalic preplacode is the formation of the olfactory and optic placodes, each with profoundly different structural and functional fates. Whereas the olfactory placode gives rise to the specialized bipolar sensory neurons of the olfactory epithelium, which send fibers to the evaginating olfactory bulb NEP, the optic placode has no neurogenic potential but gives rise to the crystalline lens of the eye. Mutant mice lacking functional *Pax6* proteins fail to develop eyes and nasal cavities (Stoykova et al., 1996), and *Pax6* and *D1x5* are initially expressed in both future olfactory cells and lens-forming cells of the eye (Bhattacharyya et al., 2004). However, as the presumptive lens cells acquire a columnar morphology, *D1x* expression is reduced in the optic placode whereas *Pax6* is lost in the olfactory placode (Bhattacharyya et al., 2004). The authors concluded that loss of *D1x* is required for the proliferative cells to adopt a lens fate and that the balance between *Pax6* and *D1x* expression regulates cell sorting in the segregating placodes. With reference to periphero-central signaling, it has been reported that extraocular signals affect optic vesicle NEP development (Kagiyama et al., 2005), and that retinoic acid (Matt et al., 2005) and *Vax2* signaling are involved in the fate-modification of retinal NEP cells and pigment epithelium cells (Kim and Lemke, 2006). It has also been reported that *Mash1* promotes the development of retinal bipolar cells, and *Math3* and *NeuroD* that of amacrine cells (Morrow et al., 1999; Inoue et al., 2002). There is little information about the molecular mechanisms involved in the specification of the third component of the cephalic preplacode, the pituitary placode, except for the report that targeted disruption of the homeobox genes *Nkx2.1*, *Ttf1*, and *Titf1* results in the disruption of pituitary gland development (Takuma et al., 1998).

A different set of genetic factors and periphero-central signaling molecules appear to be involved in the development of the hindbrain region associated with the branchial placodes. The different rhombomeres express a distinctive combination of *Hox* genes (Krumlauf, 1993; Wilkinson, 1993; Gavalas et al., 2003; McNulty et al., 2005). *Hoxa2* is involved in R2 and R3 specification (Gavalas et al., 1998; Gaufo et al., 2004), and *Hoxa1* and *Hoxb1* play a role in R4 and R5 specification and the growth of the cranial nerves associated with them (Mark et al., 1993; Arenkiel et al., 2004). Differences have also been noted in the expression of transcription factors *Krox20* and Kreisler in the different rhombomeres (Sham et al., 1993; McKay et al., 1994; Schneider-Maunoury et al., 1997; Chomette et al., 2006), and retinoic acid also appears to be involved in rhombomere specification (Niederreither et al., 2000; Dupé and Lumsden, 2001). Members of the *Fgf* family of signaling proteins, mesoderm-derived *Fgf3* and *Fgf8*, and *Ngn2* (Fode et al., 1998; Begbie et al., 2002; Holzschuh et al., 2005; Nikaido et al., 2006; Sun et al., 2007; Nechiporuk et al., 2007) appear to play a role in the early determination and diversification of the epibranchial placodes and their derivatives, the glossopharyngeal and vagal ganglia, and the homeobox genes *Phox2a* and *Phox2b* in its later stages (Morin et al., 1997). Among the signaling molecules implicated in the specification of the otic placode and the formation of the inner ear are certain members of the *Fgf* family (Vendrell et al., 2000; Adamska et al., 2001; Ladher et al., 2005; Nechiporuk et al., 2005; Martin and Groves, 2006) and *Ngn1* (Ma et al., 2000). It is noteworthy that gene expression is different in the rhombomeres, where sensory and motor neuron precursors are not obviously segregated, than in the spinal cord where the ventral NEP cells generate motor neurons and the dorsal NEP cells generate sensory interneurons. *Mash1* and *Math3* are necessary for the development of facial and trigeminal motor neurons (Ohsawa et al., 2005). The genes *Frizzled3a* and *Celsr2* are necessary for cell polarization and the guidance of the roundabout migration of facial motor neurons in the brainstem (Wada et al., 2006), and their migration is also dependent on *Phox2b* signaling (Coppola et al., 2005). The genes implicated in dorsoventral patterning in the spinal cord are the class II *Ssh*-promoting *Nkx2.2*, *Nkx2.9*, *Nkx6.1*, and *Olig2* genes, and the class I *Ssh*-repressing *Dbx1* and *Dbx2* genes (Briscoe et al., 1999; Kessaris et al., 2001; Marquardt and Pfaff, 2001).

In light of the profound structural and functional heterogeneity of the cephalic and branchial placodes, we propose that unlike the segmented somites of the trunk, the placodes of vertebrates are not reiterated metameric units but an altogether different kind of progressively diversi-

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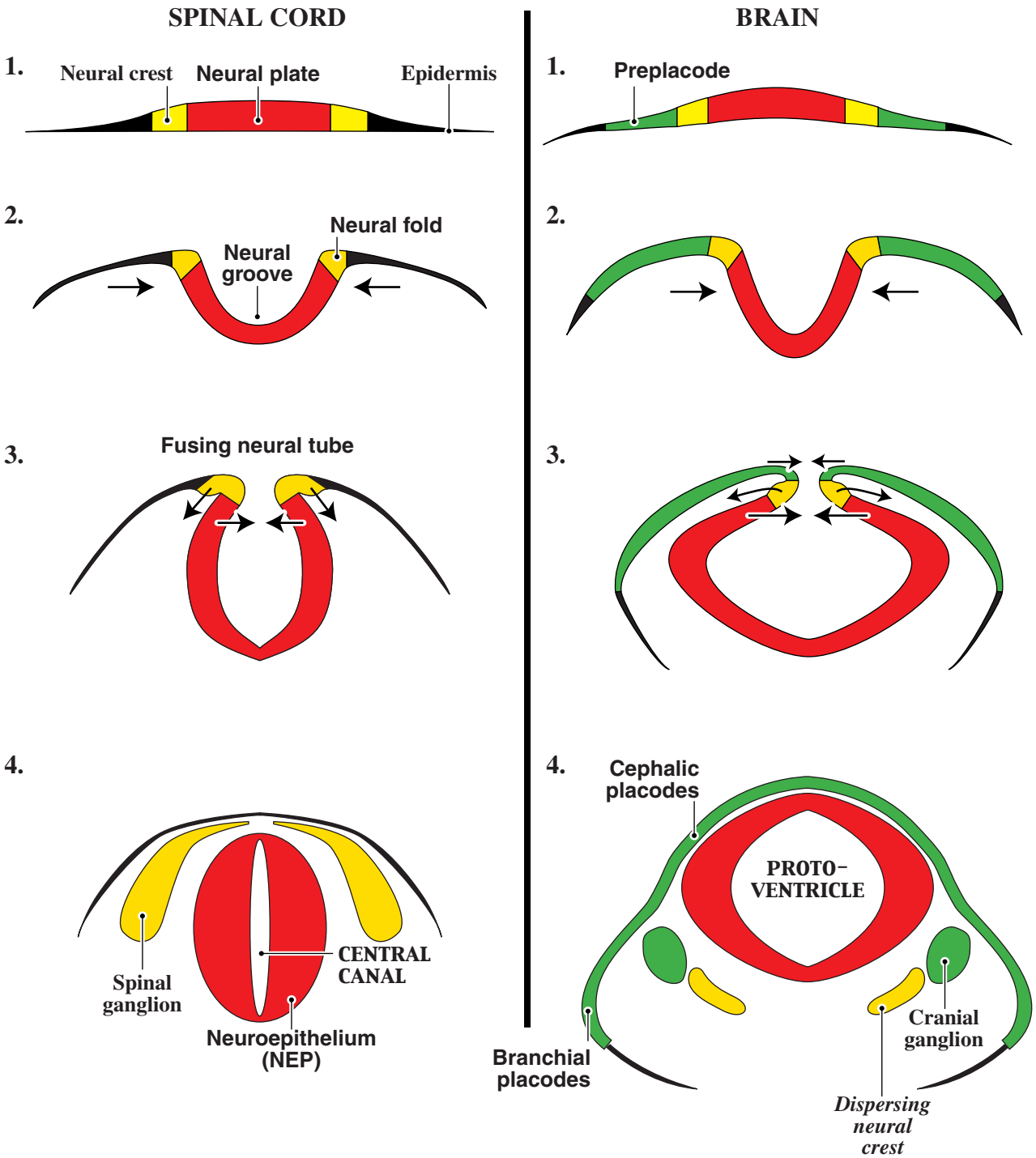


Figure 22. Hypothetical differences in the organization of the neural plate of the spinal cord (**1-4, left**) and forebrain (**1-4, right**). Neurons of the dorsal root ganglia derive from delaminating neural crest cells, whereas neurons of the cranial nerve ganglia derive from preplacodal stem cells. Cephalic placodes are close to the neuroepithelium, while branchial placodes (on the arches) are farther from the neuroepithelium.

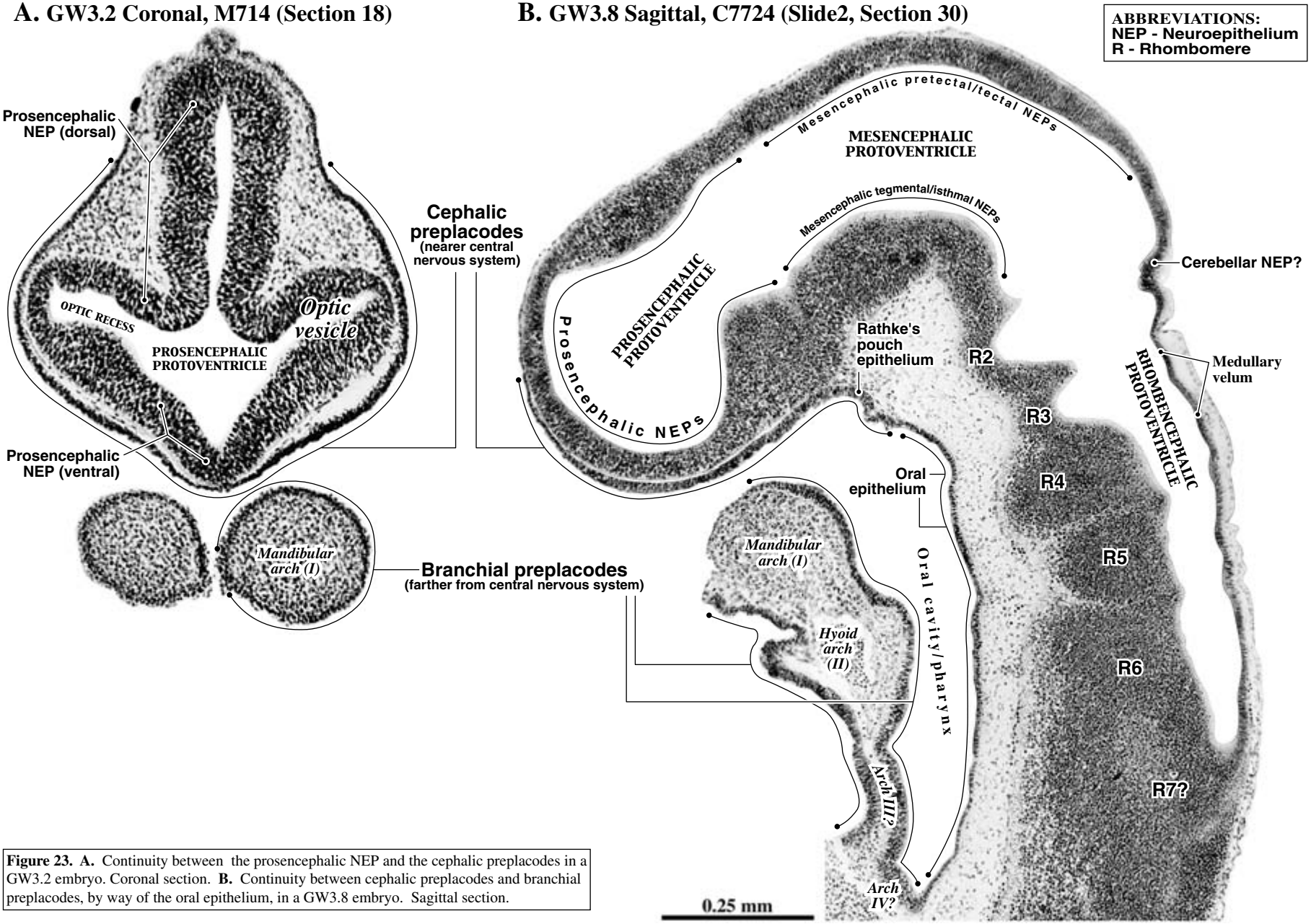
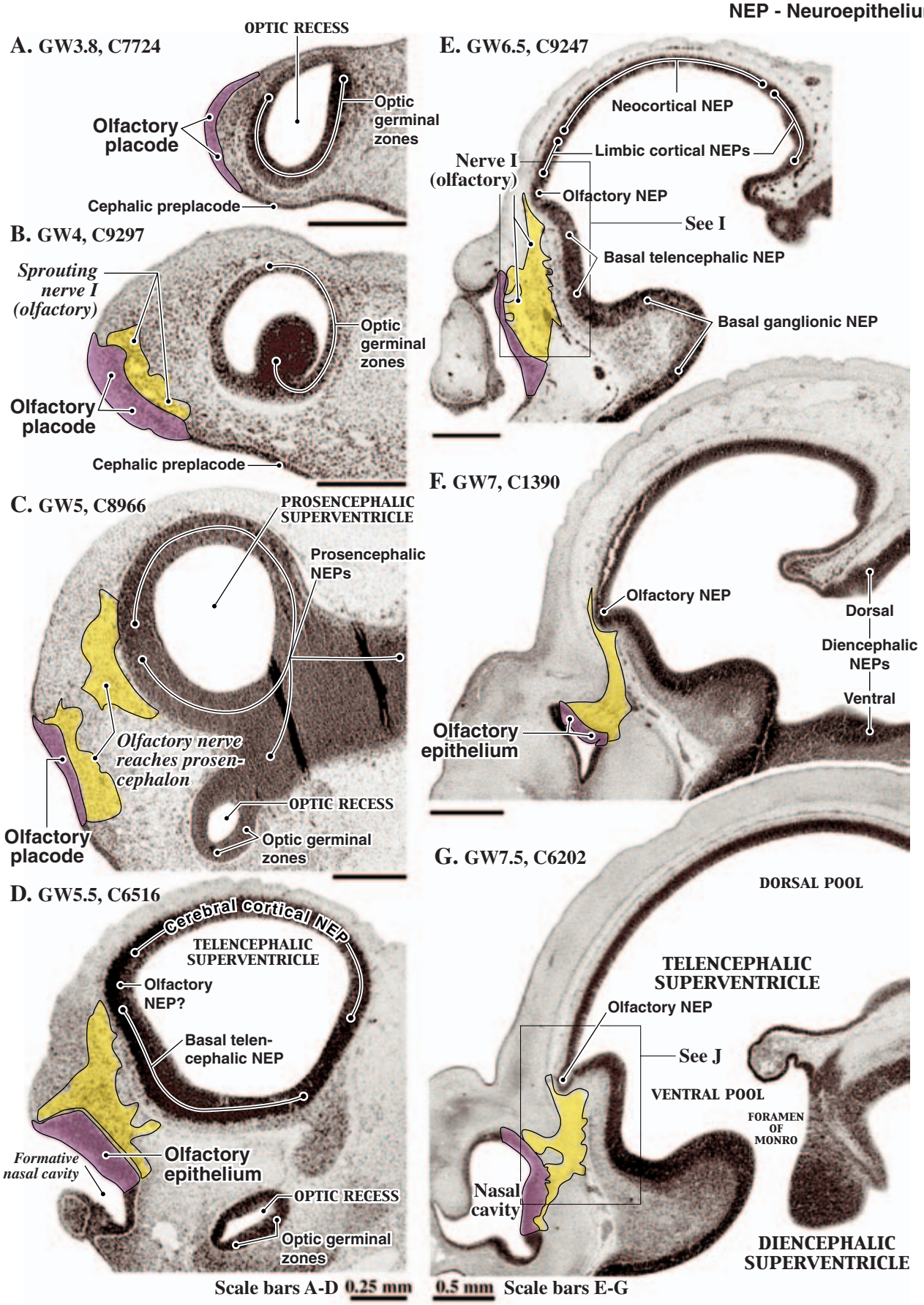


Figure 23. A. Continuity between the prosencephalic NEP and the cephalic preplacodes in a GW3.2 embryo. Coronal section. **B.** Continuity between cephalic preplacodes and branchial preplacodes, by way of the oral epithelium, in a GW3.8 embryo. Sagittal section.


A. GW3.8, C7724
OPTIC RECESS
Optic germinal zones
Olfactory placode
Cephalic preplacode
B. GW4, C9297
Sprouting nerve I (olfactory)
Optic germinal zones
Olfactory placode
Cephalic preplacode
C. GW5, C8966
PROSENCEPHALIC SUPERVENTRICLE
Prosencephalic NEPs
Olfactory nerve reaches prosencephalon
OPTIC RECESS
Optic germinal zones
Olfactory placode
D. GW5.5, C6516
Cerebral cortical NEP
TELENCEPHALIC SUPERVENTRICLE
Olfactory NEP?
Basal telencephalic NEP
Formative nasal cavity
Olfactory epithelium
OPTIC RECESS
Optic germinal zones
E. GW6.5, C9247
Neocortical NEP
Limbic cortical NEPs
Nerve I (olfactory)
Olfactory NEP
See I
Basal telencephalic NEP
Basal ganglionic NEP
F. GW7, C1390
Olfactory NEP
Dorsal
Diencephalic NEPs
Ventral
Olfactory epithelium
G. GW7.5, C6202
DORSAL POOL
TELENCEPHALIC SUPERVENTRICLE
Olfactory NEP
See J
VENTRAL POOL
FORAMEN OF MONRO
Nasal cavity
DIENCEPHALIC SUPERVENTRICLE
Scale bars A-D 0.25 mm
0.5 mm Scale bars E-G

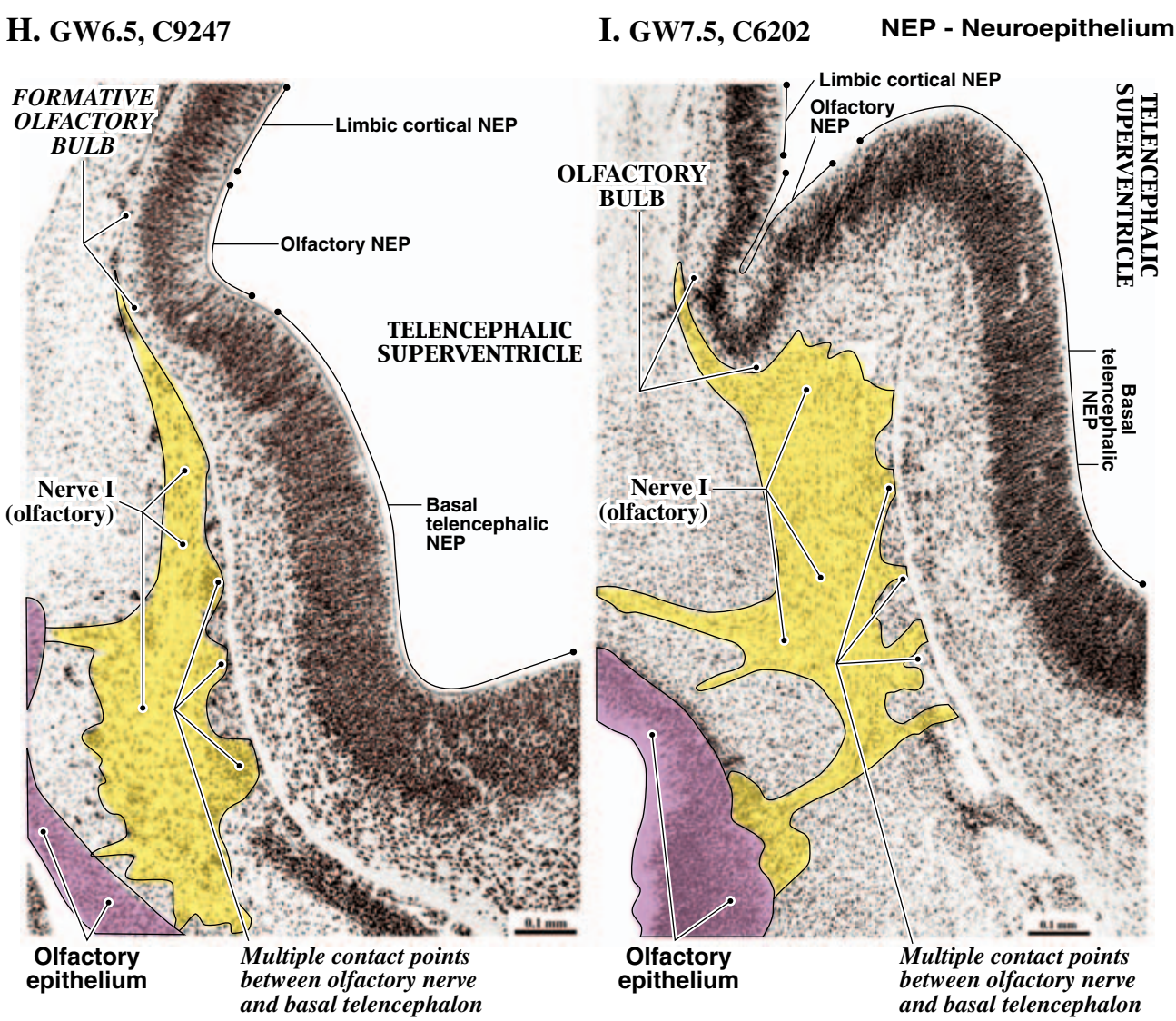


Figure 24. The time course of the thickening and invagination of the olfactory placode, the formation of the olfactory epithelium (*pink*), the outgrowth of the olfactory nerve fibers (*yellow*), and the evagination of the olfactory NEP, at lower (**A-G**, *facing page*) and higher magnification (**H-I**, *this page*). Sagittal sections.

fying germinal system. Starting as a pluripotent preplacodal germinal matrix, this system gives rise to several fate-restricted placodes that, in turn, contribute to the generation of various non-neural components of different cranial organs (eyes, nose, jaws, ears, palate, etc.) as well as to the neurons of the various cranial ganglia that innervate these organs and connect them with specific NEP compartments. This coordinated diversification of the peripheral elements of the head region with complimentary NEP mosaics is exemplified by the development of the rhombomeres, which are distinguished from one another by forming different peripheral and central connections and serving different functions. In this view, neither the different cranial ganglia nor the rhombomere NEPs are reiterated metameric units but are more like the other diversifying NEP mosaics of the CNS, except that they are more conspicuous and short-lived than many other NEP mosaics. This may be due to a transient role of the rhombomeres in the morphogenesis of the cranial nerve system and their drastic reorganization as the hindbrain develops in higher vertebrates and humans. We speculate that the fleeting presence of rhombomeres 2-7 in higher vertebrates constitutes a recapitulation of a stage of hindbrain evolution in ancestral fish. The rhombencephalic NEP mosaics of fishes, as seen in extant piscine species, produce such hypertrophied structures as the facial lobe, the target of nerve V and VII afferents, the octavolateral lobe, the target of nerve VIII afferents, and the vagal lobe, the target of nerve IX and X afferents (Evans, 1952; Wagner, 2001). However, these paleocephalic central sensory structures, much like the large optic lobe, became reorganized during the phylogeny of higher vertebrates as new neencephalic (forebrain) circuits evolved to process sensory input. Correspondingly, the sensory systems of higher vertebrates and

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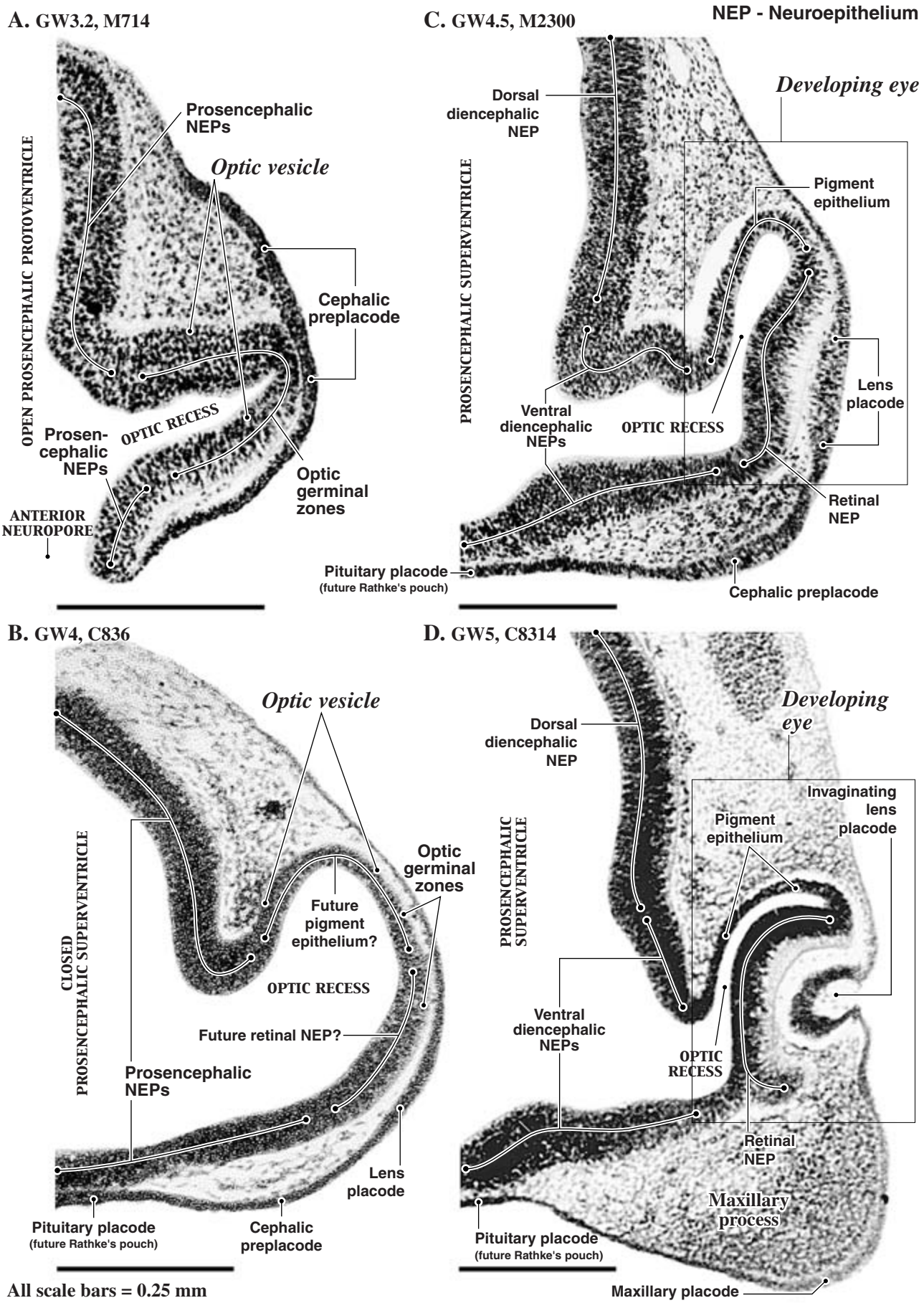

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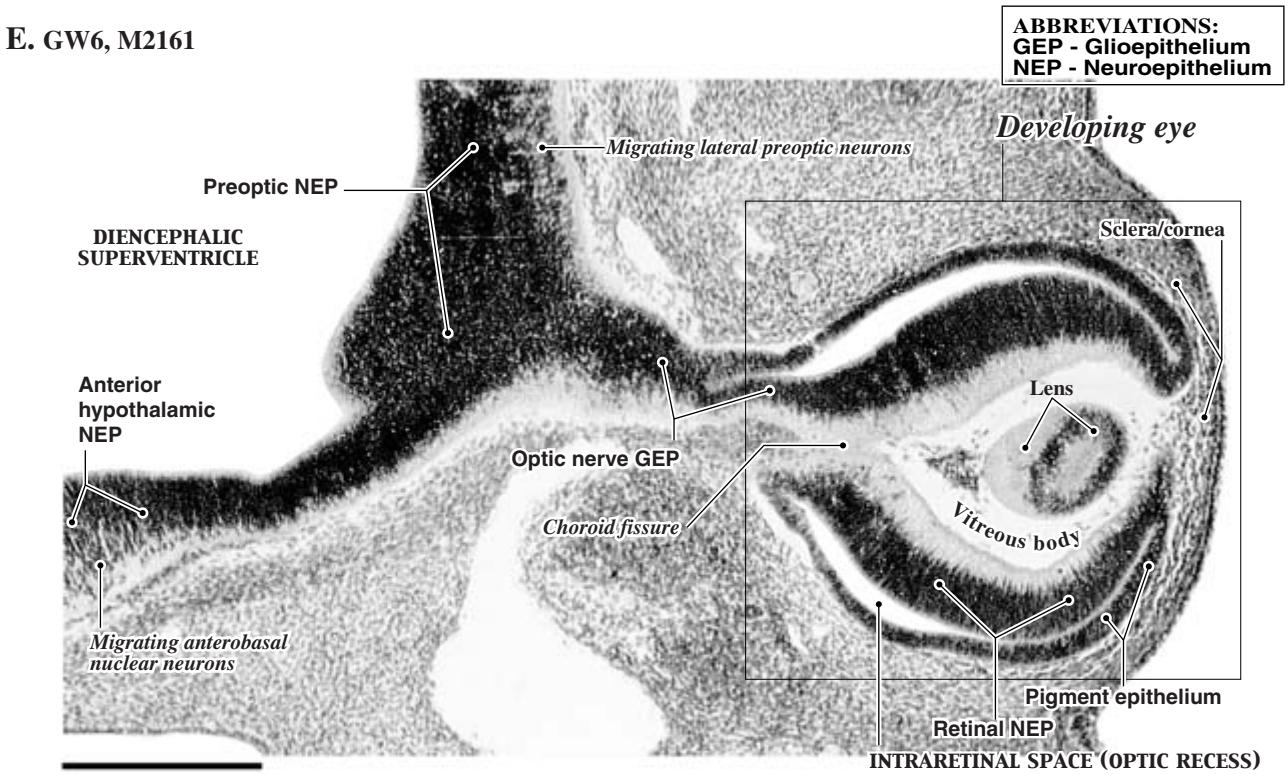

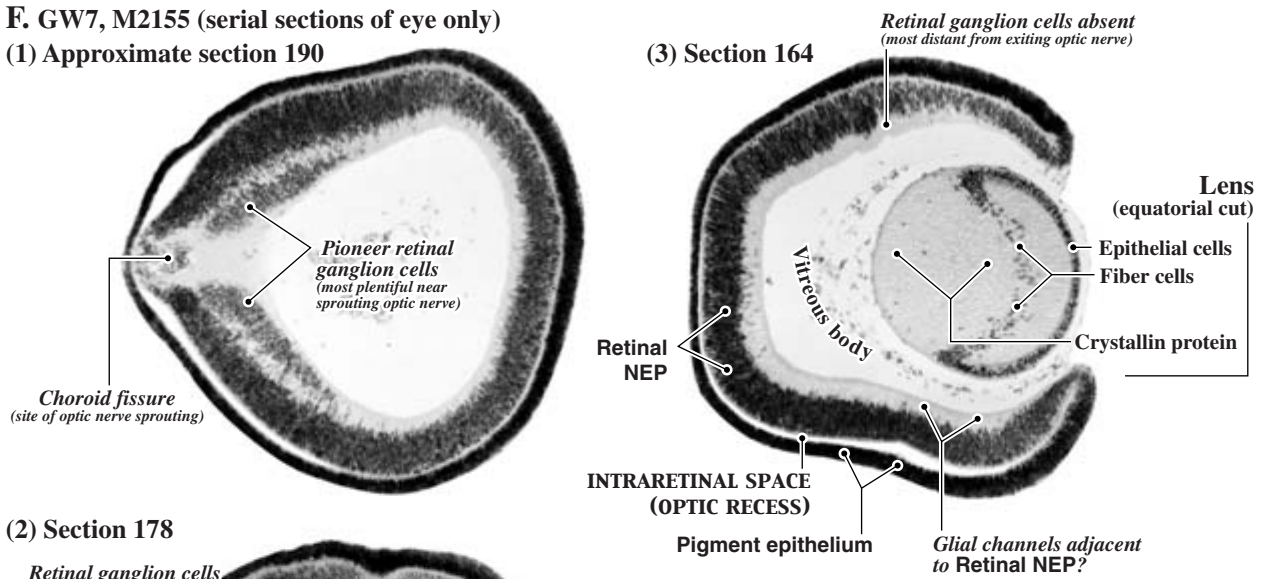

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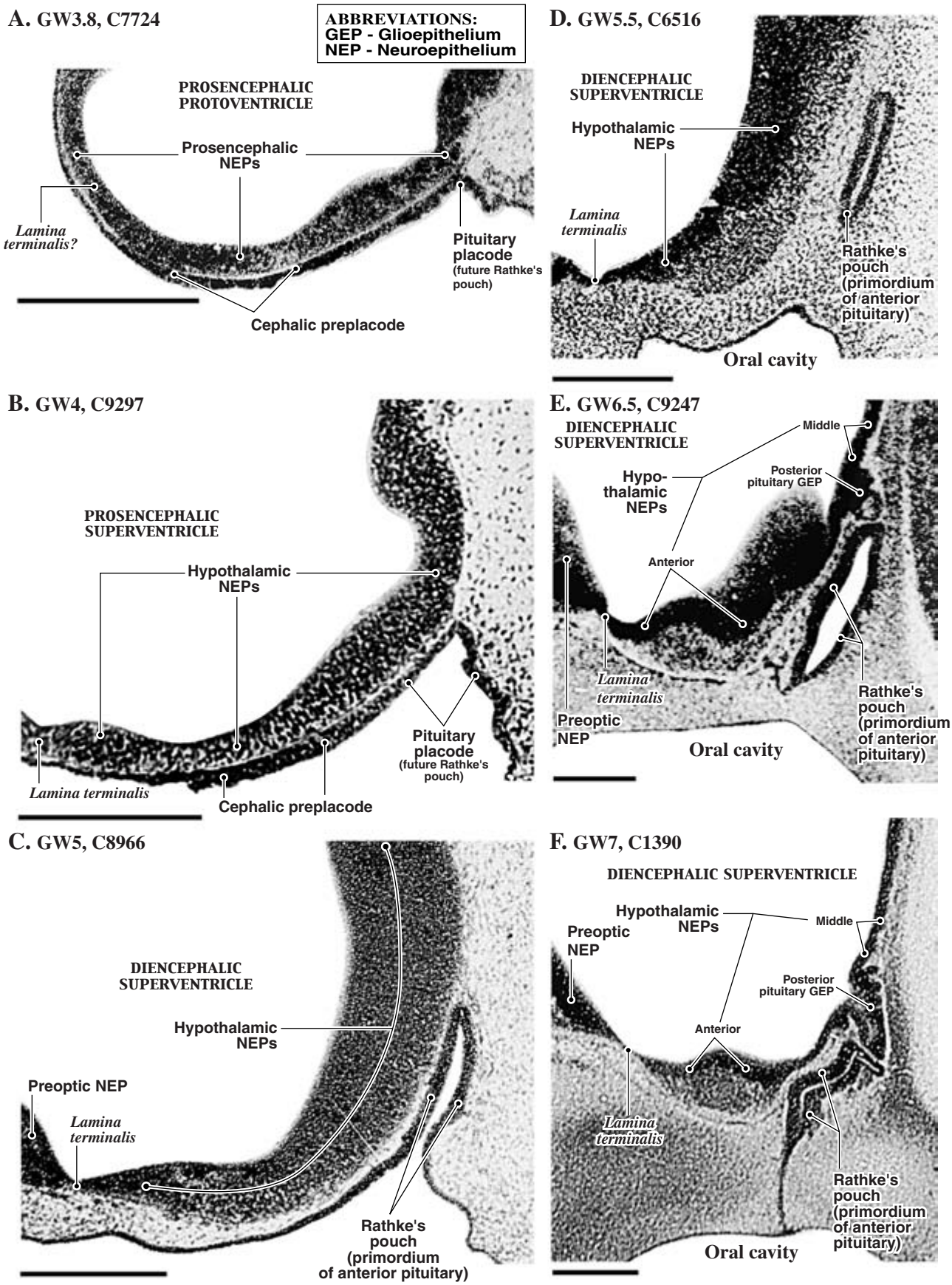
Figure 25. Time course of the development of some components of the eye. Already evaginated when the anterior neuropore closes at GW3.2 (**A**, *facing page*), the optic vesicle interacts with the cephalic prepladode to differentiate a lens placode opposite the future retinal NEP on GW4 and GW4.5 (**B, C**, *facing page*); the lens placode invaginates on GW5 (**D**, *facing page*). Development of the crystalline lens is well underway by GW6 (**E**, *this page*) as well as the differentiation of the optic germinal zones into the retinal NEP, the pigment epithelium, and the optic nerve GEP. Pioneer ganglion cells and optic nerve fibers emerge by GW7 (**F**, *this page*). Coronal sections.



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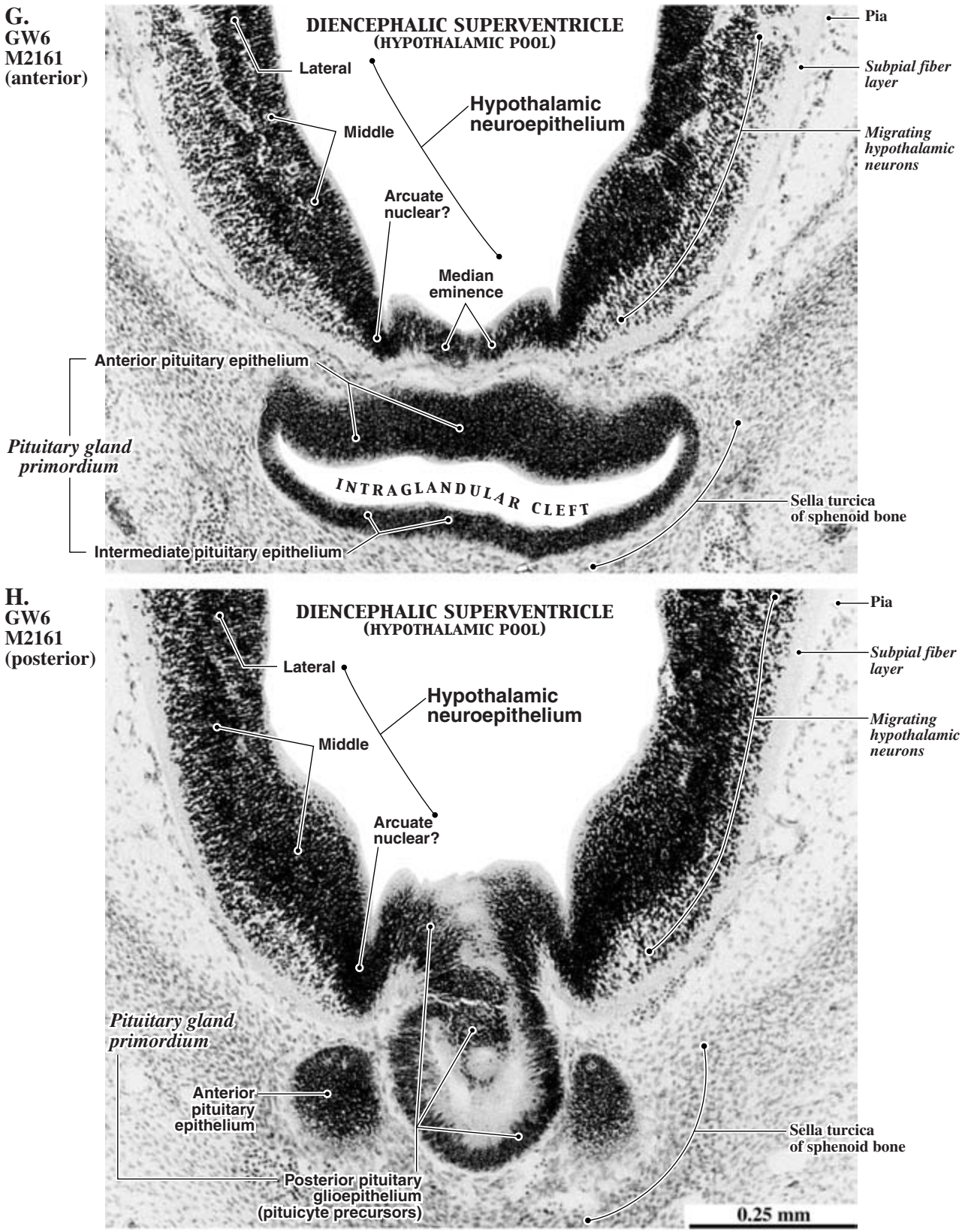
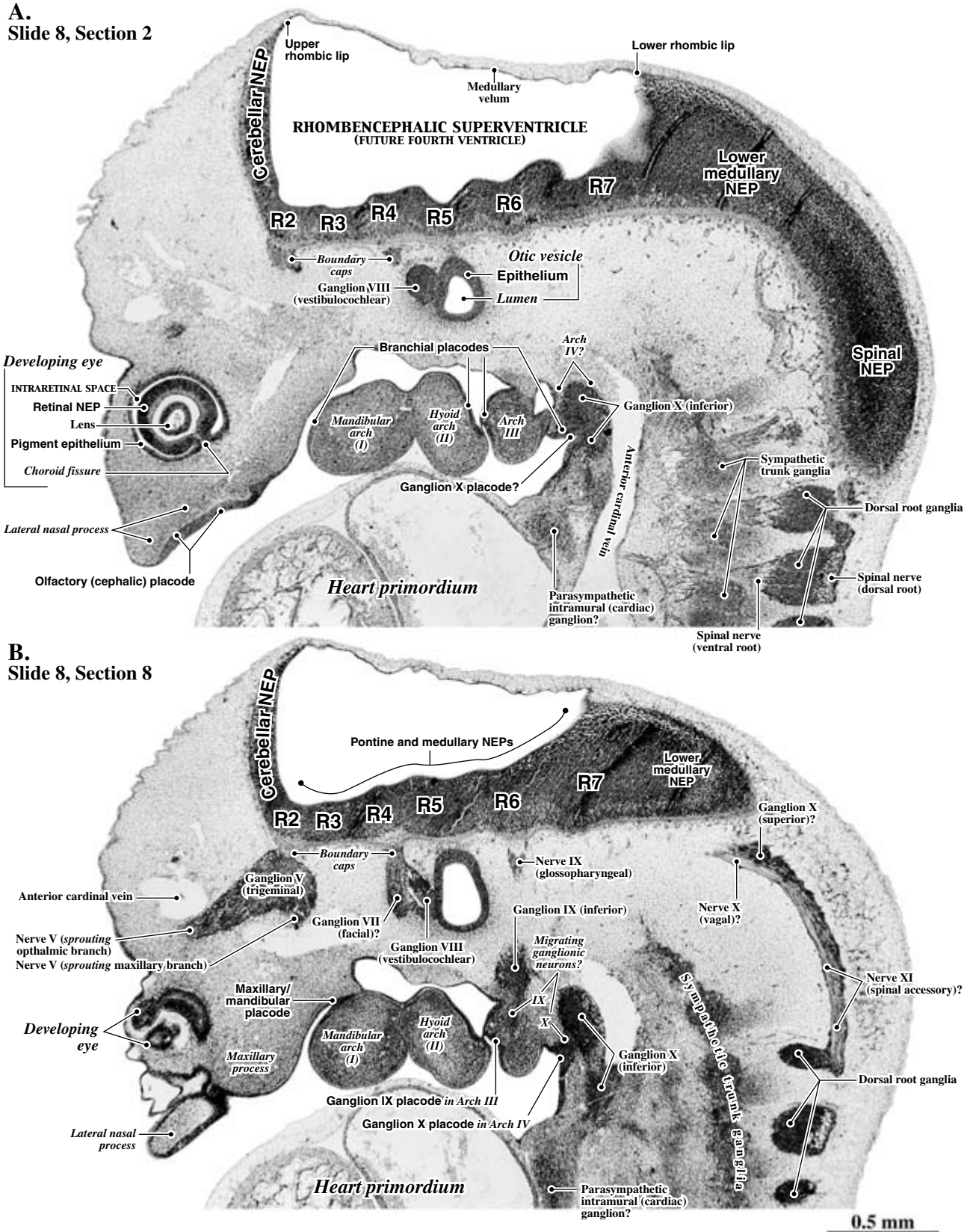


Figure 26. Time course of the development of the anterior and posterior parts of the pituitary gland. In GW3.8, GW4.0, and GW5.0 embryos (**A-C**, *facing page*), the pituitary placode folds in and fuses to form Rathke's pouch on GW5.5 (**D**, *facing page*), the primordium of the anterior pituitary gland. Continuity between the pituitary placode-derived anterior pituitary gland and the hypothalamic NEP-derived posterior pituitary gland is established in the GW6.5 and GW7.0 embryos (**E, F**, *facing page*). Sagittal sections. The contiguity between the anterior and posterior pituitary glands is illustrated at a higher magnification in a GW6.0 embryo (**G, H**, *this page*). Coronal sections.

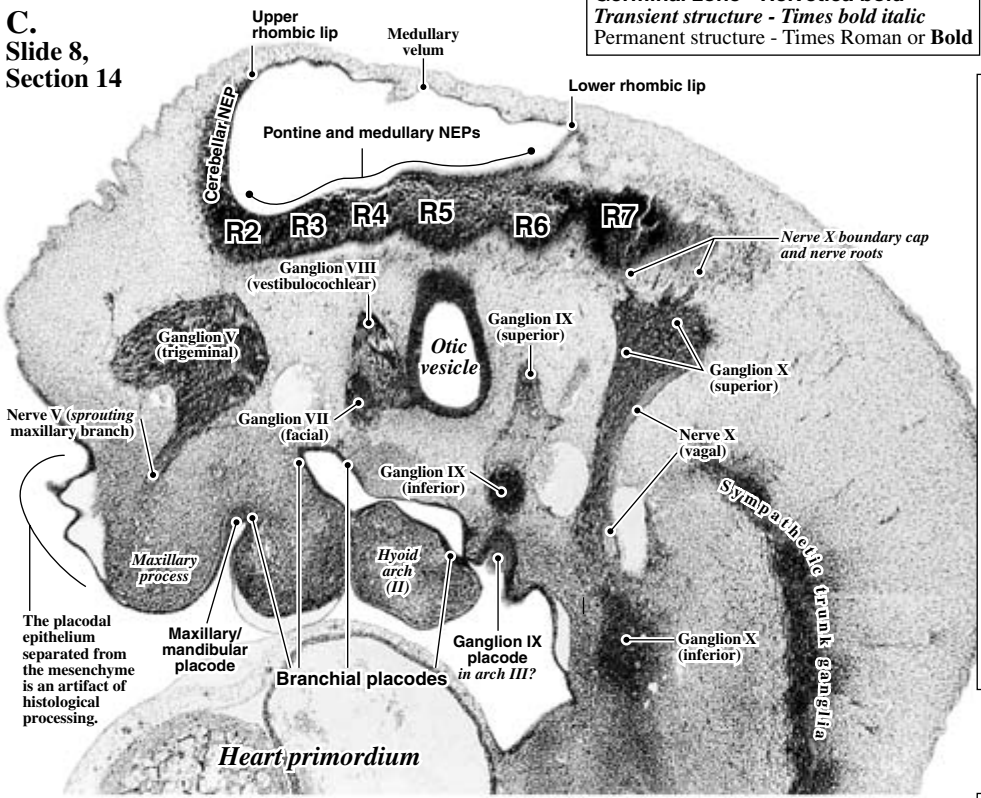
GW5 Sagittal, CR 7.1 mm, C8966



FONT KEY:
VENTRICULAR DIVISIONS – CAPITALS
Germinal zone - Helvetica bold
Transient structure - Times bold italic
Permanent structure - Times Roman or **Bold**

ABBREVIATIONS:
NEP - Neuroepithelium
R - Rhombomere

C.
Slide 8,
Section 14



D.
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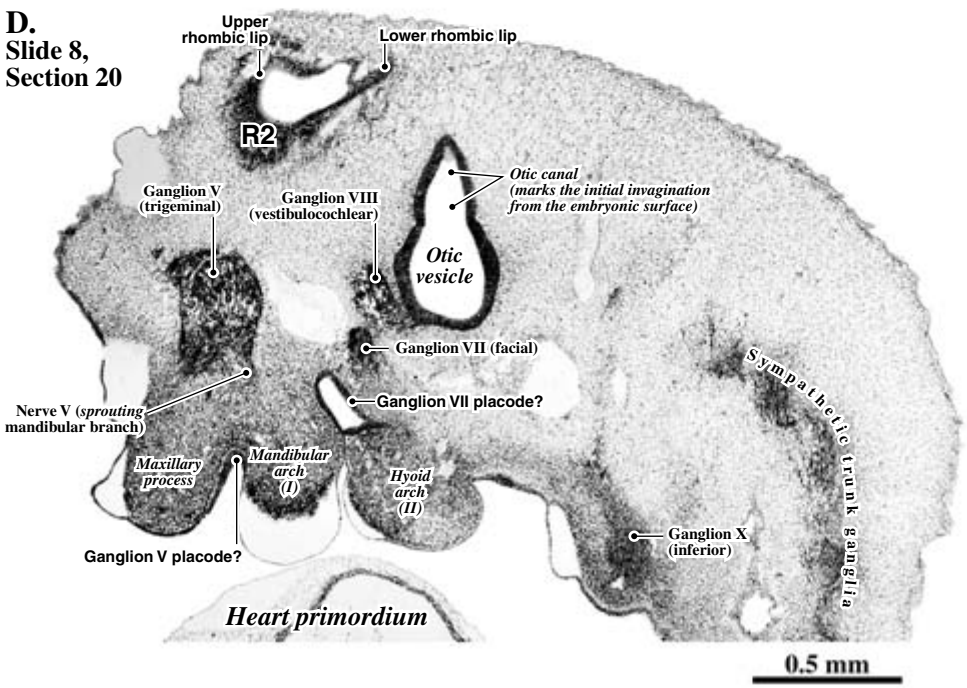

PROPOSED RHOMBOMERE IDENTITIES

R2	Trigeminal NEP - germinal source of the central trigeminal nuclei except the mesencephalic nucleus.
R3	Facial NEP - germinal source of facial motor and sensory receptor neurons of the facial (VII) ganglion.
R4	Vestibulo-auditory NEP - germinal source (with **R5**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R5	Vestibulo-auditory NEP - germinal source (with **R4**) of central auditory nuclei and vestibular nuclei, except the cochlear nuclei.
R6	Glossopharyngeal NEP - germinal source of sensory neurons that receive input from the glossopharyngeal (IX) ganglion.
R7	Vagal (X) sensory NEP - germinal source of the dorsal sensory nucleus and other sensory vagal nuclei.

RHOMBOMERE/GANGLION RELATIONSHIPS

R2	Axons from the trigeminal ganglion enter the brain here.
R3	Axons from the facial ganglion (VII) enter the brain at the junction between **R3** and **R4**.
R4	Vestibulocochlear ganglionic (VIII) axons enter the brain here.
R5	The ***otic vesicle*** touches this part of the brain.
R6	Axons from the glosso-pharyngeal ganglia (IX superior and inferior) enter the brain here.
R7	Axons from the vagal ganglia (X superior and inferior) enter the brain here.

GANGLION/PLACODE RELATIONSHIPS

V	Derived from a placode at the junction of the maxillary process and mandibular arch.
VII	Derived from a placode in the hyoid arch.
VIII	Both the vestibular and spiral ganglia are derived from the **otic vesicle epithelium**.
IX	The inferior and possibly most of the superior ganglionic neurons are derived from a placode in arch III.
X	The inferior and possibly most of the superior ganglionic neurons are derived from a placode in arch IV.

Figure 27. Serial sagittal sections, from medial (**A**) to lateral (**D**), through the head and neck region of a GW5.0 embryo (*facing page and this page*). They illustrate the vertical alignment and contiguity between cranial ganglia V, VII, VIII, IX, and X, and rhombomeres R2, R3, R4, R5, R6, and R7, respectively. The spatial relationship of the cranial ganglia and the maxillary process, the mandibular arch (I), the hyoid arch (II), and arches III and IV are also visible.

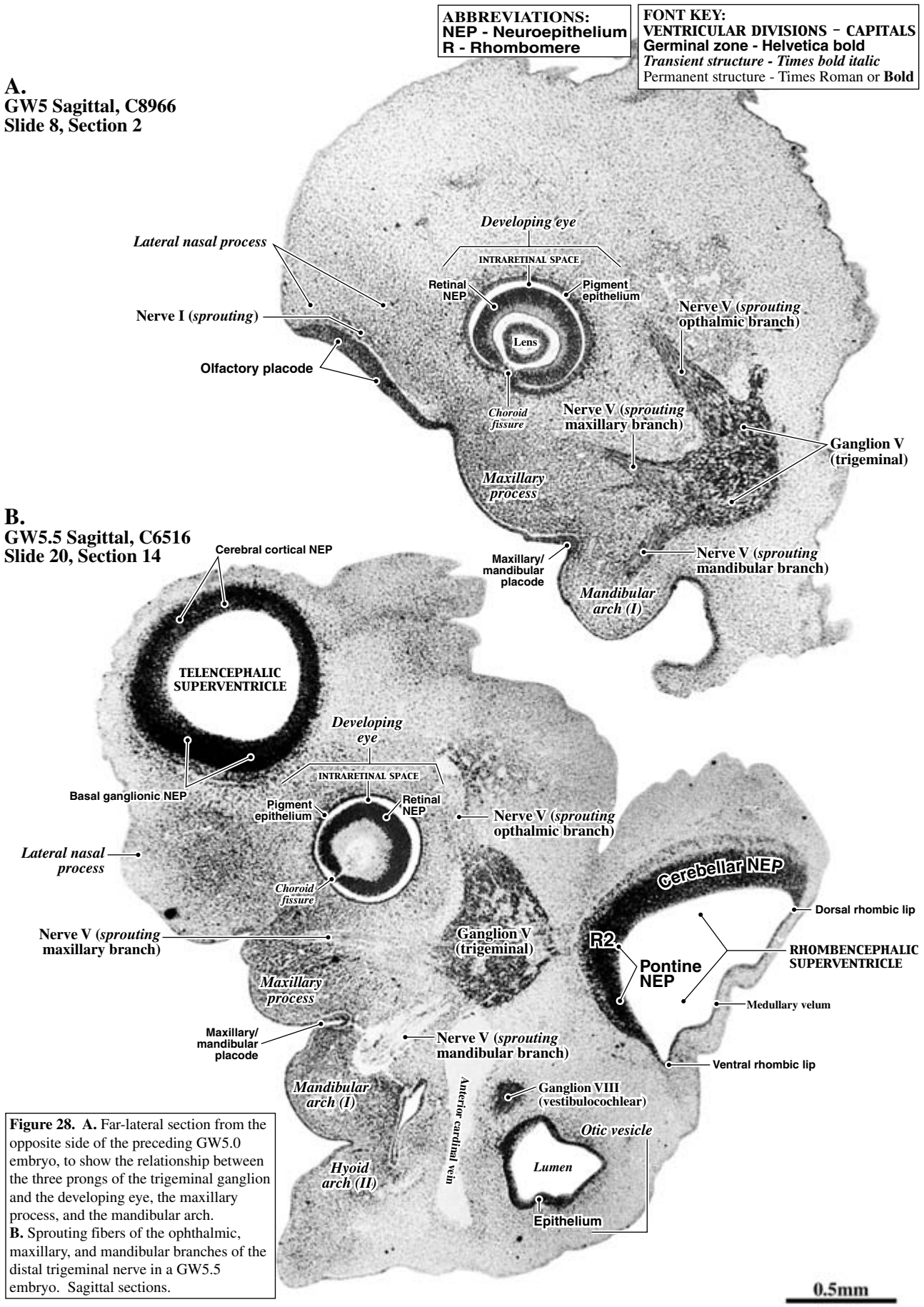

Figure 28. A. Far-lateral section from the opposite side of the preceding GW5.0 embryo, to show the relationship between the three prongs of the trigeminal ganglion and the developing eye, the maxillary process, and the mandibular arch.
B. Sprouting fibers of the ophthalmic, maxillary, and mandibular branches of the distal trigeminal nerve in a GW5.5 embryo. Sagittal sections.

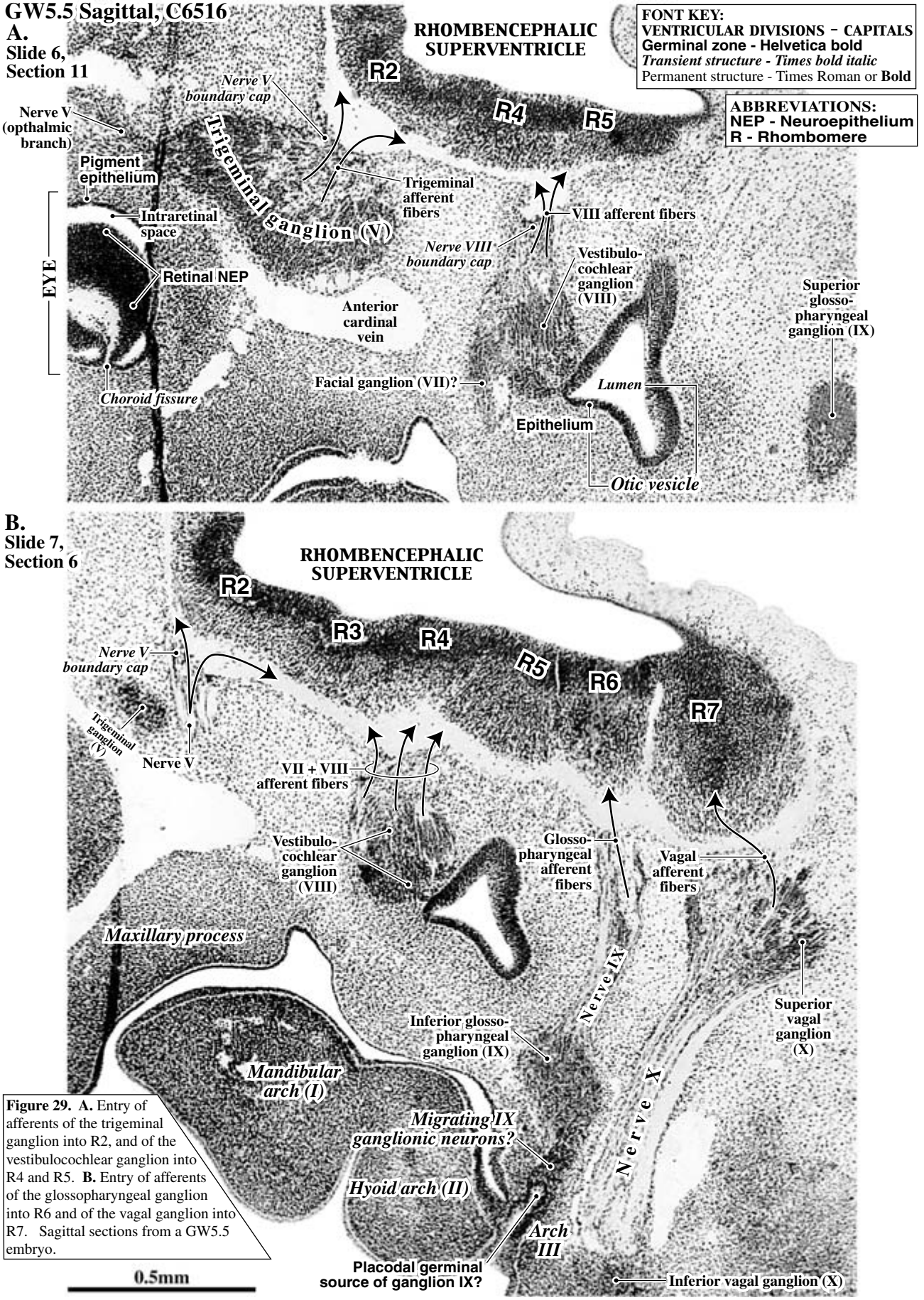

Figure 29. A. Entry of afferents of the trigeminal ganglion into R2, and of the vestibulocochlear ganglion into R4 and R5. **B.** Entry of afferents of the glossopharyngeal ganglion into R6 and of the vagal ganglion into R7. Sagittal sections from a GW5.5 embryo.

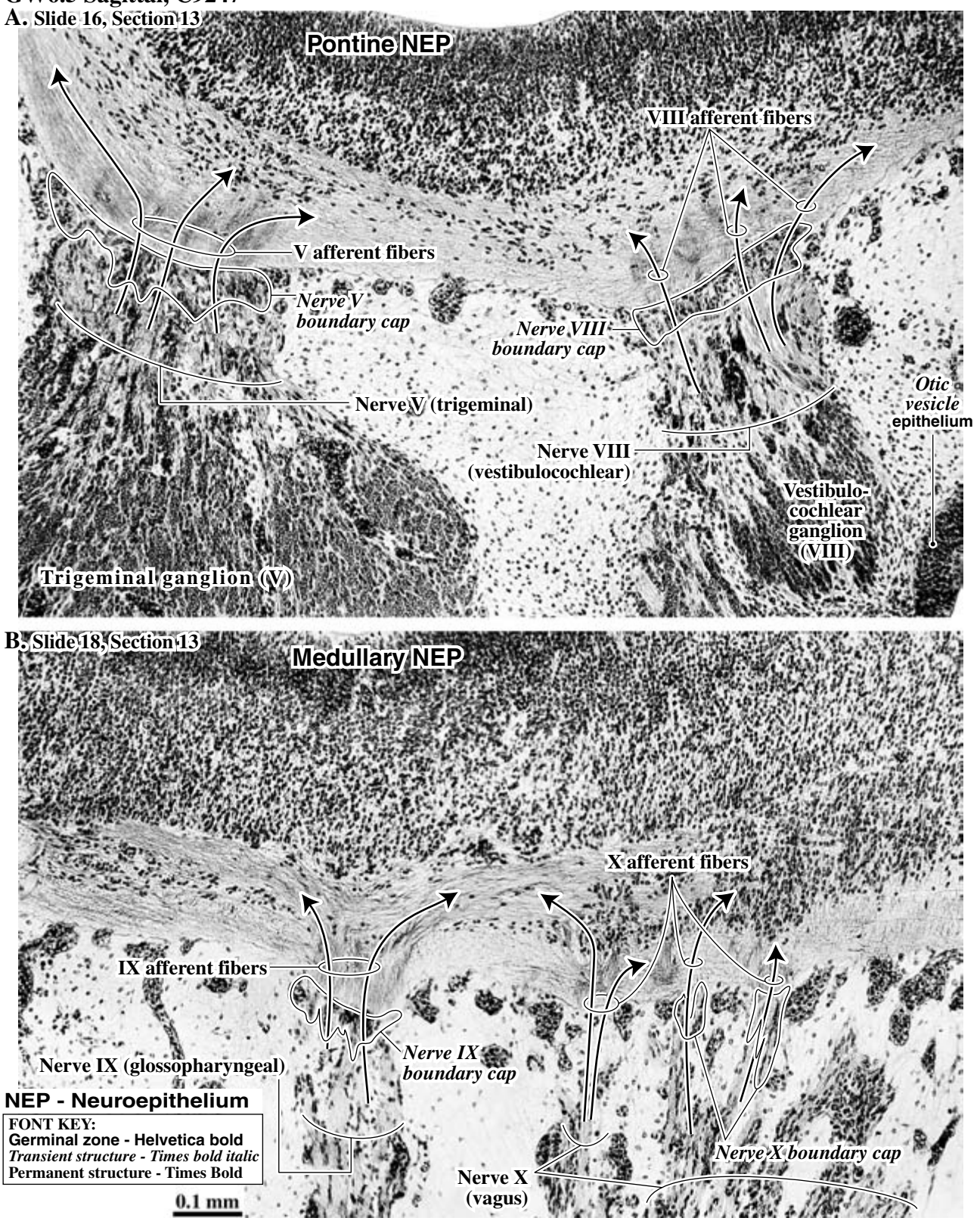

Figure 30. A. Penetration of trigeminal and vestibulocochlear afferents into the pons (former R2 and R4-R5). **B.** Penetration of glossopharyngeal and vagal afferents into the medulla (former R6 and R7). Sagittal sections from a GW6.5 embryo.

humans become reorganized during ontogeny. An example may be the necessary reorganization of the octaval system of aquatic fish, which have a lateral line organ but lack a cochlea, into the cochlear system of land vertebrates. The innervation of this complex tonotopically organized auditory system required profound reorganization of the auditory system in terrestrial vertebrates. Indeed, the neurons of the dorsal and ventral cochlear nuclei do not derive from the rhombomeres but from a new germinal system, the cochlear NEP and EGL located in the region of the lower rhombic lip.

Passing from hypothetical phylogeny to empirically based observations, we may summarize the differences between the development of the spinal cord and the brain as follows. First, unlike the segmented mesodermal somites in the trunk region, the head mesoderm is unsegmented. Second, whereas the neural crest-derived and somite-dependent spinal ganglia are reiterated structures, the branchial arches, the diversifying olfactory, optic lens, and pituitary placodes, and the trigeminal-facial, otic, and glossopharyngeal-vagal placodes and ganglia derived from them are not reiterated structures but functionally diverse systems. Third, while there is no hint of any longitudinal (rostrocaudal) metameric compartmentation either in the spinal NEP or the differentiating components of the spinal cord gray matter (although there is a pronounced dorsoventral compartmentation), there is, in contrast, a marked compartmental heterogeneity in the brain vesicles. This is marked at the outset by the presence of variegated NEP mosaics of different sizes and shapes both in the hindbrain and the forebrain. Finally, since these NEP regions—e.g., the NEPs of the different thalamic nuclei and the different areas of the cortex—become linked to the periphery much later (after synaptic connections are established with the primary afferents and the lower motor neurons), their diversification cannot be attributed to periphero-central signaling mechanisms but must be due to either endogenous regulation and/or centro-central signaling processes.

Endogenous Genetic Regulation in NEP Cell Diversification. While in conventional histological preparations individual NEP cells look alike throughout the neuraxis, the NEP matrix consists of morphologically dissimilar NEP compartments from the beginning. The configuration and cellular dynamics of these NEP compartments—those of the rhombencephalon, mesencephalon, diencephalon and telencephalon—are quite different from the outset, and so are the different classes and varieties of neurons and brain structures they generate. While the dome-like expanse of dorsal telencephalic NEP matrix, for instance, generates an immense number of relatively homogeneous classes of neocortical neurons, the variegated ventral telencephalic NEP matrix produces a much greater variety of neurons for such diverse brain structures as the septum, the basal telencephalic nuclei, the basal ganglia, the amygdala, etc.—each with its own neurogenetic timetable, population size, and cell composition. The same applies to the variegated diencephalic and mesencephalic NEP compartments. And as development progresses, the larger NEP matrix divisions become subdivided into a series of bilaterally symmetrical smaller protuberances, cavities, and discontinuous stretches and patches marked by different cell depth and cell packing density. In our earlier experimental studies in rats, we used ^{3}H-thymidine autoradiography to date the changing spatial and temporal dynamics of cell proliferation in many of these NEP mosaics, track the migratory paths and settling patterns of the tagged neurons, and correlate these data with the chronology of neurogenesis in various structures of the mature brain. Based on that information, we named the identified NEP mosaics by their putative target structures. Thus, we have such divisions as the neocortical, limbic-cortical, and basal ganglionic NEPs in the early telencephalon; the thalamic, subthalamic, and hypothalamic NEPs in the early diencephalon; and the tectal and tegmental NEPs in the early mesencephalon. And as embryonic development progresses, most of these early NEP compartments become partitioned into smaller components, such as the tectal NEP into the superior collicular and inferior collicular NEPs, the tegmental NEP into the NEPs of the red nucleus, oculomotor nuclei, substantia nigra, etc. We illustrate this progressive NEP matrix compartmentation at a select coronal level of the human prosencephalon which begins with three diencephalic divisions—the all-thalamic, all-subthalamic and all-hypothalamic—and each of which becomes subsequently divided into smaller NEP mosaics (**Figure 31**).

The fact that dissimilar proliferative and differentiation dynamics are expressed by many NEP compartments—e.g. cortical, basal ganglionic, hippocampal, thalamic, etc.—that have no direct peripheral connections suggests that their diversification is due not to exogenous signaling but to endogenous signaling. (Although we postulate that the superventricles and the superarachnoid reticulum influence NEP cell proliferation and differentiation, respectively, their diffuse or global influences cannot explain the local diversification of NEP cells.) The inference that the germinal cells forming certain NEP compartments are intrinsically different is supported by genetic studies that are currently carried out in mice and other experimental animals. For instance, it has been reported that *Pax6* is expressed by NEP cells throughout the prosencephalic neural plate before it folds and fuses (Inoue et al., 2000); thereafter, *Pax6* expression persists in the dorsal telencephalic NEP but vanishes from the ventral telencephalic NEP (Stoykova et al., 2000). *Six3* (Oliver et al., 1995) and retinoic acid expression (Mic et al., 2004; Halilagic et al., 2006; Ribes et al., 2006) have been implicated in the early phases of prosencephalic development. The dorsal telencephalic NEP cells that are destined to generate cortical neurons also express the transcription factors *Emx1* and *Emx2*, whereas the ventral NEP cells destined to generate basal ganglionic neurons express *Nkx2.1*, *Dlx1*, *Dlx2*, and *Gsh2* (Torreson et

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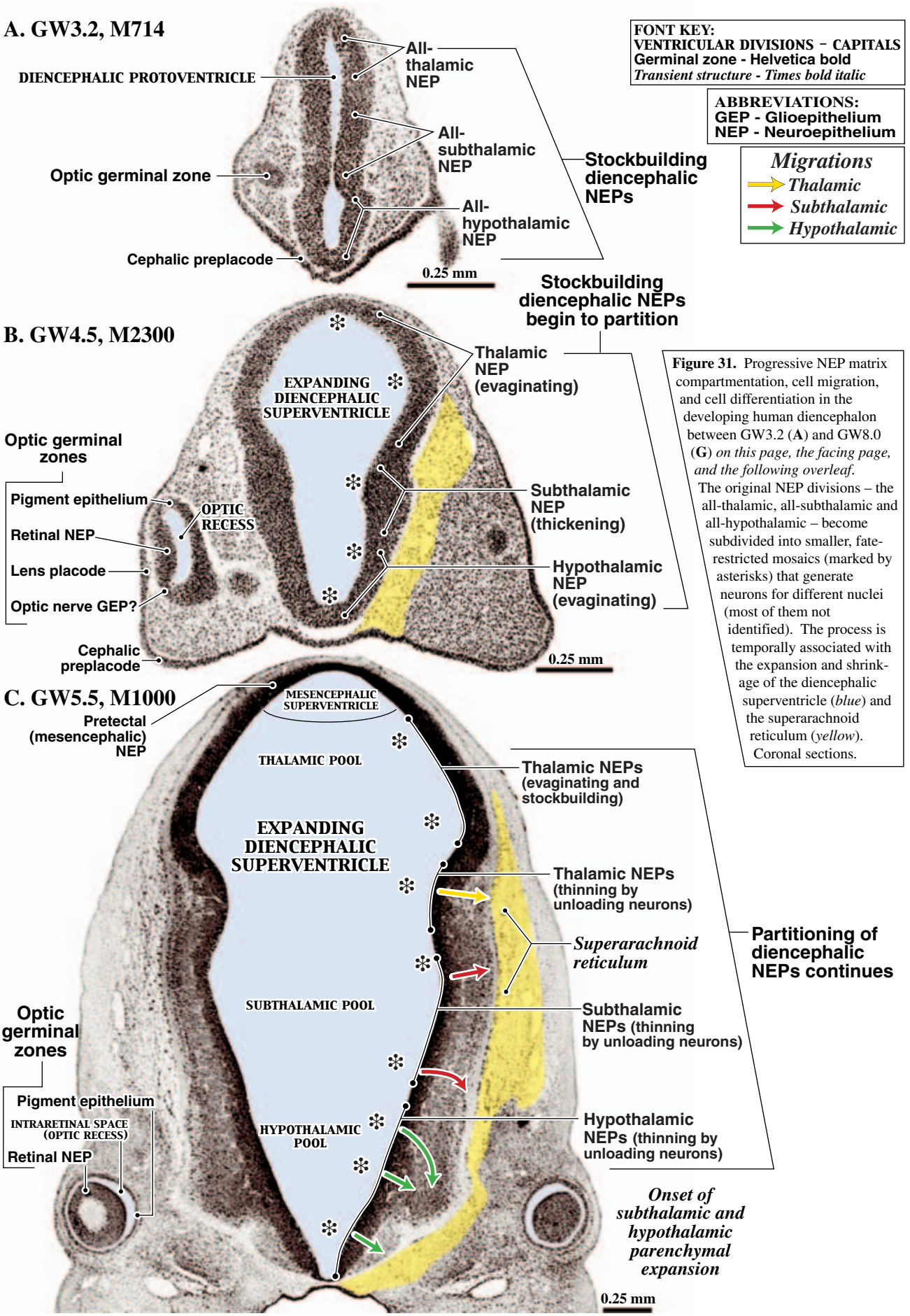
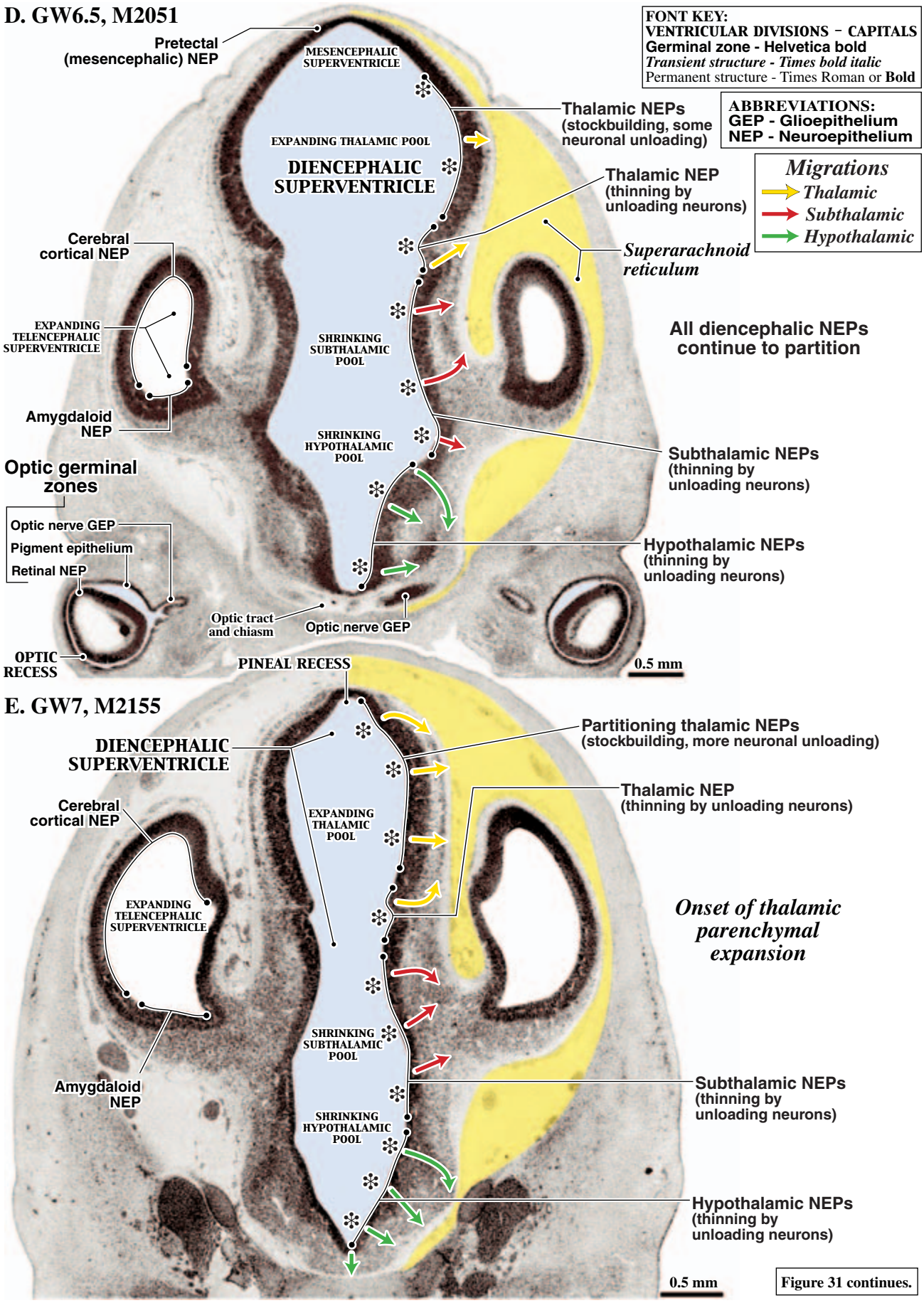


Figure 31. Progressive NEP matrix compartmentation, cell migration, and cell differentiation in the developing human diencephalon between GW3.2 (**A**) and GW8.0 (**G**) *on this page, the facing page, and the following overleaf.* The original NEP divisions – the all-thalamic, all-subthalamic and all-hypothalamic – become subdivided into smaller, fate-restricted mosaics (marked by asterisks) that generate neurons for different nuclei (most of them not identified). The process is temporally associated with the expansion and shrinkage of the diencephalic superventricle (*blue*) and the superarachnoid reticulum (*yellow*). Coronal sections.



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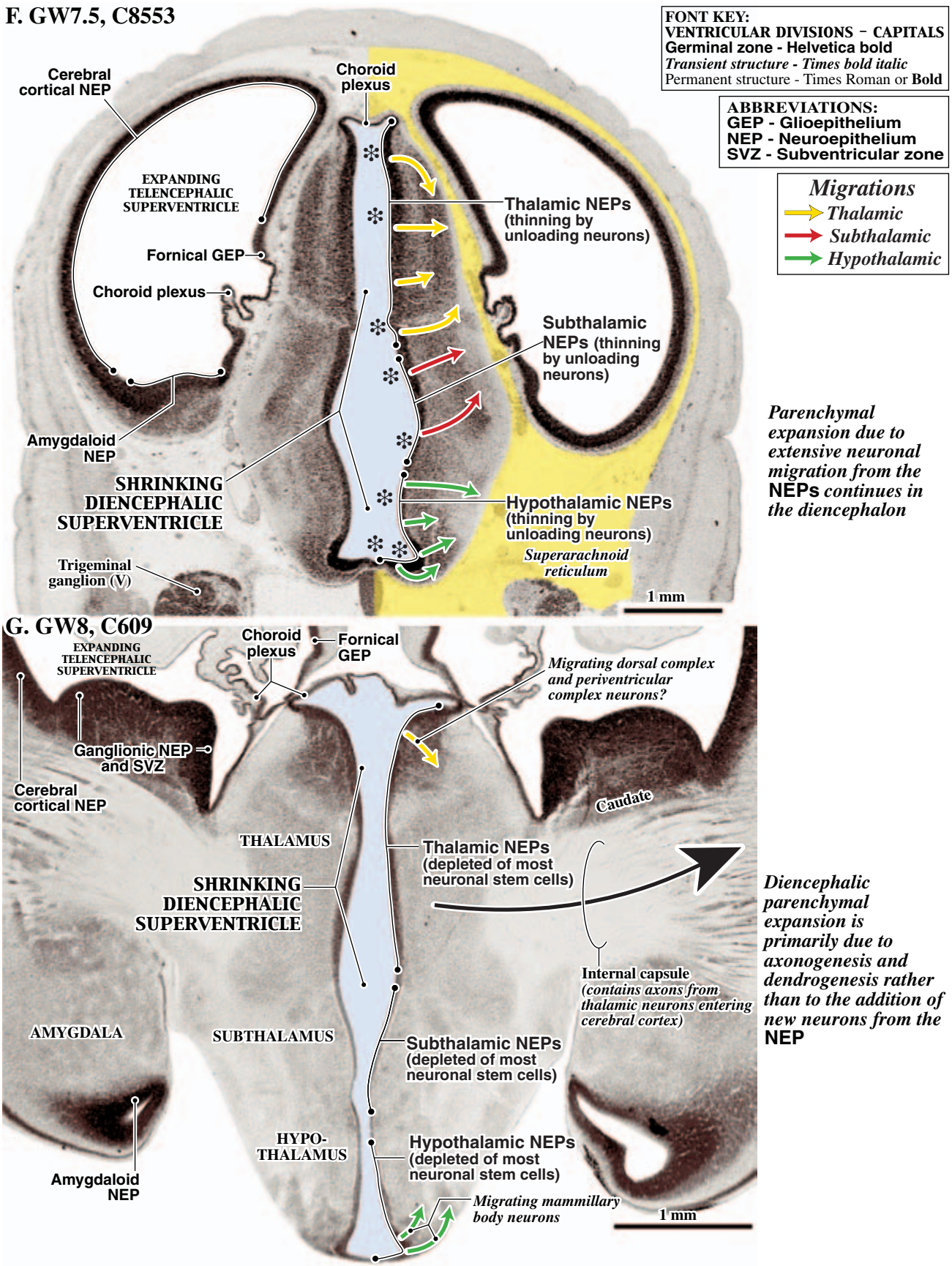

Figure 31 concludes.

al., 2000; Wilson and Rubenstein, 2000; Yun et al., 2001; Corbin et al., 2003; Muzio and Mallamaci, 2003). Similarly, *Ngn1* and *Ngn2* are expressed in the dorsal telencephalic NEP, whereas *Mash1* is expressed in the ventral telencephalic NEP (Ma et al., 1997; Fode et al., 2000; Parras et al., 2002). It has also been reported that *Emx2* expression in the rodent cortical NEP shows a high-caudal to low-rostral gradient, and a high-medial to low-lateral gradient (Leingartner et al., 2003). Since these gradients are the opposite of cortical maturation gradients, not only in rodents (Bayer and Altman, 1991a) but also in humans (as illustrated in the preceding Volumes of this Atlas), it may be inferred that *Emx2* expression declines as cortical neurogenesis and differentiation progresses. The importance of *Emx* signaling in dorsal telencephalic development is indicated by observations that cortical development, including that of the hippocampus, is greatly retarded in *Emx* mutants (Bishop et al., 2003). In light of the importance we attribute to the growth of the fetal telencephalic choroid plexus in cortical development, an interesting aspect of *Emx* gene action is its suppression of telencephalic choroid plexus development (von Frowein et al., 2006). The production of choroid plexus progenitor cells is apparently associated with *Otx2* and *BMP7* expression. (The cells of the non-neuronal rhombencephalic choroid plexus are reported to express *Lmx1a* and *Gdf7*; Landsberg et al., 2005). Finally, according to a study (Kimura et al., 2005) that has used a different nomenclature from the one we use in this Atlas, *Wnt8b* expression demarcates the hippocampal primordium in the medial cortex as well as other components of the limbic circuit, including the diencephalic epithalamus and mammillary body. Within the hippocampus, *Ephb1* demarcates the ammonic NEP that generates pyramidal cells, *Wnt3a* the dentate NEP that generates granule cells, and TTR the primordium of the non-neuronal telencephalic choroid plexus.

There are currently few studies available regarding the genetics of diencephalic and mesencephalic NEP cell specification. *Pax6* is expressed in the diencephalic NEP (Warren and Price, 1997) but not in the mesencephalic NEP where, instead, *Pax3* and *Pax7* are expressed (Kammermeier and Reichert, 2001). It has been reported that *Msx1* genes induce *Wnt1* expression at the dorsal midline region of the mesencephalic and diencephalic junction, and in homozygous *Msx1* mutant mice several structures fail to develop at this site (Bach et al., 2003). *Mash1* is required for the specification of NEP cells that produce the neuroendocrine neurons of the ventral, arcuate, and ventromedial hypothalamic nuclei (McNay et al., 2006). The bHLH transcription factor *SCL* is expressed in pretectal, midbrain, and hindbrain NEPs but not elsewhere in the CNS (van Eekelen et al., 2003), and the transcription factor *Otx2* appears to control neurogenesis and progenitor identity in the midbrain tectum and tegmentum (Vernay et al., 2005). There are more data regarding the genetics of cerebellar development. *FGF* and *Wnt* expression are early events in cerebellar morphogenesis (Morales and Hatten, 2006; Waters and Lewandoski, 2006). *Pax6*, *Math1*, *Tbr1*, and *Tbr2* have been implicated in the generation of the NEP cell line that produces cerebellar deep nuclear neurons, and these factors are expressed sequentially as the young deep neurons enter the nuclear transition zone (Fink et al., 2006). Among other transcription factors expressed in this lineage are *Otx3-Dmbx1* (Kimura et al., 2005). The Purkinje cell lineage expresses *Math1* (Jensen et al., 2004; Wang et al., 2005), *Ptf1a* (Hoshino, 2006), and *Ebf2* (Croci et al., 2006). The cell lineage of the EGL, which gives rise to cerebellar microneurons (see below) and can be visualized with the marker *RU49* (Alder et al., 1996), expresses *Math1* (Machold and Fischell, 2005) and Zic1 (Aruga et al., 1998). Integrin-linked kinase (*ILK*) is reported to be a critical agent in the proliferation of granule cell precursors (Mills et al., 2006) and Bergmann glial cell differentiation (Belvindrah et al., 2006). Finally, the transcription factor *Zpf423* has been implicated not only in the production of cerebellar granule cells but also in the proliferation of other late-generated precursors in the cerebral cortex and the hippocampus (Alcaraz et al., 2006). In conclusion, there is growing evidence for genetically controlled diversification of some of the NEP mosaics that are not direct targets of exogenous (peripheral) influences. We return later to a third source of morphogenetic regulation, i.e., the centro-central signaling between developing components of the CNS.

F. Timetables of Neurogenesis

There is no direct way to determine the time of origin of neurons in the human CNS. But that can be done indirectly by using the quantitative data obtained in rats with ^{3}H-thymidine autoradiogaphy. Notwithstanding the great difference in the speed of their development, embryonic (E) days versus gestational weeks (GW), there is a close morphological correpondence between prenatal rat CNS development (E11 to E21) and human CNS development during the first trimester (GW3-GW12). This matching relationship is shown in sagittal sections (**Figure 17A, B**), anterior coronal sections (**Figure 17C, D**), and posterior coronal sections (**Figure 36A, B**). We re-examined this relationship in the material presented in this atlas series by matching sections from the spinal cord and the brain in the two species. **Tables** of the estimated chronological eqivalence of human CNS neurogenesis with the empricially-based rat CNS neurogenesis are summarized in the **Appendix** (page 490). We emphasize that the correpondence is limited to the first trimester and early second trimester in humans. Rats are born at a time equivalent to the early second trimester in humans. After birth on E22/P1, the rat CNS rapidly matures and has an adult appearance by the time of weaning (approximately P21). In contrast, human CNS maturation is stretched out over a long time span through the remaining second trimester, the third trimester, and even into the early postnatal years.

G. Cell Migration, Sojourn Zones, Secondary Germinal Matrices, and Fate-Restricted Glioepithelia

Cell Migration and Migratory Streams. Following the production of neurons, cell migration is one of the most important mechanisms in the morphogenetic organization of the developing and maturing CNS. Cell migration is a very complex and regionally diversified process. There are small cohorts and large streams of migrating neurons; short-distance and long-distance migrations; and migrations with a straight path or a tortuous route. Some young neurons migrate through interstitial tissue, like the precerebellar neurons that form the inferior olive (Altman and Bayer, 1987b); others migrate beneath the pia, like the neurons of the posterior extramural migratory stream that produce the neurons of the pontine gray (Altman and Bayer, 1987d); still others migrate in a subventricular position, like the rostral migratory stream (RMS) of the telencephalon that conveys neurons to the olfactory bulb (Altman, 1969; Luskin, 1993). While most migrations are ipsilateral, there are also some that are contralateral, i.e., the neurons of the precerebellar extramural migratory stream that form the lateral reticular and external cuneate nuclei (Altman and Bayer, 1987c). The simplest form of cell migration is the short-distance radial translocation of a cohort of young neurons from a NEP mosaic to a nearby parenchymal destination. This mode of migration, often at a right angle to the NEP matrix, is known as radial migration. It is a widespread phenomenon during early embryonic development throughout the CNS before the expanding parenchyma becomes filled with aggregates of cell bodies and crisscrossing fiber tracts that obstruct the path of migrating neurons toward their final destination. For instance, in the developing cerebral cortex, the earliest Cajal-Retzius neurons migrate radially to the primordial plexiform layer **(Figure 32A, B)** before the cortical plate begins to form **(Figure 32C)**. As Golgi studies have shown, these cells have a trailing process in the NEP and a leading process approaching the pial surface (Morest, 1970). Although radial migration has been attributed to guidance by "radial glia" (*see* **Section B**, page 428), a far more likely or prevalent mechanism is perikaryal (or somal) translocation (Berry and Rogers, 1965; Morest, 1970; Nadarajah et al., 2003; Hatanaka et al., 2004). As we noted earlier, nuclear translocation within the spindle-shaped cytoplasm is a fundamental property of NEP cells that shuttle to and from the ventricular lumen to undergo mitotic division. The nuclei of young neurons leaving the NEP matrix may similarly translocate inside the cells' radially extending neurite. (Such a process of nuclear translocation has been well documented for granule cells in the cerebellar cortex; e.g., Altman and Bayer, 1997). However, radial migration is only one of the many forms of neuronal locomotion. For instance in the developing cerebral cortex, the translocating young neurons interrupt their radial migration and interact with various fiber systems. The cells and fibers undertake a choreographed series of movements to form different layers in what we have called the stratified transitional field or STF **(Figure 32D)**. The evidence that clonally related cells disperse widely in the developing cerebral cortex (Walsh and Cepko, 1992; Mathis and Nicolas, 2006) indicates that cells may migrate both radially and non-radially (tangentially) within the same brain region (Bayer et al., 1991a, b). Tangential migration is better accounted for by an amoeboid form of locomotion rather than perikaryal translocation, with the philopodia of a neuron's leading process sampling the local milieu or responding to distal signals, and determining the direction of cell progression in one or another direction.

Radial translocation at a right angle from the NEP matrix to the surface of the cortex is obviously a simpler task than the guidance of tangential migration to some distant site that may require multiple navigation cues. Cell polarization, guidance by attractive and repulsive forces in the immediate vicinity of the moving cell, and long-range signaling by molecular diffusion gradients have been postulated to act as directional biases, signposts, and beacons. However, little is currently known about their exact nature. Filamin-A has been implicated in the control of the shape of migrating cortical neurons and their direction of migration (Sato and Nagano, 2005). The subpial Cajal-Retzius cells of the primordial plexiform layer secrete reelin, a large extracellular matrix protein. Reelin has been implicated as a signaling factor in the columnar (vertical) and laminar (horizontal) organization of cortical cells (Ogawa et al., 1995; Nishikawa et al., 2002). The absence of reelin in mutant mice results in abnormal cell migration and cell lamination not only in the cerebral cortex but also in the hippocampus, the cerebellum (D'Arcangelo et al., 1995), the olfactory bulb (Hack et al., 2002), and some hindbrain nuclei (Rossel et al., 2005). In the developing human cerebral cortex, reelin expression is present in the primordial plexiform layer by GW7 to GW8 (Zecevic et al., 1999) and somewhat later in the hippocampus (Abraham et al., 2004). Among other factors that appear to play a role in the migration and settling of cortical neurons is *Cdk5* (Hammond et al., 2004), presenilin-1 (Louvi et al., 2004), *COUP-TF* nuclear receptors (Tripodi et al., 2004), and GABA(B) receptors (Lopez-Bendito et al., 2003).

The properties of the rostral migratory stream (RMS) associated with the forebrain subventricular zone (SVZ), which forms prenatally in animals (Pencea and Luskin, 2003) and humans (Volume 4 of this Atlas), but persists through adulthood, has received considerable experimental scrutiny recently (though mostly in postnatal animals). In the human forebrain, the RMS is recognizable as a distinct entity by GW11, and it expands greatly during the second and third trimesters (Volumes 2-3 of this Atlas). In adult rats, progenitor cells stream in this glia-encased tube (Peretto et al., 1997) and supply not only microneurons (granule cells) to the olfactory bulb but also neuroglia

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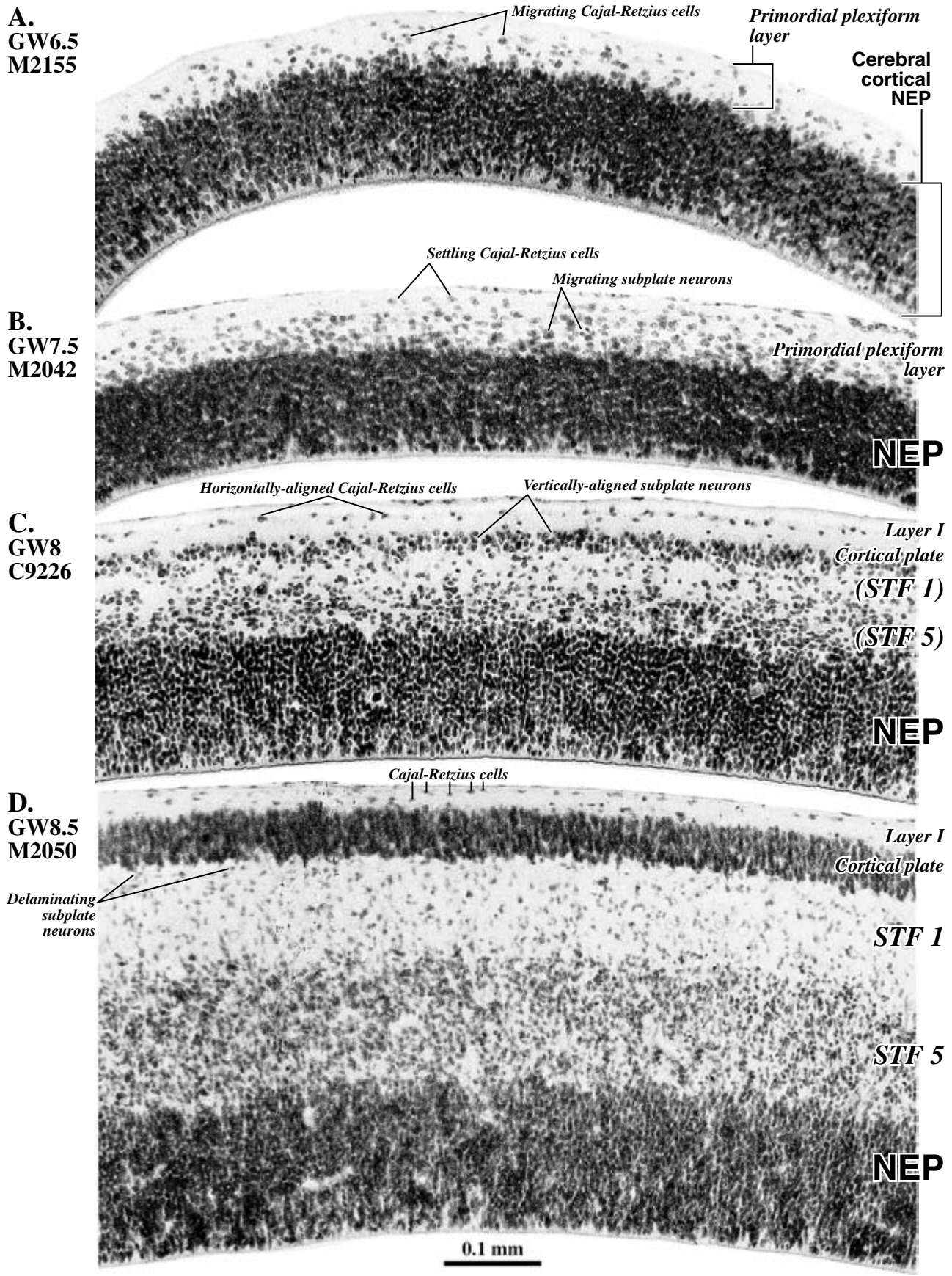

Figure 32. Onset of the parenchymal development of the neocortex. The first differentiating neurons to leave the neocortical NEP, at about GW6.5, are the Cajal-Retzius cells (**A**), followed by the subplate neurons at about GW7.5 (**B**). The cortical plate begins to form, at the site illustrated, at about GW8.0 (**C**), and the first two layers of the stratified transitional field (STF) at about GW8.5 (**D**). (Modified Figure 9 from Altman and Bayer, 2002.)

(Aguirre et al., 2002; Fukushima et al., 2002). The proliferating SVZ cells and the migrating RMS cells express the microtubule associated protein, doublecortin (Yang et al., 2004) and stathmin (Jin et al., 2004). The homeobox gene *Vax1* (Soria et al., 2004) and nitric oxide (Moreno-Lopez et al., 2004) were found to exert an inhibitory influence on SVZ and RMS cell proliferation, and integrin and laminin have been implicated in the migration of RMS cells (Emsley and Hagg, (2003). *Slit1* and *Slit2*, repellents of neurite growth secreted by cells of the septum bordering the RMS stream, exert a guiding influence on migrating RMS cells (Nguyen-Ba-Charvet et al., 2004).

In contrast to the RMS, relatively little is known about the guidance mechanisms of the unique migratory stream of neurons that form the precerebellar nuclei (Altman and Bayer, 1997). The progenitors of olivary neurons (the source of climbing fibers) that migrate in the posterior intramural migratory stream express *Math1*. *Netrin1* is involved in the migration of inferior olivary neurons (Bloch-Gallego et al., 1999; Alcántara et al., 2000; de Diego et al., 2002). The pontine neurons (a source of mossy fibers) that migrate in the anterior extramural migratory stream express *Ngn1,* and their migration is abnormal in mutant mice lacking the chemokine receptor *CXCR4* (Vilz et al., 2005). The precerebellar nuclei are absent or disorganized in *netrin1* homozygous mutant mice (Kubota et al., 2004). As in the rat, the precerebellar migratory streams are also prominent in the developing human CNS. The posterior intramural migratory stream begins to form by GW6.5-GW7.0 (this Volume) and the expanding inferior olive is evident by GW7.5 (Volume 4 of this Atlas; Bayer and Altman, 2006). The anterior extramural migratory stream is not recognizable until GW9 and the pontine gray nucleus starts to form about GW11, at about the same time that the earliest descending corticofugal fibers begin to traverse it.

Transitional Fields and Sojourn Zones. We have illustrated during the second trimester (Volume 3 of this Atlas; Bayer and Altman, 2005) the prominence of the cortical transitional stratified field (STF) situated between the NEP and the expanding cortical plate, the future gray matter. We identified six cellular and fibrous layers within the STF, distinct strata where cortical neurons sojourn for some time and mingle with afferent, efferent, and commissural fibers before they resume their migration and settle in the cortical plate. We postulated that the STF is a staging area where connections form between the topographically unspecified sojourning cortical neurons and the somatotopically, tonotopically and retinotopically specified thalamocortical afferents that provide input to them. The STF begins to form in the earlier-maturing anterolateral cortical region, and it spreads slowly dorsally and medially. Where present, the STF consists initially of two layers, the fibrous STF1, and the cellular STF5 **(Figure 32D)**. By GW10, the bilayered STF is present throughout the anterior cortex, and it is evident that STF5 is composed of sojourning young cortical neurons that have left the NEP, and STF1 is the target of thalamocortical afferents that have crossed over from the diencephalon into the telencephalon in the internal capsule **(Figure 33A)**. Between GW9 and GW11 an additional layer, STF4, begins to emerge slowly and uncertainly in the earlier maturing lateral aspect of the neocortex. The emergence of STF4 may be associated with the onset of the descent of corticofugal fibers. The other STF layers (STF3, STF2, and STF6) begin to form thereafter and all six of the STF layers are present by GW13.5 **(Figure 33B)**. By the latter age, there is also a clear difference in the organization of the STF in the future motor cortex anteriorly and the future sensory cortex posteriorly. STF5 is best developed in the motor areas **(Figure 34A)** and STF3 is a unique feature of the sensory areas **(Figure 34B)**. The different cytological organization of STF in the motor cortex and visual cortex is illustrated at higher magnification in a GW20 fetus **(Figure 35)**. In the visual cortex, STF3 is composed of three sublayers (the honeycomb matrix). We hypothesize that the trilaminar STF3 contains sojourning neurons that will form the granular layer (layer IV), the principal target of thalamocortical afferents, and the STF5 contains sojourning neurons that will form the pyramidal layer (layer V), the source of corticospinal efferents.

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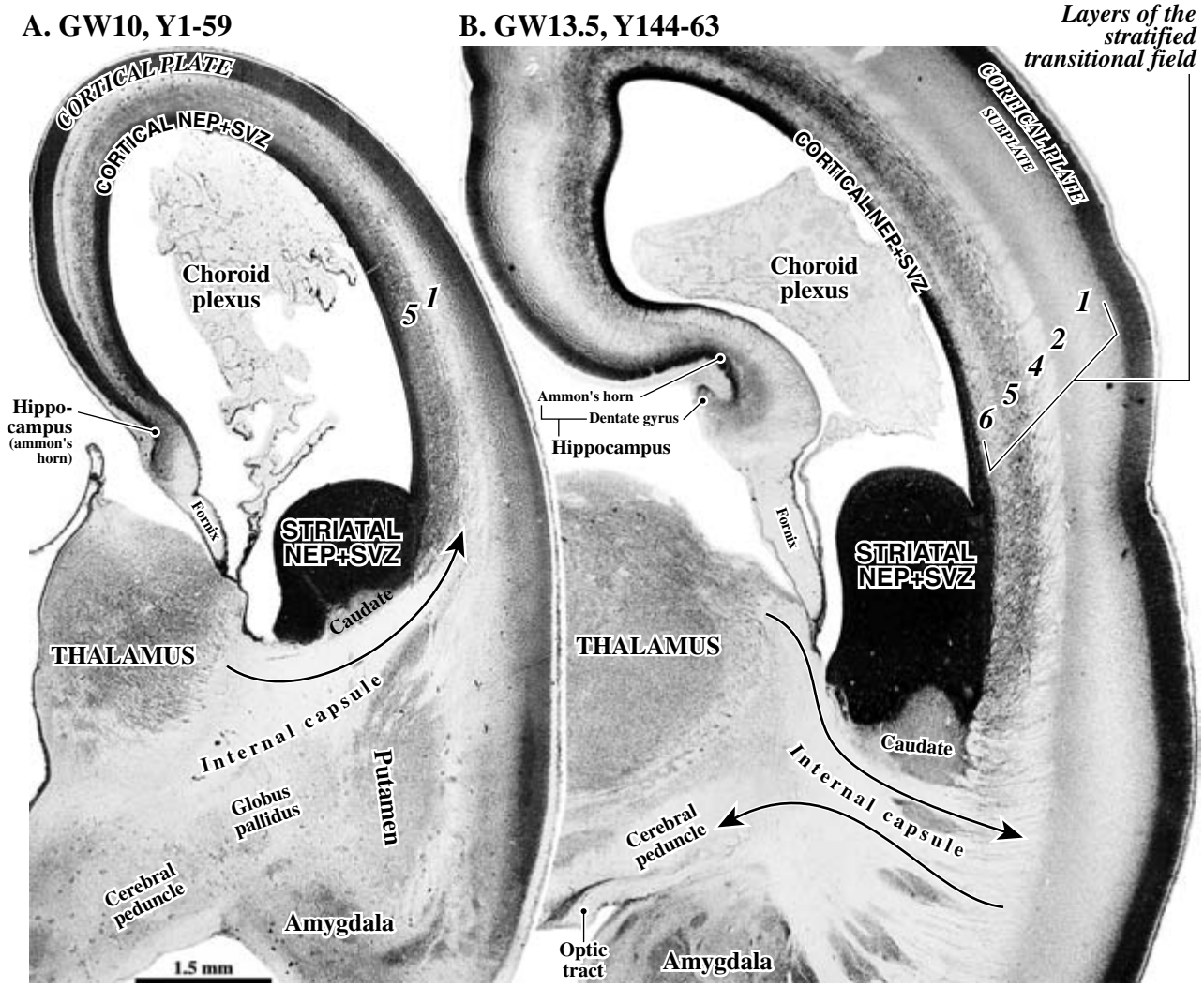

Figure 33. Increase of the STF from two layers in the GW10 fetus (**A**) to six layers in the GW13.5 fetus (**B**). Coronal sections. (Modified Figure 8 in Altman and Bayer, 2002.)

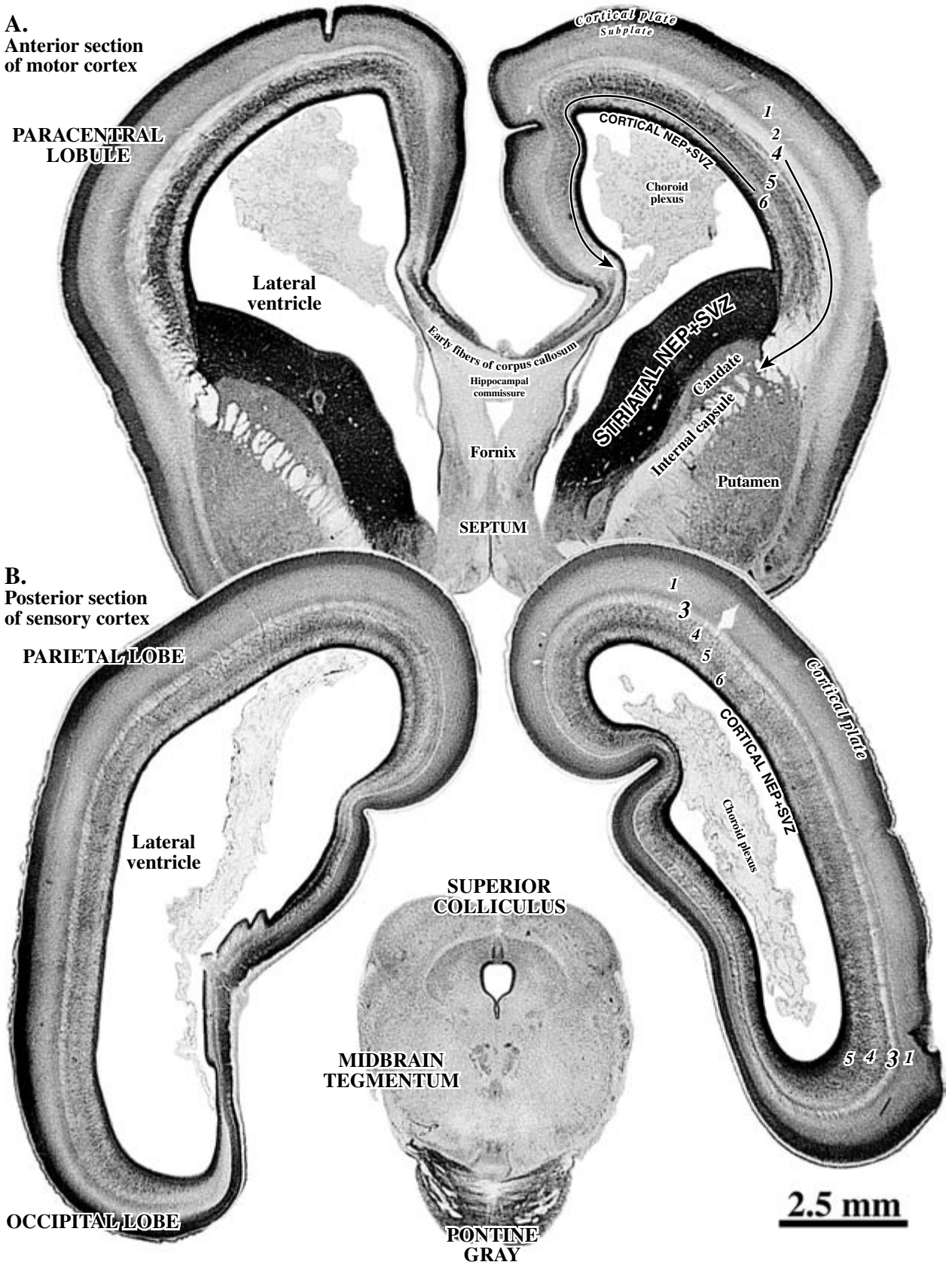

Figure 34. Regional differences in STF organization in the future motor cortex anteriorly (**A**) and the future sensory cortex posteriorly (**B**) in a GW13.5 fetus. Coronal sections. (Modified Figure 11 in Altman and Bayer, 2002.)

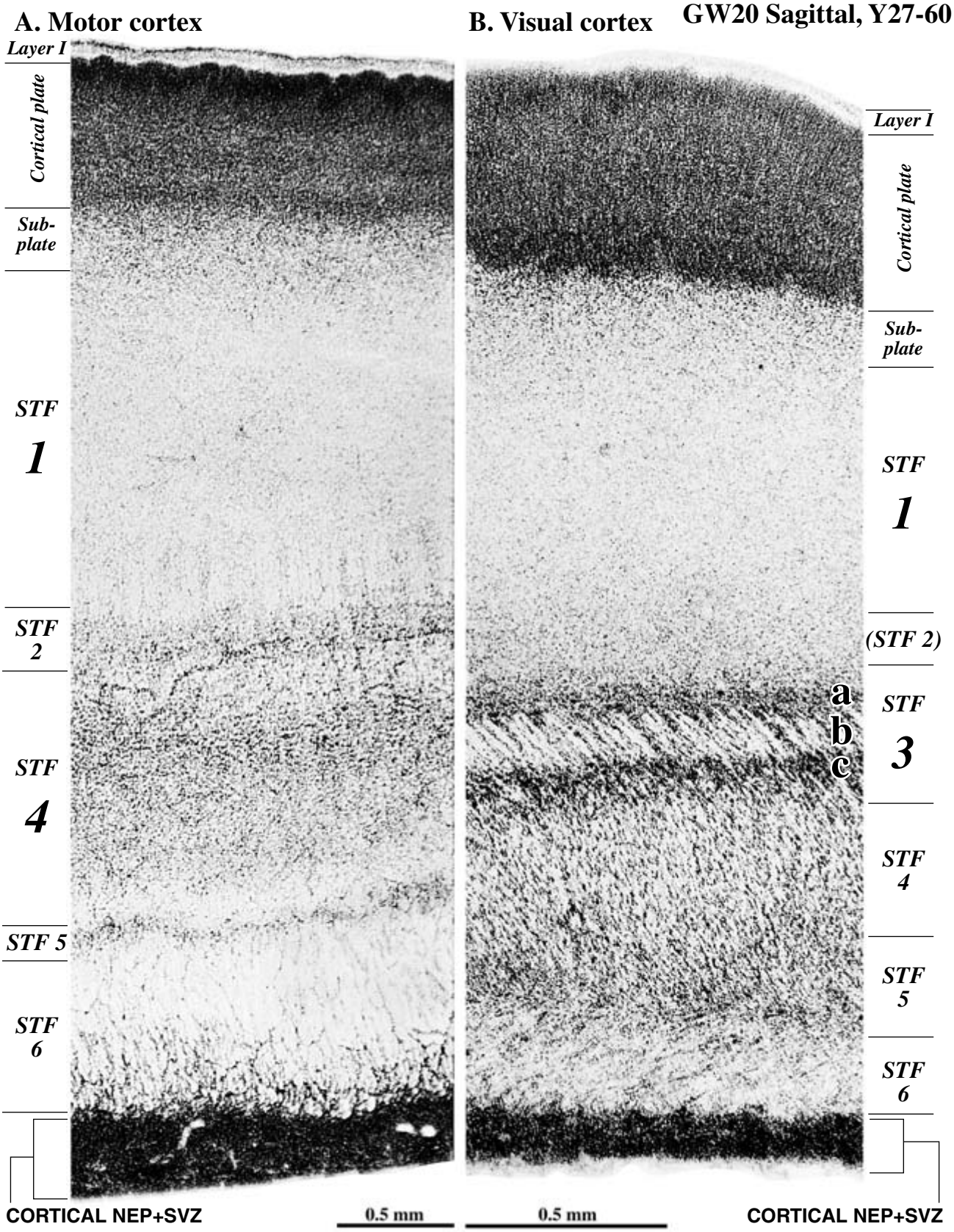

Figure 35. Regional differences in STF organization in the motor cortex (**A**) and the visual cortex (**B**) in a GW20 fetus (specimen #5, Volume 4, Bayer and Altman, 2005). Note the thickness of STF4 in the developing motor cortex and the complex organization of STF3, with the honeycomb matrix, in the developing visual cortex. Sagittal sections. (Note the scale differences between A and B; the motor cortex is much thicker than the visual cortex at this stage.)

Like the developing cerebral cortex, the developing cerebellar cortex has transitional fields and sojourn zones. In contrast to the cerebellar NEP of the rat, which has only two divisions, C1 and C2 (**Figure 36A**), the primordia of the medial vermis and a single ("intermediate") hemisphere, the human cerebellar NEP also has a true "lateral" or neocerebellar division, identified as C3 (**Figure 36B**). Surrounding these three NEP divisions are complex migratory and sojourn zones, the cerebellar transitional field (CTF). As seen in a GW6.5 embryo (**Figure 37**), CTF1 is a superficial fibrous layer, CTF2 consists mostly of tangentially migrating early generated neurons, CTF3 is an inner fibrous layer, and CTF4-5 consists mostly of radially-migrating and sojourning younger neurons that have recently left the cerebellar NEP. On the basis of neurogenetic dating studies in the rat, we identify the first wave of cells in CTF2 as the early-generated deep nuclear neurons which form the nuclear transition zone or NTZ (Altman and Bayer, 1997). The human NTZ has three components, the presumed migrating and sojourning neurons of the future fastigial nucleus (NTZ1), interpositus nucleus (NTZ2), and the late-developing, and as yet small, dentate nucleus (NTZ3).

The cerebellar NEP may begin to form as early as GW4.0 (**Figure 20B**) and it is clearly recognizable as a distinct entity by GW5.0 (**Figure 21A**). By GW5.5, the cerebellar NEP has two components, the vermal C1 and intermediate C2 posteriorly (**Figure 38A**, *top*), and an additional division, the lateral C3, anteriorly (**Figure 38A**, *bottom*). The cells of NTZ1 and NTZ2 that uniformly abut C1 and C2 posteriorly are presumed to be young neurons that have recently radially migrated a short distance from the NEP matrices. The presumably earlier generated neurons situated superficially in the NTZ of the anterior cerebellum appear to migrate tangentially toward the midline. In older embryos—GW6.5 (**Figure 38B**), GW7.0 (**Figure 38C**) and GW7.5 (**Figure 38D**)—the tangentially migrating cells of the NTZ (particularly those of NTZ1 in the anterior cerebellum) begin to form a growing superficial mass of cells, which we identify as the sojourning neurons of the fastigial nucleus. As the vermis fuses in the GW8.5 embryo (**Figure 38E**), the axons of these neurons cross the midline to form the hook bundle. As the cells of the cerebellar NTZ migrate tangentially, new waves of radially migrating cells (CFT4+5) appear to leave the cerebellar NEP in the GW 6.5 and GW7.0 embryos (**Figure 38B, C**). These may be straggling deep neurons and/or the earliest complement of Purkinje cells. The radial migration of the bulk of Purkinje cells appears to reach its peak in the GW7.5 embryo when they form a crescent-shaped mass of densely packed and darkly staining cells outside the NEP both in the posterior cerebellum (**Figure 38D**, *top*) and the anterior cerebellum (**Figure 38D**, *bottom*). The packing density of these cells decreases in the GW8.5 (**Figure 38E**) and GW9 (**Figure 39A**) specimens, suggesting that the Purkinje cells begin to disperse as they ascend toward the surface. By GW11, the ascending Purkinje cells form a crescent-shaped mass superficially, and the dentate, interpositus and fastigial nuclei are now settling in the depth of the cerebellum (**Figure 39B**). We have suggested earlier that these elaborate migratory movements, and some others that we describe below, are part of a choreographed morphogenetic process responsible for the wiring of the complex circuitry of the maturing cerebellum (Altman and Bayer, 1997). The first step in this process, the upward migration of Purkinje cells, is associated with the spreading of a secondary germinal matrix, the external germinal layer, over the surface of the formative cerebellar cortex, as we describe below.

Secondary Germinal Matrices. Proliferative NEP cells in some regions of the CNS generate not only differentiating neurons but also fate-restricted neurogenic precursor cells that retain their proliferative potency after they have left the ventricular shoreline. These secondary matrices include the subventricular zone (SVZ) of the neocortex and the basal ganglia, the subgranular zone (SGZ) of the hippocampal dentate gyrus, and the external germinal layers (EGL) of the cerebellar cortex and cochlear nuclei. We proposed some time ago (Altman and Das, 1965b) that these secondary germinal matrices share two properties. First, they generate microneurons, neurons that develop locally arborizing short axons that form the fine (local) circuitry of specific brain regions. This is in contrast to the primary NEP matrix that generates macroneurons, a variety of large neurons that sprout long axons that interconnect distant brain regions and form the gross (global) circuitry of the CNS. Second, the microneurons of a particular brain region are generated after its macroneurons have been produced. This occurs in some brain regions during the late gestational period, in other regions postnatally during infancy, and in a few of them through adulthood. For instance, the subpial EGL of the cerebellum, which spins off a component of the dorsal rhombic lip (the germinal trigone) and spreads over the surface of the cerebellum, begins to produce its microneurons (granule, basket, and stellate cells) after the cerebellar NEP has generated its macroneurons, the deep neurons and the Purkinje cells (Altman and Bayer, 1997). The EGL begins to form in the human cerebellum between GW7.5 and GW8.5 (**Figure 38D, E**) and by GW11 it forms a subpial canopy over the entire formative cerebellar cortex (**Figure 39B**). Significantly, the EGL that persists in rats until about postnatal day 21, the age they are weaned (Altman and Bayer, 1997), is still present in human cerebellum through the second year of postnatal life (Raaf and Kernohan, 1944; our unpublished observations). The descent of cerebellar granule cells into the formative cerebellar cortex to form the internal granular layer, leaving behind their axons, the parallel fibers, in the molecular layer, begins after the ascending Purkinje cells have commenced to sprout dendrites. The outcome of these choreographed movements of macroneurons and microneurons, such as the ascent of

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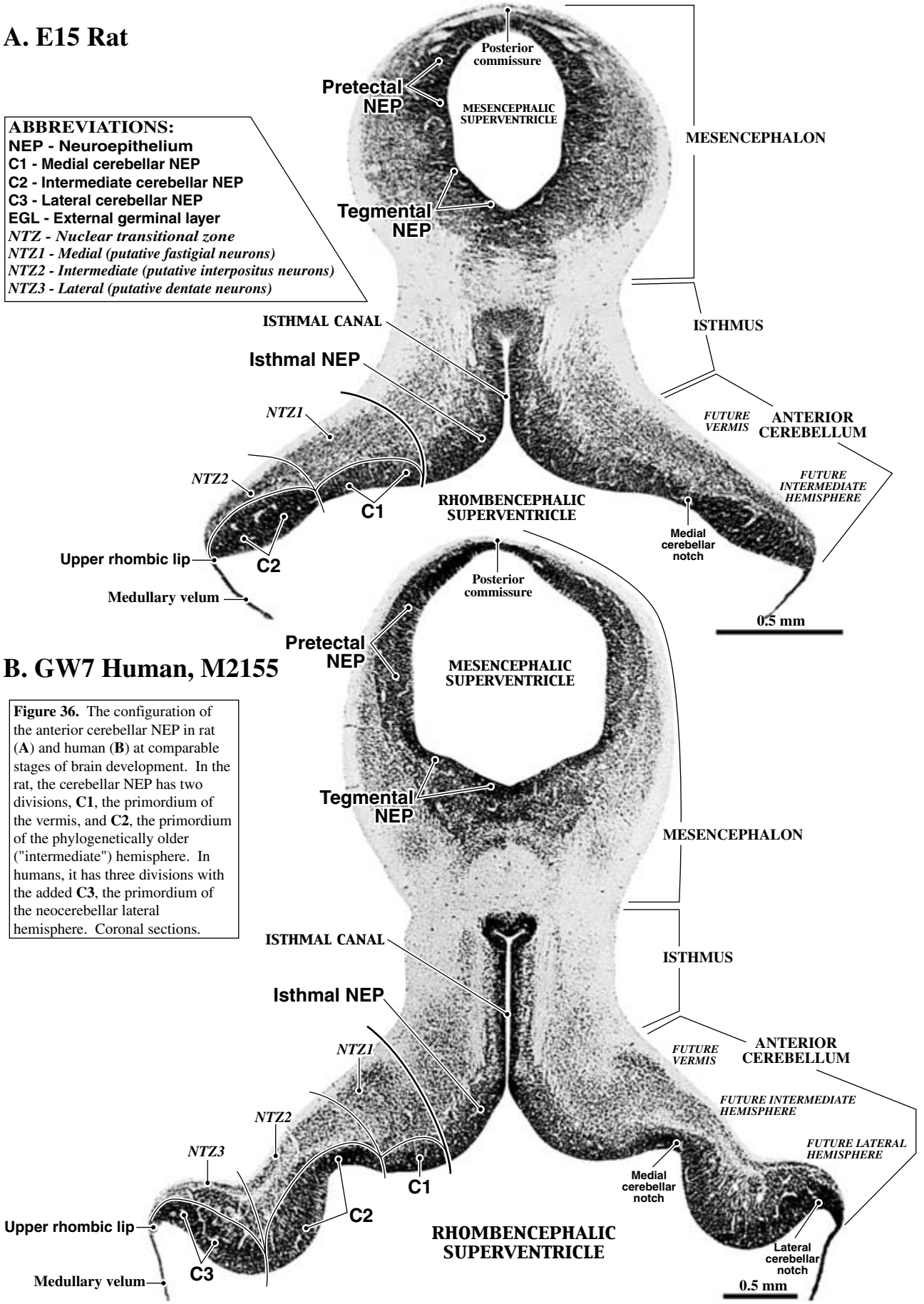


Figure 36. The configuration of the anterior cerebellar NEP in rat (**A**) and human (**B**) at comparable stages of brain development. In the rat, the cerebellar NEP has two divisions, **C1**, the primordium of the vermis, and **C2**, the primordium of the phylogenetically older ("intermediate") hemisphere. In humans, it has three divisions with the added **C3**, the primordium of the neocerebellar lateral hemisphere. Coronal sections.

GW6.5 Coronal, M2051, Anterior Cerebellum

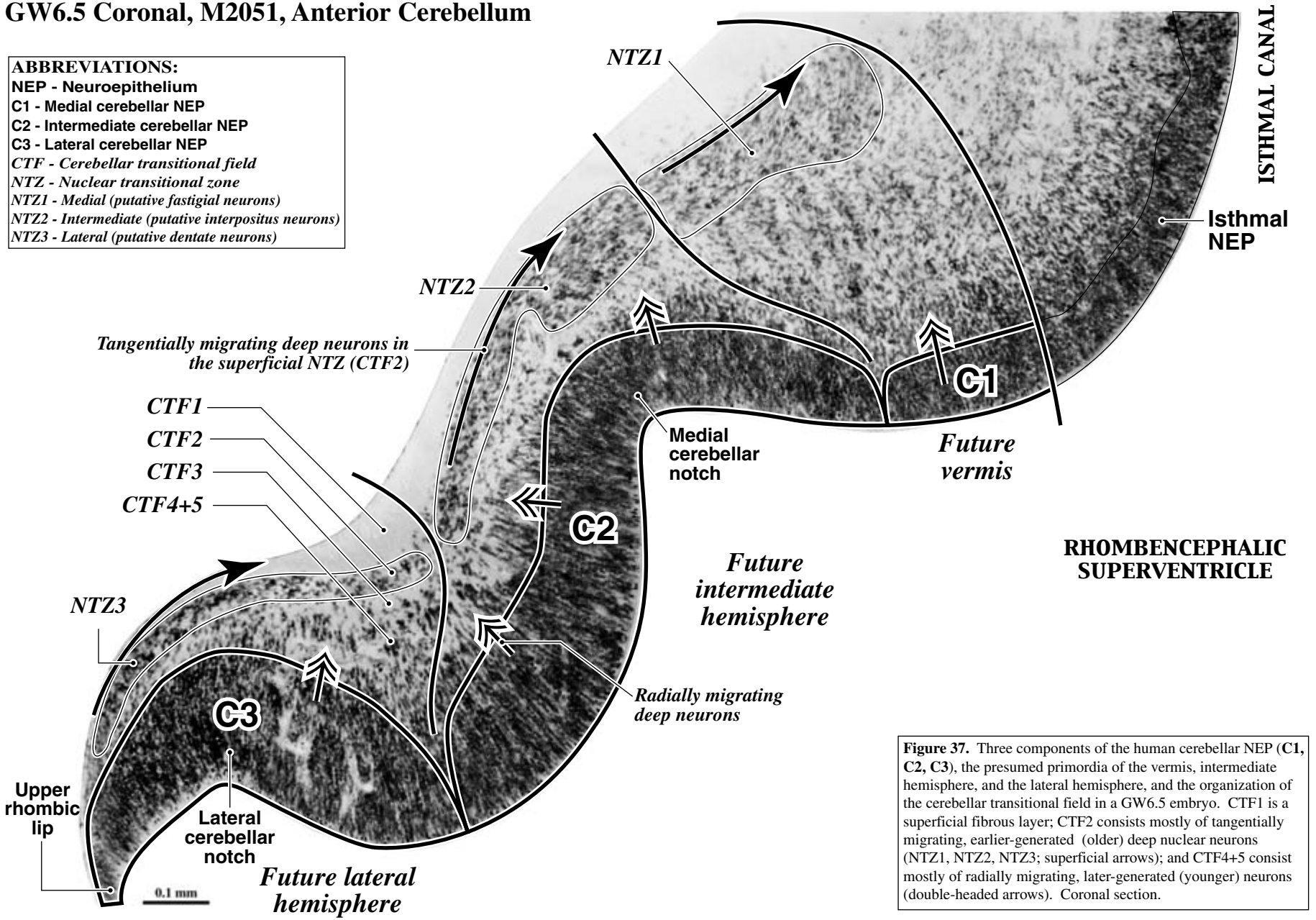


Figure 37. Three components of the human cerebellar NEP (**C1, C2, C3**), the presumed primordia of the vermis, intermediate hemisphere, and the lateral hemisphere, and the organization of the cerebellar transitional field in a GW6.5 embryo. CTF1 is a superficial fibrous layer; CTF2 consists mostly of tangentially migrating, earlier-generated (older) deep nuclear neurons (NTZ1, NTZ2, NTZ3; superficial arrows); and CTF4+5 consist mostly of radially migrating, later-generated (younger) neurons (double-headed arrows). Coronal section.

Figure 38A. GW5.5 Coronal, M2161

ABBREVIATIONS:
NEP - Neuroepithelium
C1 - Medial cerebellar NEP
C2 - Intermediate cerebellar NEP
C3 - Lateral cerebellar NEP
GEP - Glioepithelium
NTZ - Nuclear transitional zone
NTZ1 - Medial (putative fastigial neurons)
NTZ2 - Intermediate (putative interpositus neurons)
NTZ3 - Lateral (putative dentate neurons)

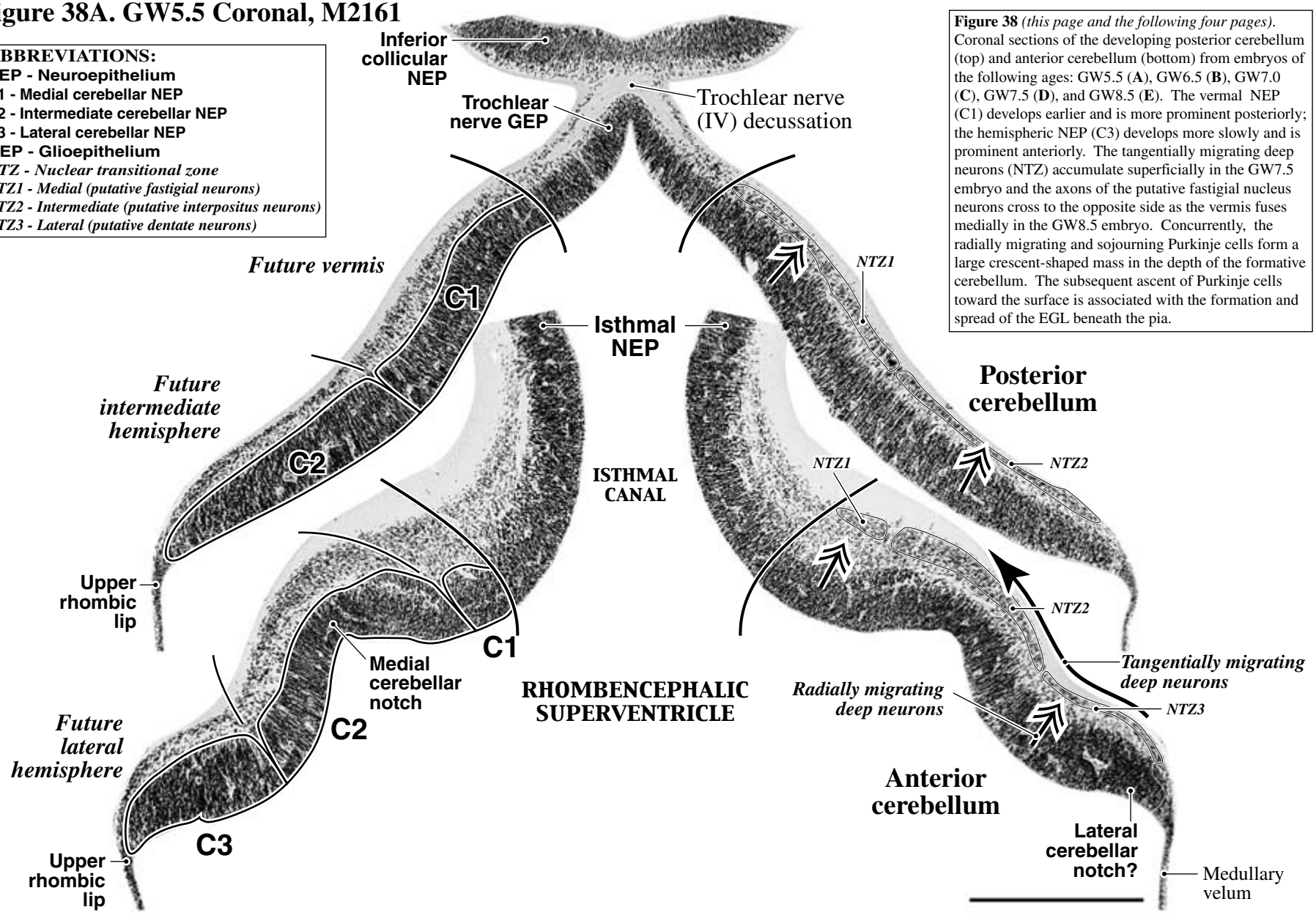


Figure 38 *(this page and the following four pages).* Coronal sections of the developing posterior cerebellum (top) and anterior cerebellum (bottom) from embryos of the following ages: GW5.5 (**A**), GW6.5 (**B**), GW7.0 (**C**), GW7.5 (**D**), and GW8.5 (**E**). The vermal NEP (C1) develops earlier and is more prominent posteriorly; the hemispheric NEP (C3) develops more slowly and is prominent anteriorly. The tangentially migrating deep neurons (NTZ) accumulate superficially in the GW7.5 embryo and the axons of the putative fastigial nucleus neurons cross to the opposite side as the vermis fuses medially in the GW8.5 embryo. Concurrently, the radially migrating and sojourning Purkinje cells form a large crescent-shaped mass in the depth of the formative cerebellum. The subsequent ascent of Purkinje cells toward the surface is associated with the formation and spread of the EGL beneath the pia.

Figure 38B. GW6.5 Coronal, M2051

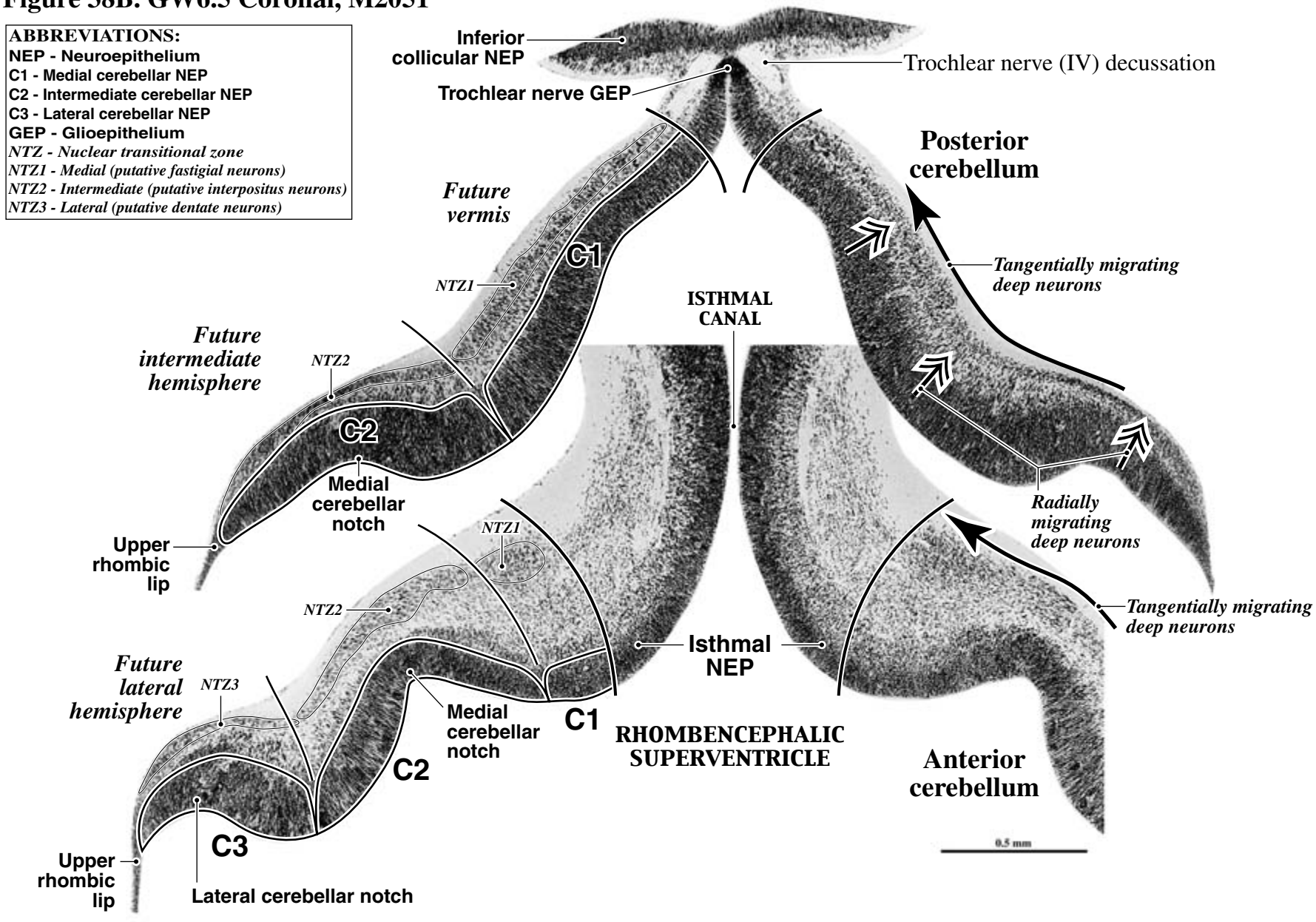


Figure 38C. GW7 Coronal, M2246

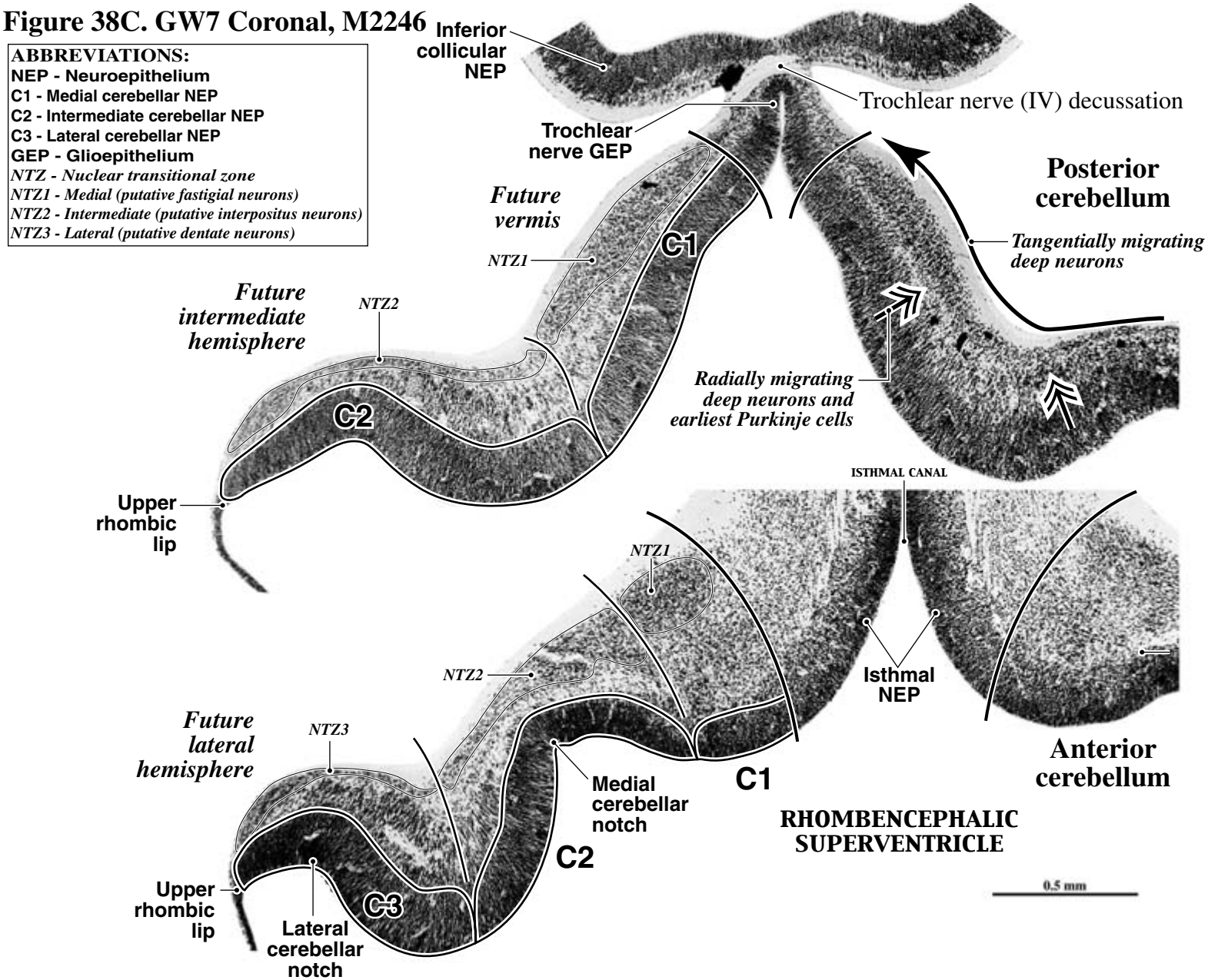


Figure 38D. GW7.5 Coronal, M2248

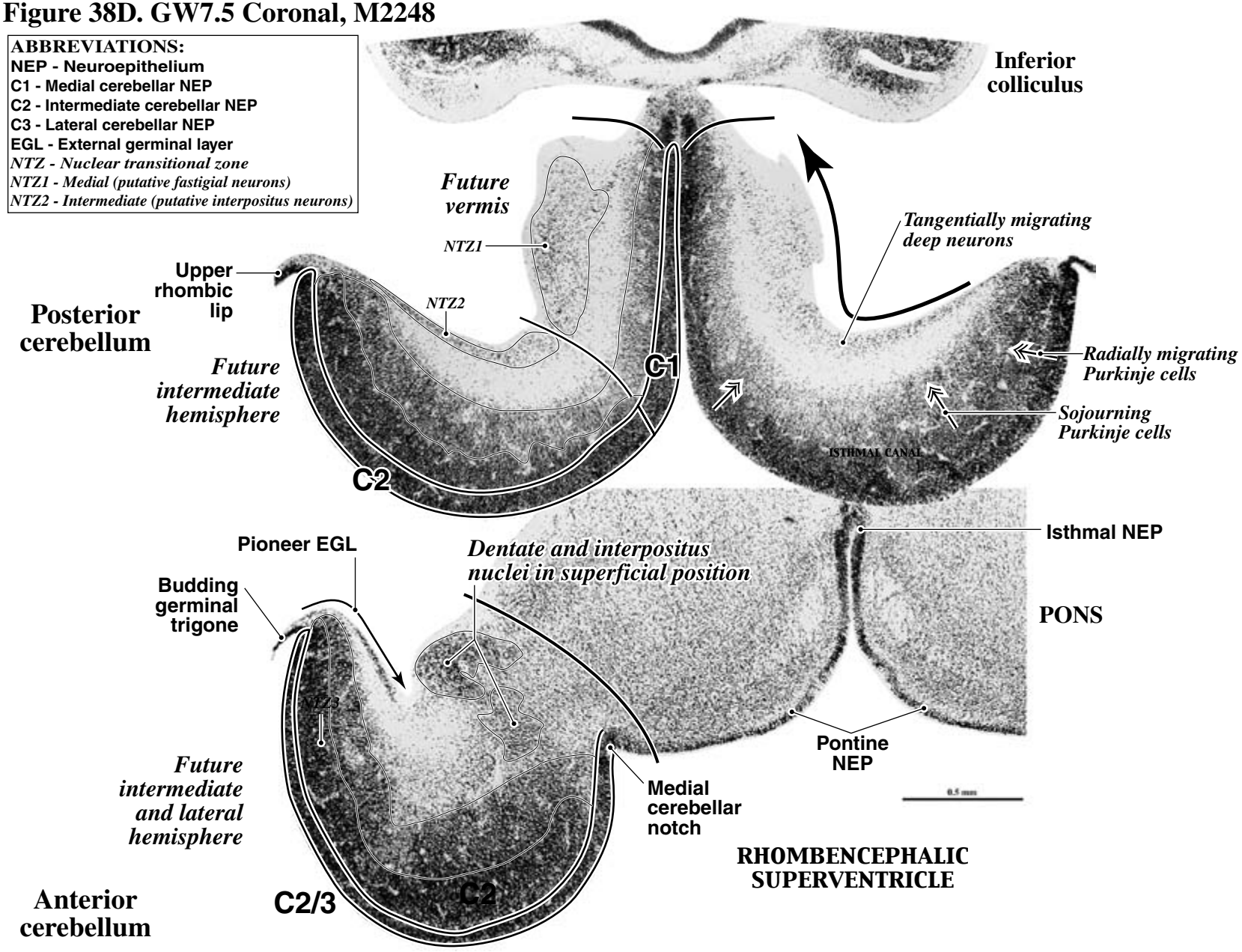
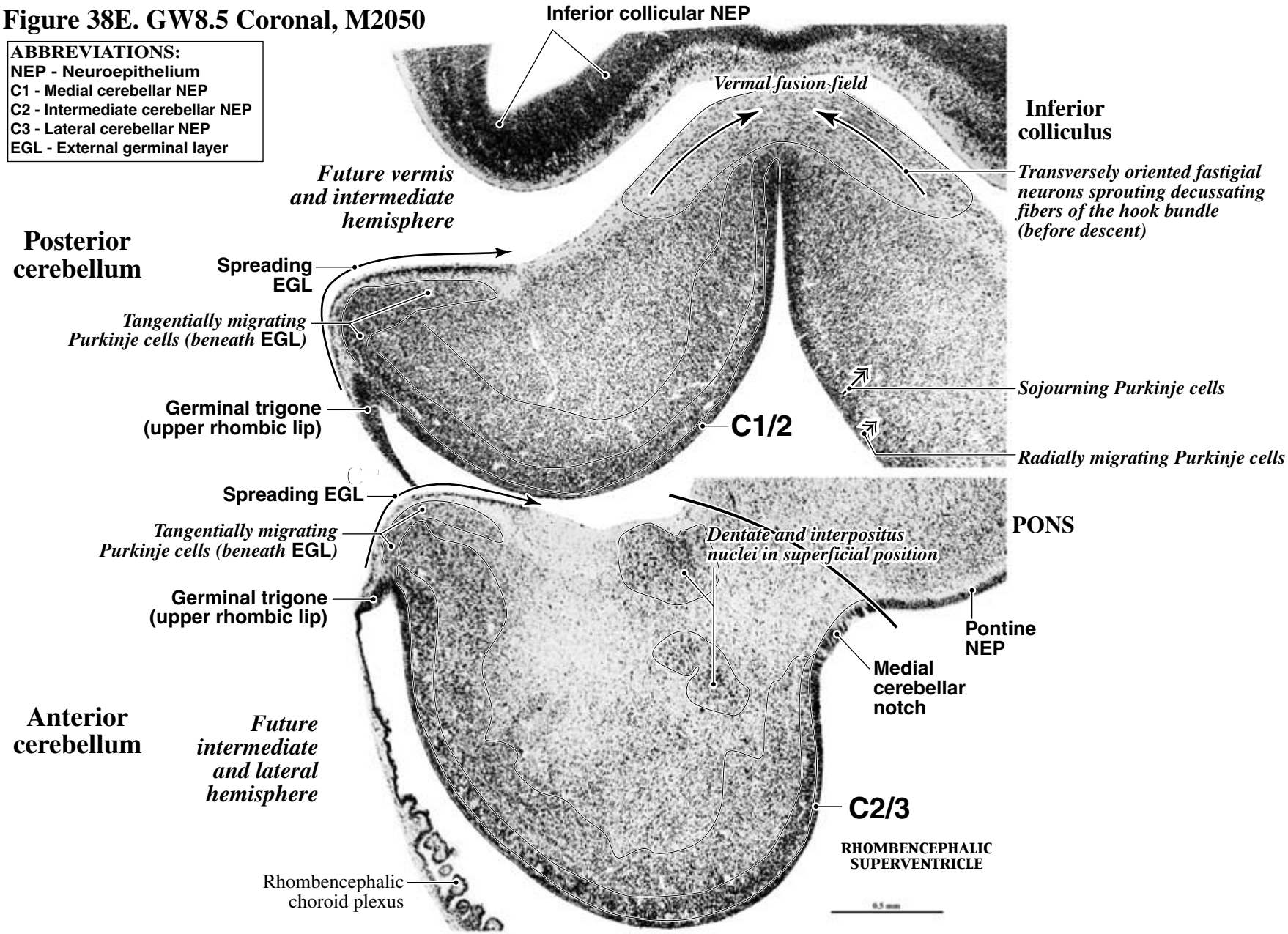
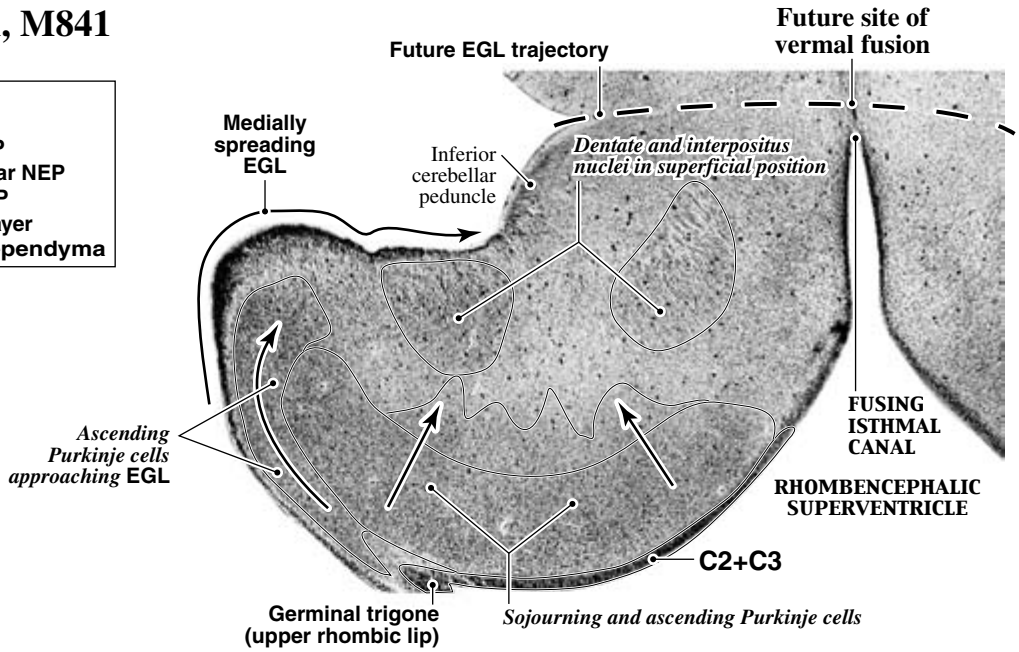


Figure 38E. GW8.5 Coronal, M2050



A. GW9 Coronal, M841

ABBREVIATIONS:
NEP - Neuroepithelium
C1 - Medial cerebellar NEP
C2 - Intermediate cerebellar NEP
C3 - Lateral cerebellar NEP
EGL - External germinal layer
G/EP - Glioepithelium/ependyma



B. GW11 Coronal, Y1-59

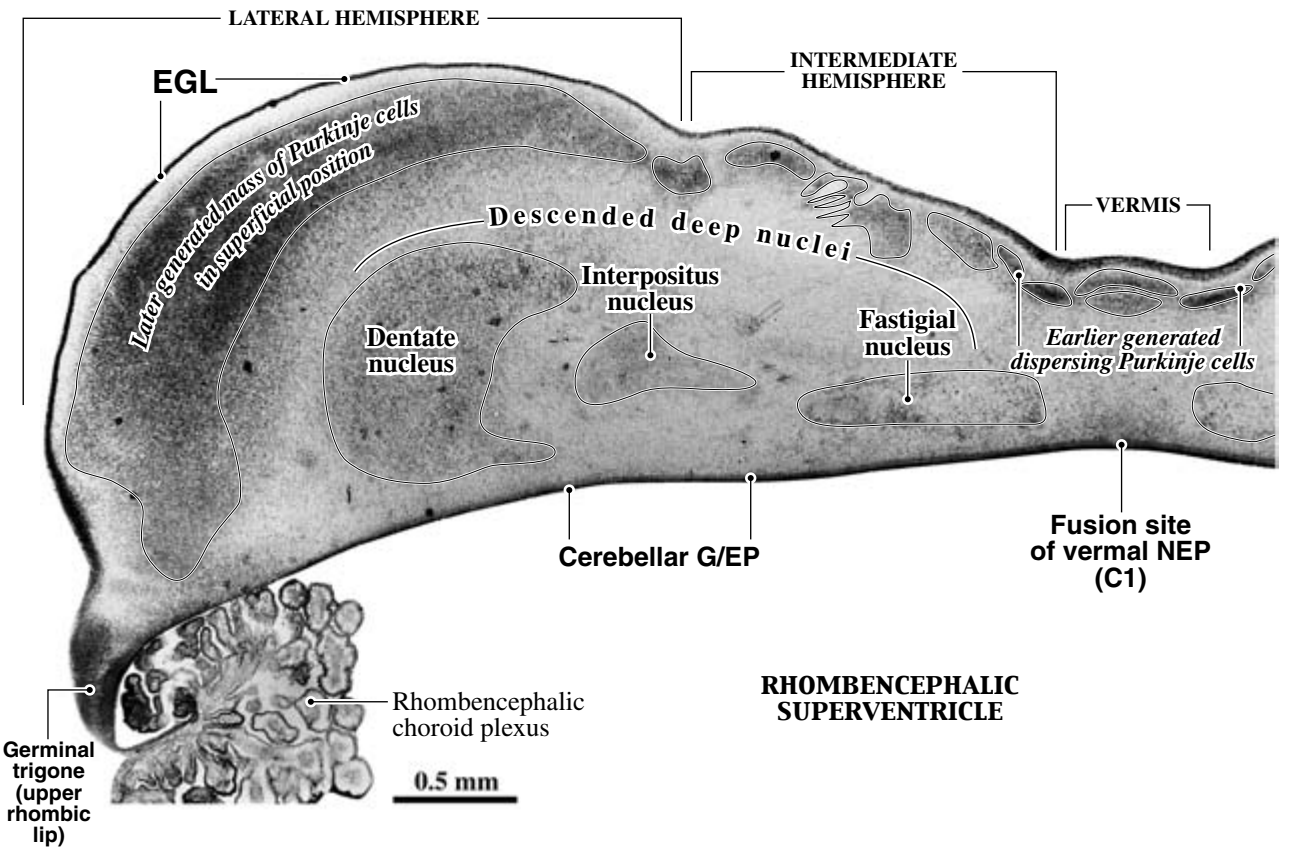


Figure 39. A. The ascent of Purkinje cells toward the surface in a GW9 embryo as, concurrently, the EGL begins to spread medially. **B.** The Purkinje cells are settling superficially beneath the canopy of EGL cells in this GW11 fetus, and the fastigial, interpositus, and dentate nuclei are assuming their final position in the depth of the vermis, and the intermediate and lateral hemispheres. Coronal sections.

Purkinje cells through the field of deep neurons, and the descent of granule cells through the Purkinje cell layer is that, by leaving behind their trailing axons, the stereotypic input-output circuitry of the cerebellum is established (Altman and Bayer, 1997).

The pattern of neurogenesis and migration of hippocampal macroneurons and microneurons is quite different than that of the cerebellum. As it was demonstrated in the rat, hippocampal macroneurons (the pyramidal cells of Ammon's horn) are produced early during fetal development (Bayer, 1980a, b). The dentate NEP produces an early set of perinatal microneurons (granule cells), while another set of progenitor cells forms the secondary germinal matrix of the subgranular zone (SGZ), which persists through adulthood (e.g., Altman and Bayer, 1975; Kempermann, 2006). It is now known, that the production of hippocampal granule cells through adulthood is not limited to lower mammals but is also a significant phenomenon in primates (e.g., Gould et al., 1999). In the human telencephalon, the hippocampal dentate NEP is present by GW9; but the dentate gyrus is not recognizable as a distinct entity until the second trimester (Volume 3 of this Atlas: Bayer and Altman, 2005). The time course of secondary matrix neurogenesis is again different in the cerebral cortex, a site where, according to experimental evidence in rodents, early- and late-generated neurons settle in an "inside-out" pattern in the gray matter (Angevine and Sidman, 1961). The lateral ventricles that are lined by NEP cells shrink considerably during the third trimester but, where present, an appreciable NEP/SVZ matrix is still present at the time of birth (Volume 2 of this Atlas: Bayer and Altman, 2004a). The SVZ that persists anteriorly through adulthood in animals has been shown to be a source of neurons that, migrating by way of the rostral migratory stream, supply neurons to the olfactory bulb not only in the rat (Altman, 1969) but also in monkeys (e.g., Pencea et al., 2001) and humans (Bedard and Parent, 2004). According to our interpretation of the experimental data obtained in rats, the early-generated layer VI and layer V cortical output neurons are progeny of the cortical NEP, and the later-generated granule cells that settle in the granular layer (IV) and other locally arborizing neurons that settle in the supragranular layers (III-II) are progeny of both the NEP and SVZ (Bayer and Altman, 1991a). Others have argued that the SVZ of the basal ganglia is the source of cortical interneurons (e.g., Anderson et al., 2002). It has been reported that the transcription factor *Tlx* is necessary for the full formation of the supragranular layers (Land and Monaghan, 2003). In the material available to us, we could not accurately date the emergence of the cortical SVZ because of the difficulty of distinguishing it from the NEP. However, as Kershman (1938) illustrated some time ago, the SVZ is prominent in the GW11 cerebral cortex (**Figure 40**). The basal ganglionic SVZ may begin to form as early as GW7.5-GW8 (**Figure 16H, I**), and both the cortical and the striatal SVZ persist as prominent germinal zones in newborns (Volume 2: Bayer and Altman, 2004a). The formation of the internal capsule as early as GW8 (**Figure 31B**) may initially contain only thalamocortical fibers. The outflow of corticofugal efferents and the formation of the cerebral peduncle between GW10 and GW13.5 (**Figure 33A, B**) suggests that the cortical output

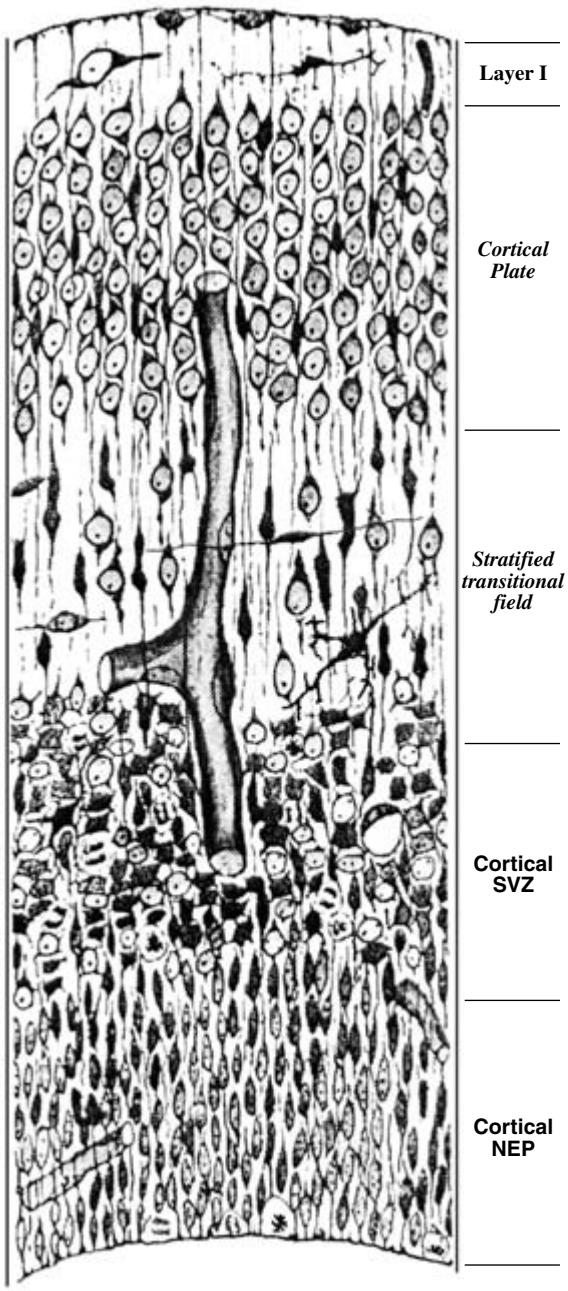


Figure 40. Kershman's (1938) illustration of the developing cerebral cortex in a GW11 human fetus, showing the cytological difference between the neuroepithelium (NEP) adjacent to the ventricle and the subventricular zone (SVZ). The spindle-shaped (pseudostratified) NEP cells are oriented at a right angle to the ventricular lining and they undergo mitotic division near the lumen. The variably shaped SVZ cells undergo mitosis within this secondary germinal matrix. Labeling modified.

neurons are probably generated before the cortical SVZ is forming or becomes prominent. Indeed, the cortical plate that forms between GW8.0 and GW8.5 (**Figure 32C, D**) may contain the earliest layer VI corticofugal neurons generated by the primary NEP and the generation of layer V neurons may follow soon thereafter.

Gliogenesis and Fate-Restricted Glioepithelia. Within a given brain region, neurogenesis and gliogenesis are generally sequential processes, and the generation of certain types of neuroglia, like astrocytes, antedates the production of oligodendrocytes that myelinate axons. As we have documented in the rat with ^{3}H-thymidine autoradiography, there are many CNS sites where germinal matrices with proliferating cells persist for some time after the cessation of neurogenesis (e.g., Bayer and Altman, 1991). We called these transformed germinal matrices glioepithelia (GEPs). These proliferating cells leave the GEP, become dispersed through the parenchyma, and generate fate-restricted neuroglial precursors that multiply through adulthood (Altman, 1966). We have also found that at sites where the enduring ventricle will be lined with specialized ependymal cells, the administration of ^{3}H-thymidine at a late phase of fetal or early prenatal development tags ependymal cells that remain labeled in adults; we call these germinal sites glioepithelial/ependymal matrices (G/EPs). Finally, cytological observations in the human CNS, in particular in myelin-stained sections of the spinal cord, have established that myelination gliosis (the high rate of glial cell proliferation preceding the myelination of particular fiber tracts) is a late developmental phenomenon (Altman and Bayer, 2001; Volume 1 of this Atlas: Bayer and Altman, 2002). Lineage studies have confirmed that NEP cells can generate both neurons and glia, although it remains unclear whether it is the same line of proliferative cells that first gives rise to neurons and then to neuroglia or that there are two separate lines that are sequentially activated by external signals (Luskin et al., 1988, 1993; Walsh and Cepko, 1992; Williams and Price, 1995). The report that cultured cortical progenitor cells generate neurons when plated with cortical tissue from young embryos but produce neuroglia when plated with cortical tissue from adults (Morrow et al., 2001) supports the idea that extracellular influences can modify NEP cell fate. The gene, *Brg1*, has been implicated in the switch from neurogenic to gliogenic cell production, and proteins, such as *Sox1* and *Pax1*, implicated in the maintenance of neurogenic potential are drastically reduced in *Brg1* mutant mice (Matsumoto et al., 2006).

In addition to the NEP-derived, late-generated glial progenitors, there are specialized germinal matrices that from the outset of CNS development are destined to produce only neuroglia. Prominent among these are perifascicular GEP matrices associated with early forming large fiber tracts, such as the fornical GEP. Moreover, we can also distinguish at the latter site a germinal matrix that generates the specialized cells of the choroid plexus (Altman and Bayer, 1990a). Finally, we present suggestive evidence that, as in the rat brain (Van Hartesveldt et al., 1986), so also in the human CNS, there are specialized types of glia present at certain sites, we call them morphocytes, that play a formative role in the structural transformations of the developing CNS. For instance, in the midline of the spinal cord, morphocytes of the roof plate and the floor plate are responsible for the development of the H-shape configuration of the gray matter (Altman and Bayer, 2001), and in the hindbrain morphocytes seem to act as guy wires to produce and maintain the structural stability of the medullary, pontine, mesencephalic, and diencephalic flexures (Volume 4 of the Atlas and the present volume). Nestin expression has been associated with the midline raphe glial structure in the early human fetus (Takano and Becker, 1997).

H. Centro-Central Signaling and the Morphogenetic Maturation of the CNS

Centro-Central Induction and Signaling. From the perspective of its input-output organization, the vertebrate CNS has two principal components: (i) *first-order* structures that are in direct contact with peripheral sense organs, skeletal muscles, smooth muscles, and glands; and (ii) *higher-order* structures that are directly (synaptically) connected with one another but only indirectly (by way of the first-order structures) with the periphery. Examples of first-order sensory CNS structures are the dorsal horn in the spinal cord, which receives input from the trunk, limb, and neck sensors by way of spinal afferents; the trigeminal nuclei that receive sensory input from the face and mouth by way of trigeminal afferents; and the olfactory bulb that receives direct peripheral input from the olfactory epithelium. Examples of first-order CNS effector structures are the motor nuclei of the ventral horn and the cranial motor nuclei that directly innervate skeletal muscles, and the secretory neurons of the hypothalamus and preoptic area that produce releasing factors that, conveyed to the pituitary gland, control the visceral system. In contrast, the bulk of second- and higher-order CNS structures that relay and process sensory information and issue motor commands have no direct access to the periphery. Examples of intercalated somatosensory structures are the dorsal column nuclei in the medulla, the relay nuclei of the thalamus, the postcentral projection area in the cerebral cortex, and several cortical association areas involved in higher-order somatosensory information processing. From the perspective of morphogenetic regulation, the coordinated development of first-order CNS structures requires, as described earlier, reciprocal periphero-central induction and signaling, whereas the coordinated development of higher-order CNS structures requires centro-central signaling between components of a system that become interconnected during development. It is reasonable to assume that the induction and signaling mechanisms responsible for synchronizing the development of PNS and CNS structures, and those

responsible for interconnecting CNS structures with one another are different.

The higher-order components of the CNS are interconnected with one another by way of long-distance nerve trunks, regional neural networks, and local circuits. The establishment of modality-specific and topographically organized projection systems—such as the selective and reciprocal interconnections between subdivisions of a particular sensory relay nucleus of the thalamus with a particular area of the neocortex—is dependent on the guided pathfinding of the growing axons of projection neurons that have to navigate over long distances to find their exact target. This requires centro-central signaling between source and target structures, as well as guideposts or beacons along a tortuous path. The regional ramification of the axons of interneurons, the spread and geometric configuration of their dendritic arbors, etc. must likewise be coordinated by reciprocal centro-central signaling among neighboring structures. It may be expected that the signaling mechanisms responsible for long-distance central interconnections, which establish the gross circuitry of the CNS, and the signaling mechanisms responsible for short-distance interconnections, which produce the fine circuitry of a local brain region, are also different. Centro-central signaling between interconnected brain structures may involve parallel (synchronous) development, serial (hierarchical) development, or a combination of both. For example, the early development of lower-level components of the system (input-output structures) may trigger the later development of its higher level components (processing structures). In the human CNS, at least some of the long-range sensory connections are established by the late first trimester, and to some extent concurrently, at different levels within a system. An example is the early maturation of the medial lemniscal system in the somatosensory pathway and the relatively early maturation of the ventral thalamic nuclear complex (Volume 4 of this Atlas: Bayer and Altman, 2006). However, the establishment of the fine circuitry of CNS structures, through the interdigitation of macroneurons and microneurons, is a lengthy process that extends beyond the second and third trimesters and continues through the prenatal period of brain development. Relatively little is known about the mechanisms of centro-central signaling except for axonal pathfinding.

The Guidance of Axonal Pathfinding. The growing axons of the medial lemniscus exemplify pathfinding to a distant target. Originating in the dorsal column nuclei, these axons cross to the opposite side in the medulla (the arcuate decussation) and, bypassing various intermediate structures in the pons, isthmus, and the midbrain tegmentum, terminate in the somatosensory thalamus. Another example is the corticospinal tract whose axons, originating in the cerebral cortex, penetrate the corona radiata, move through the striatum, join the internal capsule, pass through the cerebral peduncle of the midbrain, penetrate and move through the pontine gray and, upon reaching the medulla, most of them cross to the opposite side and descend in the spinal cord. We have described earlier the developmental timetable of the latter process in the human CNS (Altman and Bayer, 2001). Modern research indicates that the directed growth of pioneer axons toward distant targets depends on molecular guidance agents along their route, cues that are detected by receptor elements within the axon's growth cones (Tessier-Lavigne and Goodman, 1996). These cues, acting as chemorepellants or chemoattractants, may adhere to or emanate from specific brain structures along the axon's path, and in that way, the growing axon can use a trial-and-error method to locate its target. Specifically, the growth cone tips that encounter repellants withdraw or collapse, and those that encounter attractants expand. Among recognized repellant cues are the semaphorins that, interacting with the growth cone receptors (plexins and neuropilins) of advancing axons, cause the depolymerization of microtubules and F-actin in the growth cones that leads to their collapse (Fan et al., 1993; He et al., 1997; Fujisawa and Kitsukawa, 1998; Pasterkamp and Kolodkin, 2003). Netrin-1 (Métin et al., 1997; Richards et al., 1997; Finger et al., 2002) and semaphorins (Polleux et al., 1998) are among the putative chemoattractants implicated in the directed growth of corticofugal axons. Netrin-1 may also be involved in the guided growth of thalamocortical fibers (Braistead et al., 2000) and in the normal development of the circuitry of the hippocampus (Barralobre et al., 2000). In some brain regions, netrin-1 signaling is required for commissural fibers to cross to the opposite side (Serafini et al., 1996); in the medulla, netrin-1 is secreted by the floor plate and its absence in homozygous mutant mice results in the failure of medial lemniscal fibers to cross to the opposite side and turn to ascend rostrally (Kubota et al., 2004).

Still another example of directed, long-distance axonal pathfinding is the guidance of the pioneering fibers of the ascending thalamocortical afferents. The internal capsule that contains the bulk of the thalamocortical fibers, is still absent in the developing human brain on GW7.5 (**Figure 31F**), and the cortical plate has yet to form. By GW8 thalamocortical fibers enter the expanding internal capsule (**Figure 31G**), which establishes a bridge between the diencephalon and the cortex, and a thin cortical plate begins to form dorsolaterally. By GW10, there is a massive outflow of afferents from the thalamus through the expanded internal capsule and, in addition to the thickening cortical plate, the different layers of the STF are beginning to form (**Figure 33A**). By GW11, we can track the different trajectories of thalamocortical fibers to some areas of the cerebral cortex; in particular, the visual radiation from the lateral geniculate nucleus, which makes a 180° turn (Meyer's loop) around the caudate nucleus, proceeds caudally, and terminates in the occipital lobe (Volume 4 of this Atlas: Bayer and Altman, 2006). According to one hypothesis there are intrinsic regional differences in the proliferative

matrix of the cerebral cortex that will become the target of different afferent fibers and these regional differences are the foundation of areal specification (Rakic, 1988). We have demonstrated anterior-to-posterior (longitudinal) and lateral-to-dorsomedial (transverse) neurogenetic gradients in the rat cerebral cortex (Bayer and Altman, 1991), and suggested that these NEP maturation gradients may control not only the modality-specific selectivity of thalamocortical innervation but also the lateral-to-medial order in the ingrowth of thalamic afferents, as demonstrated in the mouse (Caviness and Frost, 1980). One set of studies has implicated *Tbr1*, *Gbx2*, and *Pax6* in the initial outgrowth of thalamic fibers to the cortex and in the guidance of their long-range trajectory (Hevner et al., 2002; Molnár et al., 2003). Another series of investigations implicates *Emx1*, *Emx2, Pax6, Gsh2, COUP-TFI,* and *Fgf8*, which are expressed in dissimilar dorsal-to-ventral and anterior-to-posterior gradients in the developing cerebral cortex (Gulisano et al., 1996; Liu et al., 2000; Stoykova et al., 2000; Yun et al., 2001; Torreson et al., 2000; Muzio et al., 2002; Bishop et al., 2003; Garel et al., 2003). These studies have not yet taken into consideration our evidence that rather than proceeding directly to the cortical plate, the sojourning cells of the STF are an intermediary target of thalamocortical afferents, and that there are pronounced regional differences in STF lamination patterns (Altman and Bayer, 2002; Volume 3 of this Atlas: Bayer and Altman, 2005).

Once thalamocortical modality-specific projection has been established, the formation of topographic maps and the termination of arborizing axons in layer IV are probably controlled by different signaling agents than those guiding the initial growth of thalamic afferents. Among these signaling molecules are reelin secreted by the early generated Cajal-Retzius cells of the primordial plexiform layer, already discussed in the context of cell migration, and ephrins and their receptors (Castellani et al., 1998; Vanderhaeghen et al., 2000; Dufour et al., 2003; Bolz et al., 2004). One experiment compared the growth of thalamic axons toward cultured membranes from cortical layer IV to that of membranes from cortical layer V, a stratum that the thalamocortical fibers bypass on their way to layer IV. The thalamic axons exhibited arrested growth and increased branching density on their appropriate target tissues but interference with ephrin expression abolished this preferential termination pattern (Mann et al., 2002). Still other studies implicated N-cadherin (Huntley and Benson, 1999; Poskanzer et al., 2003) and *Slit2* (Ozdinler and Erzurumlu, 2002) in the laminar termination of thalamocortical fibers in the cortex. N-cadherin (Riehl et al, 1997) and ephrins also appear to serve as guidance cues in the growth of retinal fibers (Birgbauer et al., 2001). According to a recent study (Lambot et al., 2005), there are differences in the gradients of ephrin expression in the developing visual system of animals with lateral eyes, in which most (or all) retinal axons cross to the opposite side in the optic chiasma, with ephrin expression in the developing visual system of humans with medial eyes, where only the nasal half of the retina projects contralaterally but the temporal half projects ipsilaterally.

I. Summary: The Epochs, Phases, and Mechanisms of CNS Development

The reviewed descriptive and experimental evidence suggests that the prenatal development of the CNS consists of successive *epochs*, each with multiple *phases*, that are guided by different morphogenetic mechanisms. The first epoch (**Figure 41**) consists of several phases. The initial phase, which is not dealt with in this Atlas, is the formation of the neural plate, containing pluripotent progenitor cells that give rise to the neural elements of the CNS and PNS as well as some non-neural tissue and organs. The next phase is the fusion of the central component of the neural plate, which results in the formation of the neural tube (the future spinal cord) along the trunk caudally, and the cephalic vesicles (the future brain) in the head region rostrally (**Figure 22**). This is followed by the proliferation of stockbuilding NEP cells in association with the earliest specification of their future diversity through reciprocal periphero-central transactions with the primordial components of the developing body, including the neural crest, somites, and notochord caudally, and the preplacodes rostrally. That early diversification becomes manifest in the future spinal cord as the tubular NEP is partitioned into sensory and motor compartments. This occurs under the peripheral inductive and signaling influence of the neural crest and somites, on the one hand, and the notochord, on the other. The diversification of the stockbuilding NEP cells in the different divisions of the future brain is under a different set of peripheral influences. Rostrally, the stockbuilding prosencephalic NEP expands greatly in association with the ballooning of the prosencephalic superventricle, and it is under the reciprocal influence of the cephalic (olfactory, optic, and pituitary) preplacodes. Caudally, the diversifying rhombomere NEPs, which grow in association with the expansion of the rhombencephalic superventricle, interact with the branchial (orofacial, octaval, and visceral) preplacodes, and arches I, II, III, and IV with which they are associated.

The second epoch of CNS development, likewise, consists of several phases, and these phases differ caudally in the developing spinal cord and rostrally in the developing brain (**Figure 42**). In the developing spinal cord, several periphero-central morphogenetic events take place concurrently. (i) The skin senses of the trunk, limbs, and neck, and (ii) the bipolar neurons of the spinal dorsal root ganglia differentiate peripherally. The latter (iii) interconnect the sense organs with the sensory-relay neurons in the dorsal horn and dorsal column nuclei centrally. At about the same time, (iv) the various peripheral muscles of the trunk, limb and neck conjointly differentiate with (v) the motor neurons that innervate them, which form distinct columns in

the ventral horn centrally. In the developing brain, the different components of the ventral telencephalon and diencephalon (forebrain) interact with the diversifying cephalic placodes, and different components of the rhombencephalon (hindbrain) do the same with the diversifying branchial placodes. In the developing forebrain, aided by reciprocal periphero-central induction and signaling, (i) the neurons in the olfactory epithelium, the progeny of the olfactory placode, differentiate conjointly with the neurons in the olfactory bulb. (ii) The cells in the crystalline lens of the eye, derived from the lens placode, differentiate conjointly with the neurons in the retina and cells in the pigment epithelium. (iii) The secretory cells in the adenohypophysis, derived from the pituitary placode, differentiate conjointly with the neurosecretory cells in the hypothalamus and pituicytes in the neurohypophysis. In the developing hindbrain, (iv) the peripheral neurons in the orofacial (trigeminal and facial) ganglia, derived from branchial placodes, conjointly differentiate with central neurons derived from R2 and R3. (v) The peripheral neurons in the vestibulocochlear ganglion, derived from the otic vesicle, conjointly differentiate with the central neurons derived from R4 and R5. (vi) The glossopharyngeal and vagal ganglia, derived from branchial placodes, conjointly differentiate with the central glossopharyngeal and vagal neurons derived from R6 and R7.

In sharp contrast to these forebrain and hindbrain regions that have direct peripheral connections, many brain regions are devoid of surrounding placodes such as the cerebral cortex, basal ganglia, thalamus, tectum, and cerebellum. In the absence of direct contact with the developing peripheral sense organs, muscles, and other effectors, the coordinated development of these brain structures is dependent on endogenous mechanisms and centro-central induction and signaling. One facet of this process, as we described earlier, is the directed growth of axons that interconnect different brain structures and produce the brain's gross and fine circuitry. Another is the migratory movement of young neurons that contact one another in passing and leave behind trailing axons, much like a spider building its web. This phenomenon is exemplified by the choreographed movements of sequentially generated cerebellar neurons, as deduced from experimental studies in the rat. The first phase of cerebellar development is the formation and expansion of the stockbuilding cerebellar NEP (**Figure 43A**). The second phase is the radial migration of the earliest set of differentiating neurons, the future deep nuclei, which form the first parenchymal cell layer abutting the NEP (**Figure 43B**). The third phase is the exodus of a new set of differentiating neurons from the cerebellar NEP, the Purkinje cells, which displace the layer of deep neurons outward (**Figure 43C**). The fourth phase is the tangential migration of deep neurons over the cerebellar surface (**Figure 43D**), a process coupled with the sprouting of axons that cross to the opposite side in the vermis. During the fifth phase, deep neurons and Purkinje cells exchange places. Deep neurons migrate downward, while Purkinje cells migrate upward (**Figure 43E**). That establishes the mature pattern (**Figure 43F**) where the Purkinje neurons form a superficial cortical layer and the deep nuclear neurons settle in the core of the cerebellum. This important event occurs conjointly with the formation of a new neurogenic proliferative matrix, the EGL, which spreads superficially to form a subpial canopy over the expanding cerebellum (**Figure 43E, F**). Perhaps due to some dual attractant/repellant force exerted by the EGL, the sojourning Purkinje cells ascend to the surface and the deep neurons descend. We hypothesized earlier (Altman and Bayer, 1997) that cohorts of deep neurons and Purkinje cells make enduring contacts with each other while they become intermingled for a period and then pass each other. The deep neurons, which already have extracerebellar inputs and are sprouting cerebellofugal efferents, descend together with the trailing axons of Purkinje cells attached. The ascending Purkinje cells carry with them branches of some extracerebellar afferents (climbing fibers) that also contact the deep neurons. As the superficially situated masses of Purkinje cells disperse beneath the canopy of the EGL to form a monolayer (**Figure 43G**), the subsequent phases of cerebellar development begin to unfold leading to formation of the fine circuitry of the cerebellar cortex. One facet of this is the descending migration of granule cells from the EGL, through the molecular and Purkinje cell layers, and into the granular layer (*arrows*, **Figure 43G**). The descending granule cells leave their axons (the parallel fibers) behind in the molecular layer and establish contacts with growing Purkinje cell dendrites. Granule cell dendrites sprout in the granular layer to establish contact with the specialized endings of mossy fiber afferents. The major function of the elaborate choreographed movements of different cerebellar neurons, in conjunction with the directed growth of their axons and dendrites, is to produce the stereotyped complex circuitry of the cerebellar cortex.

J. A Note on the Functional Maturation of the Human CNS

The Functional Maturation of the CNS. The function of the CNS is to gather information about prevailing conditions and salient events in the external world in relation to the changing conditions and needs of the body interior, process and integrate that information, and initiate appropriate behavioral and physiological actions and reactions to them. Neither the proliferative progenitors of neurons nor the migrating and sojourning young neurons lacking axons and dendrites can mediate these functions. It is only after the settled neurons have begun to receive afferent input and establish synaptic connections with one another, and the fibers of motor neurons contact muscles, that the CNS can commence to perform its complex regulatory functions. The maturation of these functional CNS networks and circuits is a protracted process that commences during the early fetal period and continues through the late-fetal, neo-

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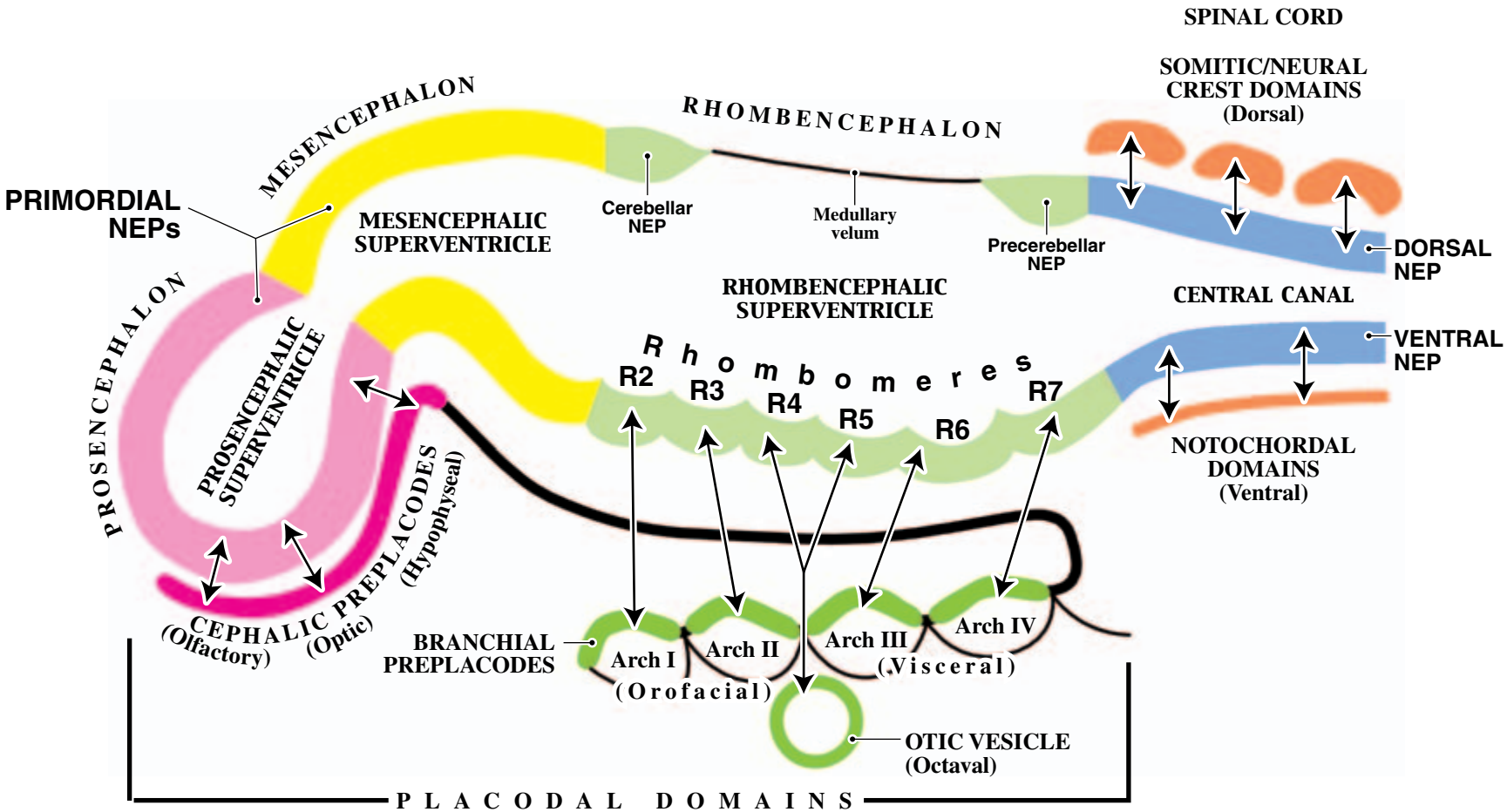


Figure 41. The first epoch of CNS development. Schematic illustration of the reciprocal periphero-central signaling potential between components of the peripheral cephalic preplacodes (*red*) and the ventral telencephalic NEP (*pink*); between components of the peripheral branchial placodes (*dark green*) and the rhombomeric NEP compartments (*light green*); and between the peripheral somites and notochord (*orange*) and the dorsal and ventral spinal NEPs (*blue*).

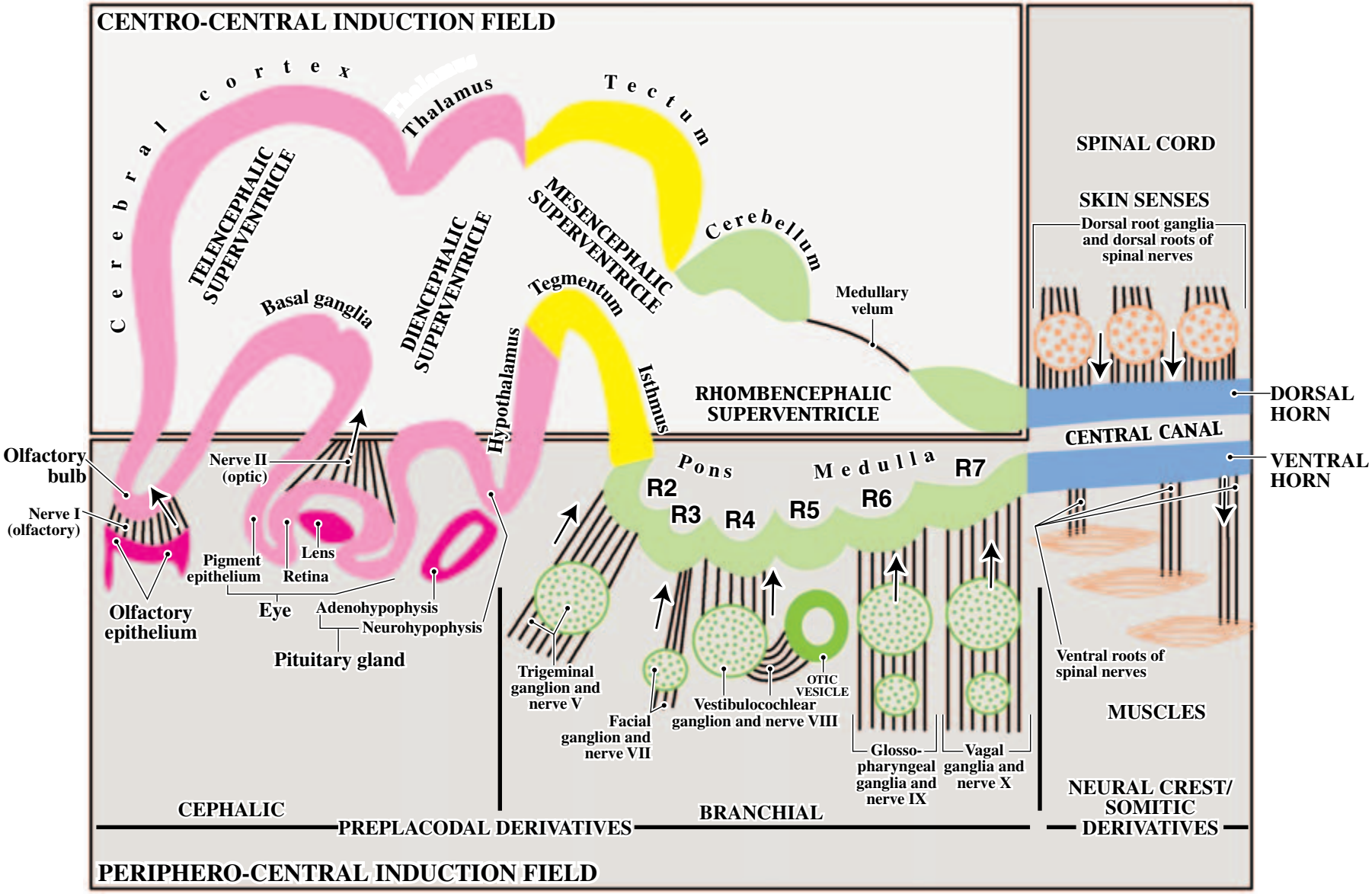


Figure 42. Second epoch of CNS development. Schematic illustration of the reciprocal periphero-central signaling potential between the olfactory epithelium, the lens of the eye, and the adenohypophysis, derived from the cephalic placodes (*red*), with the olfactory bulb, the retina, and the neurohypophysis, respectively, derived from the ventral telencephalic NEP (*pink*); between the cranial ganglia and otic vesicle derived from the branchial placodes (*dark green*) and the differentiating neurons of the rhombomeric NEPs (*light green*); and the differentiating spinal ganglia and muscles (*orange*) and the differentiating neurons of the dorsal horn and ventral horn derived from the spinal NEP (*blue*).

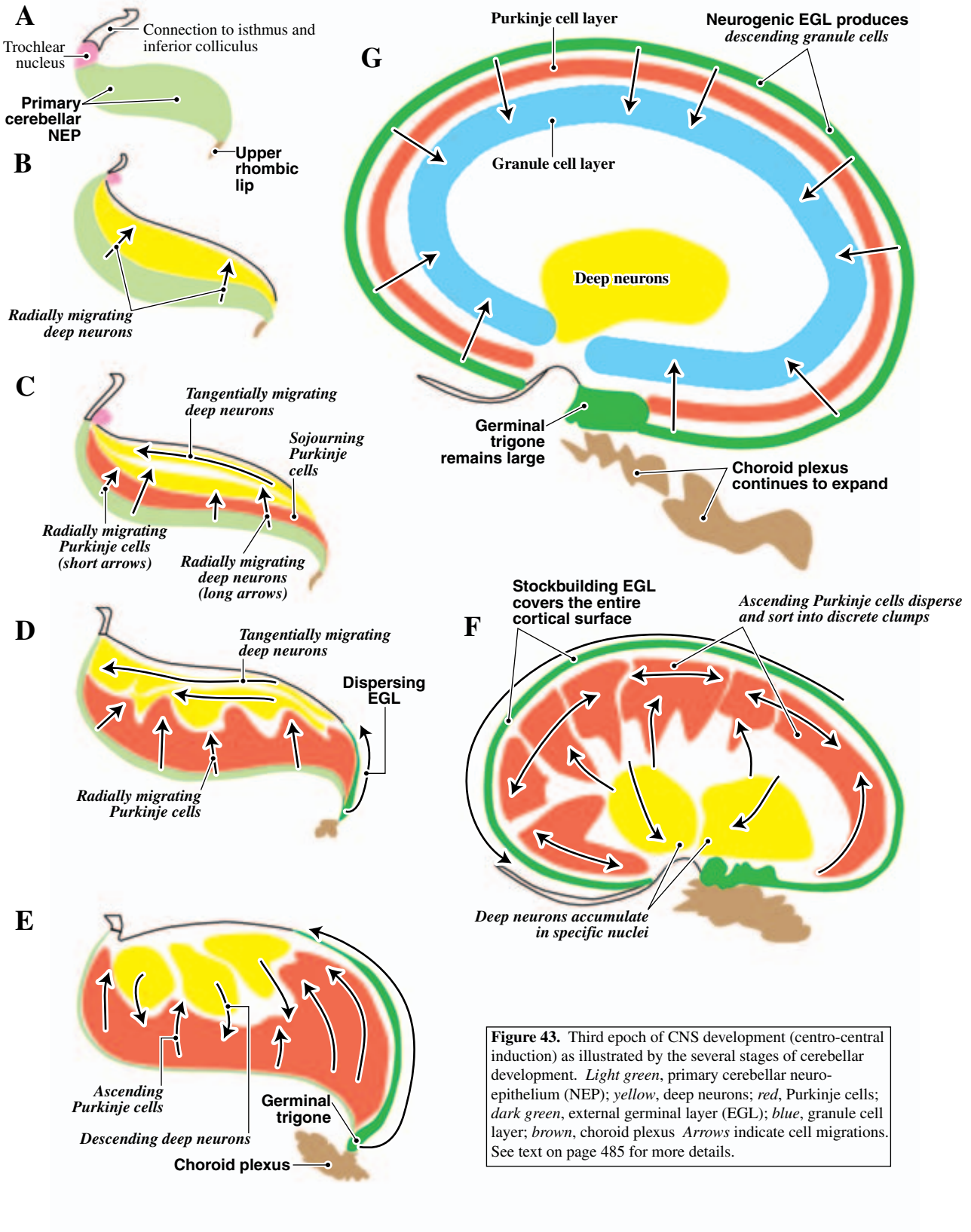


Figure 43. Third epoch of CNS development (centro-central induction) as illustrated by the several stages of cerebellar development. *Light green*, primary cerebellar neuroepithelium (NEP); *yellow*, deep neurons; *red*, Purkinje cells; *dark green*, external germinal layer (EGL); *blue*, granule cell layer; *brown*, choroid plexus *Arrows* indicate cell migrations. See text on page 485 for more details.

natal, and juvenile periods, and may not end until late adulthood. Importantly, there are pronounced differences in the maturation of different components of the CNS in relation to the specific functions they mediate and in terms of their position in the serial and hierarchic organization of those functions. For instance, in the maturating human spinal cord, motor fibers begin to exit the ventral horn as early as GW5.0. Sensory fibers of the spinal ganglia begin to penetrate the dorsal horn by GW5.5 (Altman and Bayer, 2001; Volume 1 of this Atlas: Bayer and Altman, 2002). In the maturing brain, somatosensory neurons of the trigeminal ganglion line up outside the trigeminal NEP (R2) as early as GW5.5 (**Figure 27B**), and its fibers penetrate it by GW6.5 (**Figure 29A**). This, of course, does not mean that these afferents and efferents are functional in the sense that they convey sensory messages and trigger motor commands. There is considerable scientific and public interest in the prenatal development of the human brain in relation to the mental status of the embryo and fetus. Studies in the first half of the 20th century with aborted fetuses have indicated that embryos of about 20 to 21 mm CR length (corresponding to the GW7.5 specimens illustrated in Volume 4 of this Atlas: Bayer and Altman, 2006) begin to reliably respond to tactile stimulation with *holokinetic* ("total pattern") body movements (Fitzgerald and Windle, 1942; Hooker, 1942). In GW10 fetuses (CR 48.5 mm) *ideokinetic* or isolated movements were also elicited, such as partial closure of the fingers (though not effective grasping) when the palm of the hand is stimulated (Humphrey, 1964). The more recent introduction of ultrasonic recording techniques has permitted the observation of the emergence of "spontaneous" fetal behavior in normal embryos and fetuses *in utero*. A pioneering study (de Vries, 1982, 1985) showed that the holokinetic "startle" response emerges as early as GW6, and isolated arm and leg movements emerge by GW7. These embryos would represent some of the oldest specimens presented in this volume. According to a more recent study with improved ultrasonic recording methods (Kurjak et al., 2005), isolated arm and leg movements increase in frequency during the late first trimester but head turning, and the hand contacting the head, do not occur with high frequency until the second trimester.

Are the late-embryonic and early-fetal movements *reflex* reactions mediated by lower-level spinal cord and brain stem mechanisms, or are they budding *voluntary* activities carried out under higher-level cortical guidance, by *mental* processes, such as feelings and emotions, perception and volition? We have raised these questions earlier in the context of our study of the development of the sensorimotor circuitry of the human spinal cord (Altman and Bayer, 2001). The substrate of the sensorimotor reflex arc in the spinal cord begins to form between GW7 and GW8 because the collateral branches of dorsal root afferents reach the ventral horn motor neurons during this period. Since the earliest corticospinal tract fibers do not reach the spinal cord until about GW19, we proposed that the isolated limb movements displayed by embryos of that age must be *reflex* reactions rather than *voluntary* activities. We can expand on this inference on the basis of the morphogenetic evidence presented in Volume 4 of this Atlas (Bayer and Altman, 2006) and in the present volume by stating that it is most unlikely that first-trimester embryos can experience cortically mediated *mental* processes. Cortically mediated sentient responses to somatosensory stimulation, which could be the source of internally generated sensations or perceptions *in utero*, presumes the operation of the following hierarchically arranged neural mechanisms: conduction of nerve impulses through the dorsal funiculus and through a chain of relay neurons and afferents in the dorsal column nuclei of the medulla and the medial lemniscus; synaptic maturation of the somatosensory relay nuclei of the thalamus, the site where the thalamocortical fibers terminate and afferents of the somatosensory cortex originate; and finally, the settling of late-generated cortical neurons in the cortical plate and their synaptic maturation in the cortical gray matter. While the relay neurons of the dorsal column nuclei and some of the thalamic neurons are generated during the early first trimester (we have no information when synapses are beginning to form here), the internal capsule that contains the ascending thalamocortical fibers to the cortex does not begin to form until GW8. It is at this age that, passing through the internal capsule, the earliest somatosensory fibers approach the base of the formative cerebral cortex. These fibers begin to penetrate the sojourn zone of the stratified transitional field by GW9 and that process continues through GW11. It is probable (but this needs to be experimentally verified) that the neurons of layer IV of the cortex, the principal target of thalamocortical fibers, are still in the stratified transitional field during that period and that synaptic connections in the formative gray matter, the cortical plate, are yet to develop. If this is correct, there is no functional connection between the thalamus and cells of the cortical plate during the first trimester of embryonic and fetal development and, therefore, the neural substrate for cortically mediated sentient responses to somatosensory stimuli is still missing during this period. It is possible, but this needs to be investigated morphologically and physiologically, that the neural mechanisms of rudimentary sentience begin to mature slowly some time during the second trimester.

APPENDIX
Timespans of Neurogenesis

A neuron is born when a proliferating neurogenic precursor cell gives rise to a *postmitotic* cell that displays cytological features or expresses molecular markers of a young *neuron*. While many current studies rely on molecular markers as the criterion of neurogenesis, we have used ^{3}H-thymidine autoradiography to determine the cessation of mitotic division and the birthdays of different neuronal populations. To label proliferating cells in the embryonic nervous system, we injected pregnant rats on two consecutive days with ^{3}H-thymidine. To label proliferating cells in the infant, juvenile, and adult nervous systems, we injected ^{3}H-thymidine on two to four consecutive days. The embryonic, infant, and juvenile animals survived to 60 postnatal days; by that time neurons are settled in the parenchyma and can be easily identified. The changes in the percentage of labeled and unlabeled neurons over a series of injection groups allowed us to accurately calculate the proportion of neurons generated on a single day in a given population.

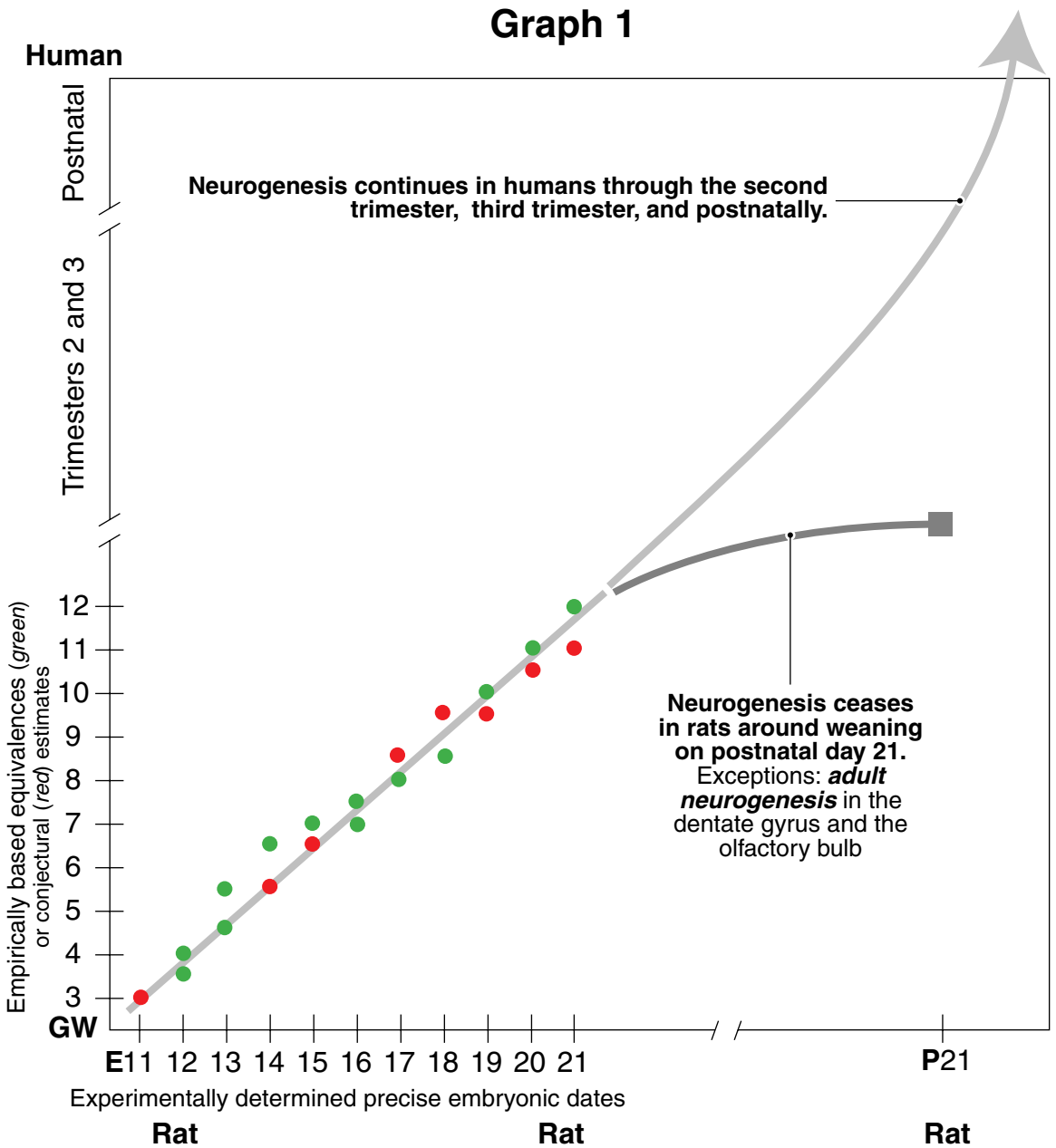
But how are we to date neurogenesis in the human nervous system? No experimental manipulation can be done. What can be done, however, is to apply the experimentally obtained data in rats to humans by *matching their morphological appearance at different stages of development*. During this matching procedure, we have found that morphological maturation of the spinal cord and brainstem are very similar in sequence. The exact chronology is different because days in rats translate to several days or a week in human development (Bayer et al., 1993).

We have re-examined this chronological relationship in the new material presented in this Atlas. In the spinal cord (Altman and Bayer, 2001; Volume 1 of this Atlas; Bayer and Altman, 2002) the following developmental sequences can be matched between embryonic days (E) in rats and gestational weeks (GW) in humans: (i) expansion of stockbuilding NEP cells without differentiating neurons [E12=GW3.2], (ii) early motor neuron differentiation [E13=GW4.5], (iii) entry of dorsal root fibers into the spinal cord [E14=GW5.5], (iv) emergence of the dorsal root bifurcation zone [E16=GW7.0], and (v) formation of the dorsal funiculus [E18=GW8.5]. We have made similar comparisons in the rhombencephalon, mesencephalon, diencephalon, and telencephalon. For instance, the comparison of whole brain development in sagittal sections of rats and humans, (**Figure 17A, B**) suggests a chronological equivalence of E18=GW9.0, and the comparison of diencephalic and telencephalic development in coronal sections (**Figure 17C, D**) suggests a chronological equivalence of E18=GW9.2. The comparison of mesencephalic and rhombencephalic development shown in **Figure 36** suggests a chronological equivalance of E15=GW7.0. In light of the small sample for comparison, we propose the human GW ranges to single E days in rats (**Table 1**); empirically based estimates are in bold.

TABLE 1
Developmental equivalance between rat and human CNS

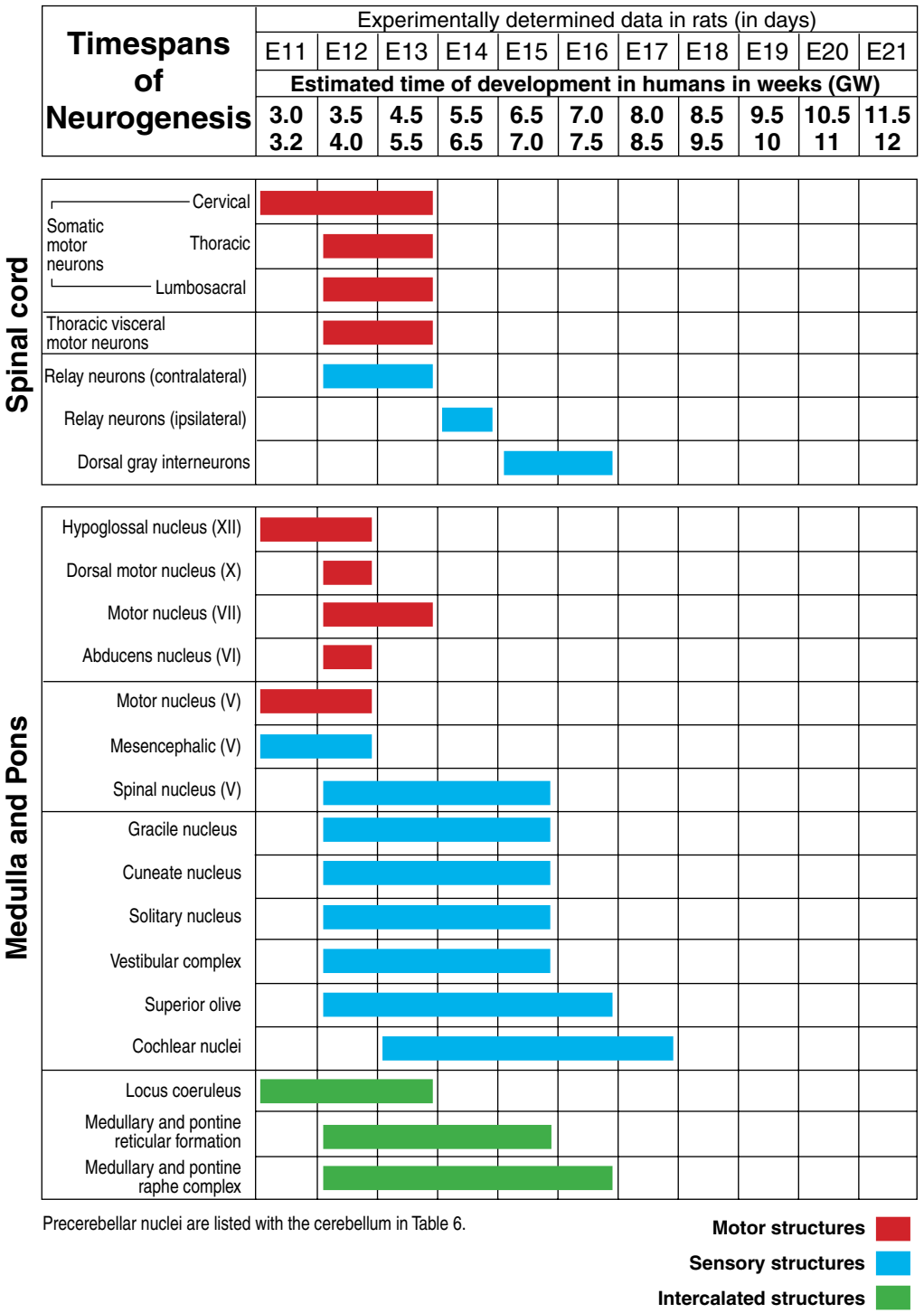
Rat (embryonic day)	Human (GW range)
11	<3.0-3.2
12	**3.5-4.0**
13	**4.5-5.5**
14	5.5-**6.5**
15	6.5-**7.0**
16	**7.0-7.5**
17	**8.0**-8.5
18	**8.5**-9.5
19	9.5-**10**
20	10.5-**11**
21	11.5-**12**

In contrast to the linear relationsip in brain development between E11-E21 prenatal rats and GW3-GW12 first trimester humans (**Graph 1**), there is no longer any linear relationship between postnatal (E22/P1+) rats and second and third trimester (GW13-GW37) humans. Whereas the newborn and infantile (preweaning, P1-P21) rat brain enters a period of quick maturation, the second and third trimester human brain retains its slow pace of prolonged development. This change in developmental tempo is par-



ticularly pronounced in brain regions that differ markedly in size (and presumably in complexity) in rats and humans. For instance, in the cerebral cortex, the stratified transtional field (STF) is still prominint in the E20 rat but is in the process of dissolution two days later (E22) as birth is imminent (Altman and Bayer, 1995; the layer is labeled as "intermediate zone"). In sharp contrast, the STF remains as a prominent developmental structure in the greatly expanding human cortex from GW13.5 at the beginning of the second trimester (Volume 3 of this Atlas: Bayer and Altman, 2005) until GW26 at the beginning of the third trimester (Volume 2 of this Atlas: Bayer and Altman, 2004a); that is, for a period of over three months. On the basis of the several good matches between cytological and anatomical development of the prenatal rat brain (in days) and the first trimester human brain (in weeks), we extrapolated neurogenetic timetable data in rats to the estimated time in humans for many CNS structures (**Tables 2** through **7**). Although we have quantitative data for the proportion of neurons generated on each particular day in the rat, we opted to conservatively extrapolate merely the time span of neurogenesis in the human brain. In very late-generated populations (granule cells of the cerebellar cortex, striatum, nucleus accumbens, microneurons in the upper layers of the cerebral cortex, and granule cells of the hippocampus), there is little equivalence other than the onset of neurogenesis. These timespans are marked with trailing arrows to indicate indeterminate cessation of neurogenesis.

TABLE 2



Precerebellar nuclei are listed with the cerebellum in Table 6.

TABLE 3

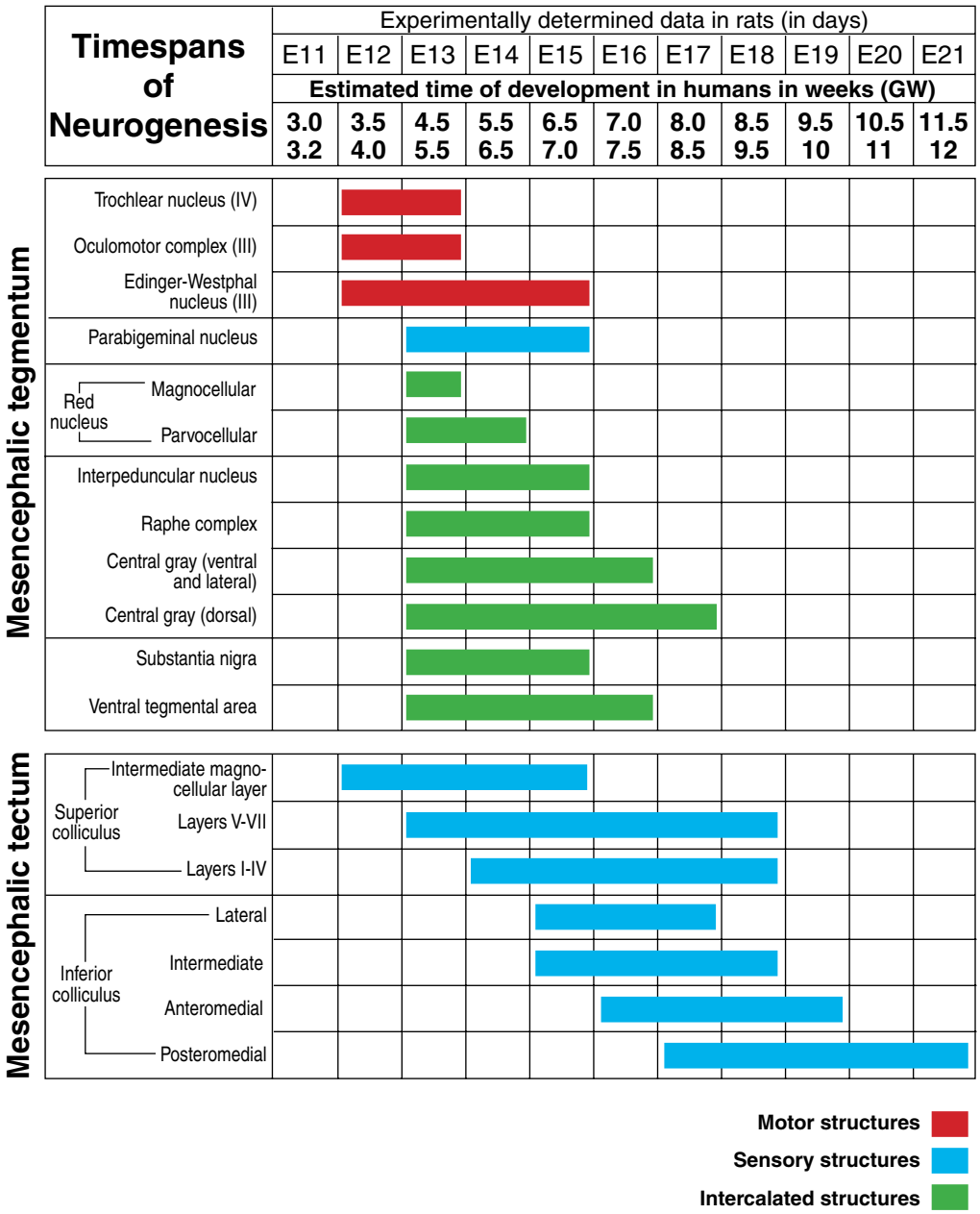
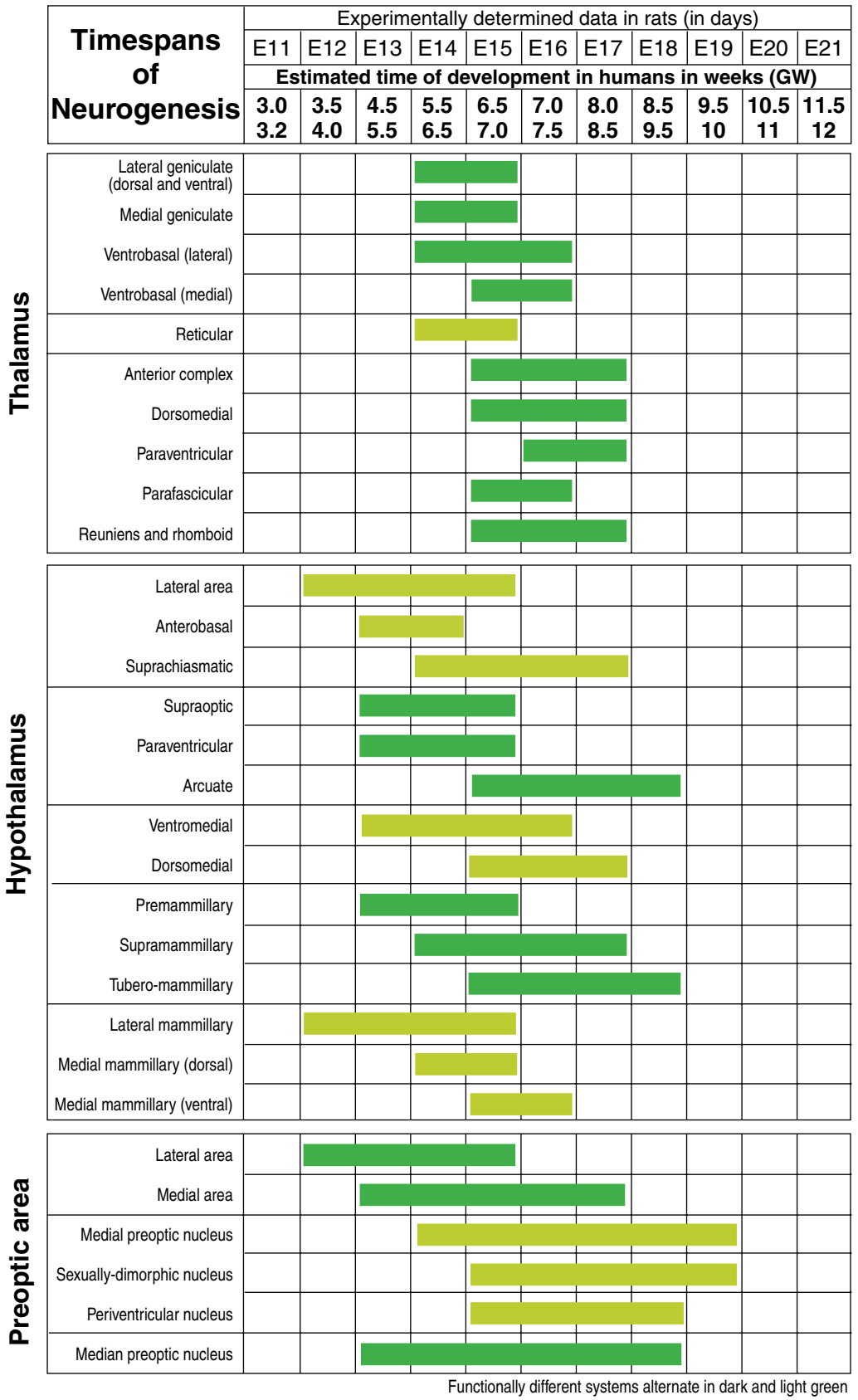

Timespans of Neurogenesis
Experimentally determined data in rats (in days)
E11 E12 E13 E14 E15 E16 E17 E18 E19 E20 E21
Estimated time of development in humans in weeks (GW)
3.0 3.5 4.5 5.5 6.5 7.0 8.0 8.5 9.5 10.5 11.5
3.2 4.0 5.5 6.5 7.0 7.5 8.5 9.5 10 11 12
Mesencephalic tegmentum
Trochlear nucleus (IV)
Oculomotor complex (III)
Edinger-Westphal nucleus (III)
Parabigeminal nucleus
Red nucleus
Magnocellular
Parvocellular
Interpeduncular nucleus
Raphe complex
Central gray (ventral and lateral)
Central gray (dorsal)
Substantia nigra
Ventral tegmental area
Mesencephalic tectum
Superior colliculus
Intermediate magno-cellular layer
Layers V-VII
Layers I-IV
Inferior colliculus
Lateral
Intermediate
Anteromedial
Posteromedial
Motor structures
Sensory structures
Intercalated structures

TABLE 4



Functionally different systems alternate in dark and light green

TABLE 5

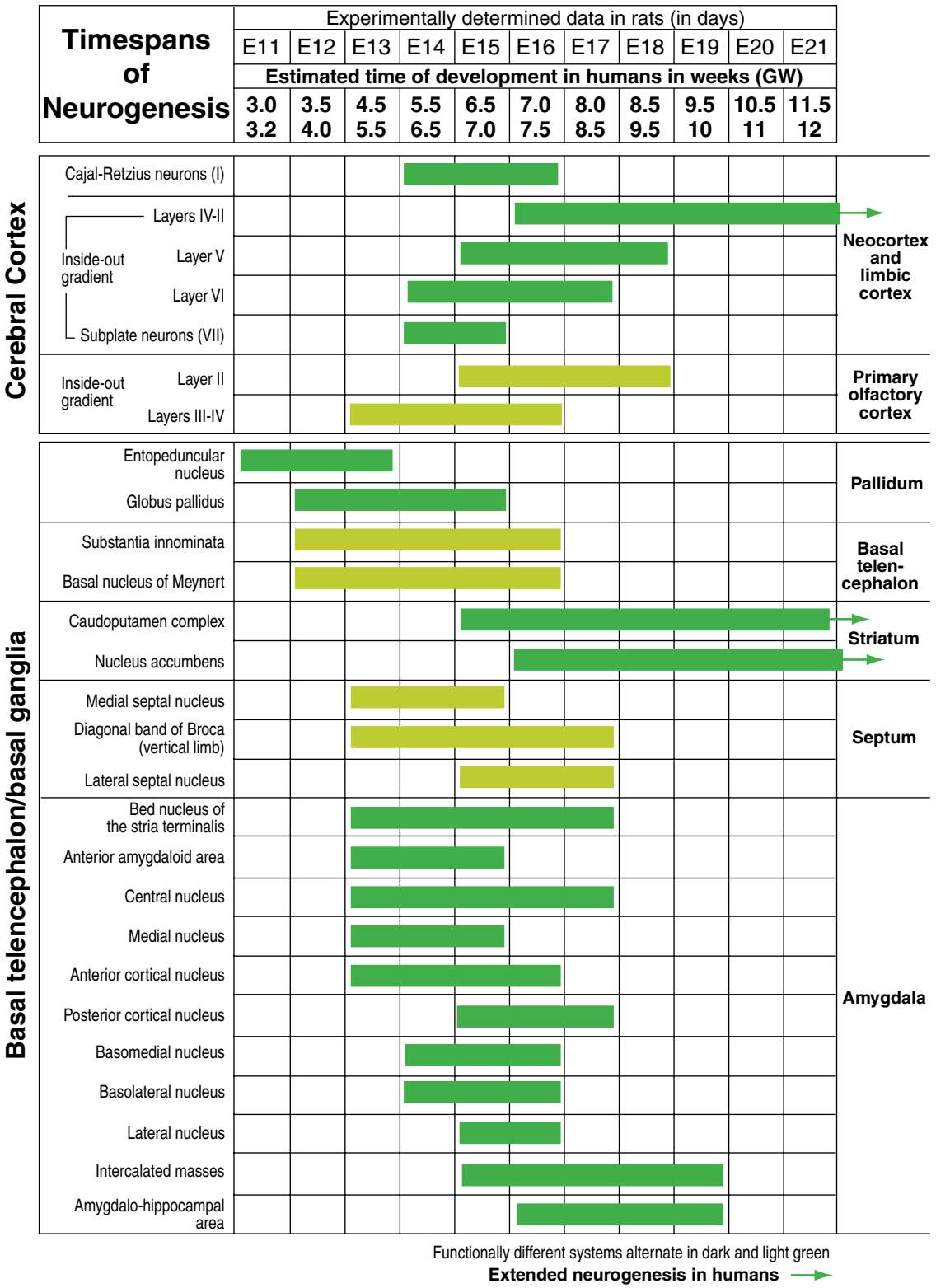

Timespans of Neurogenesis
Experimentally determined data in rats (in days)
E11 E12 E13 E14 E15 E16 E17 E18 E19 E20 E21
Estimated time of development in humans in weeks (GW)
3.0 3.2 | 3.5 4.0 | 4.5 5.5 | 5.5 6.5 | 6.5 7.0 | 7.0 7.5 | 8.0 8.5 | 8.5 9.5 | 9.5 10 | 10.5 11 | 11.5 12
Cerebral Cortex
Cajal-Retzius neurons (I)
Layers IV-II
Inside-out gradient
Layer V
Layer VI
Subplate neurons (VII)
Neocortex and limbic cortex
Inside-out gradient
Layer II
Layers III-IV
Primary olfactory cortex
Basal telencephalon/basal ganglia
Entopeduncular nucleus
Globus pallidus
Pallidum
Substantia innominata
Basal nucleus of Meynert
Basal telen-cephalon
Caudoputamen complex
Striatum
Nucleus accumbens
Medial septal nucleus
Diagonal band of Broca (vertical limb)
Lateral septal nucleus
Septum
Bed nucleus of the stria terminalis
Anterior amygdaloid area
Central nucleus
Medial nucleus
Anterior cortical nucleus
Posterior cortical nucleus
Basomedial nucleus
Basolateral nucleus
Lateral nucleus
Intercalated masses
Amygdalo-hippocampal area
Amygdala
Functionally different systems alternate in dark and light green
Extended neurogenesis in humans

TABLE 6

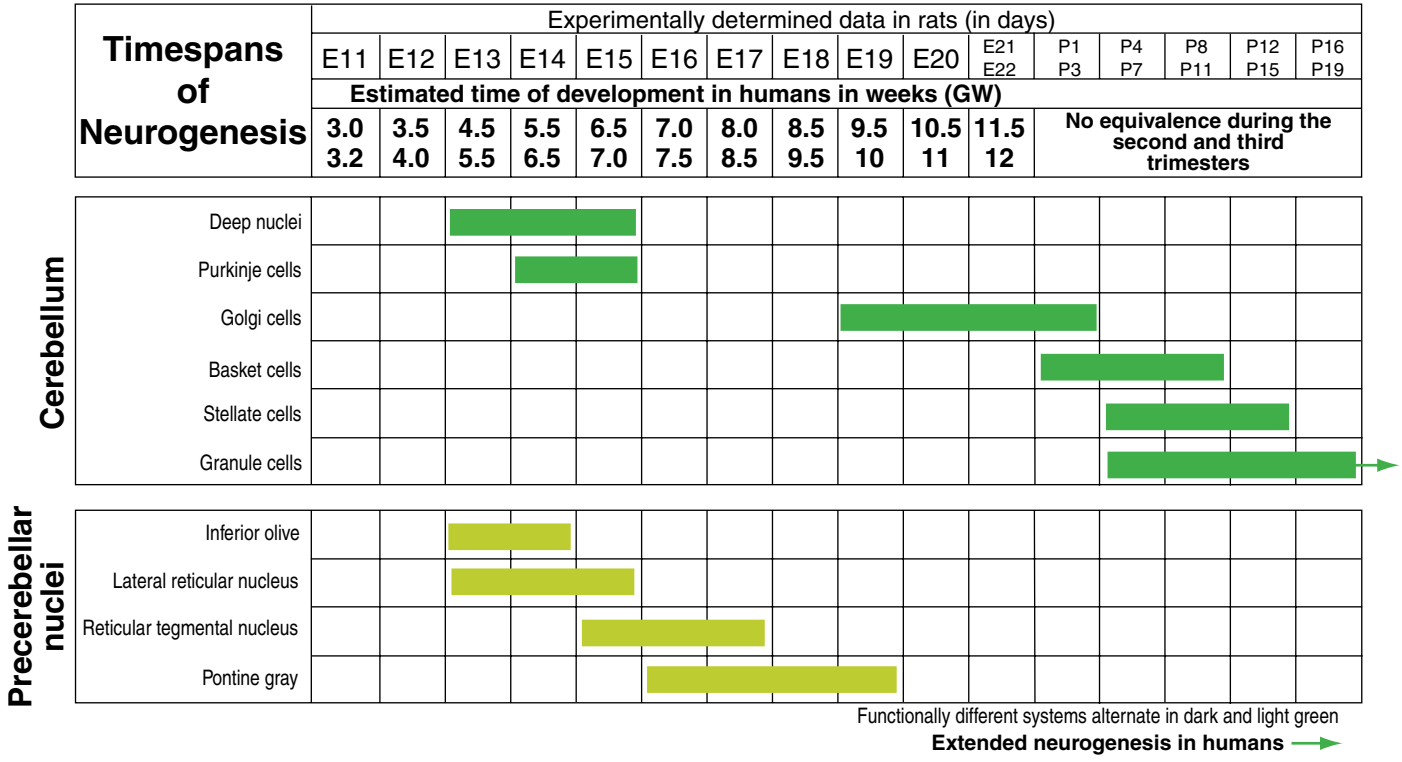
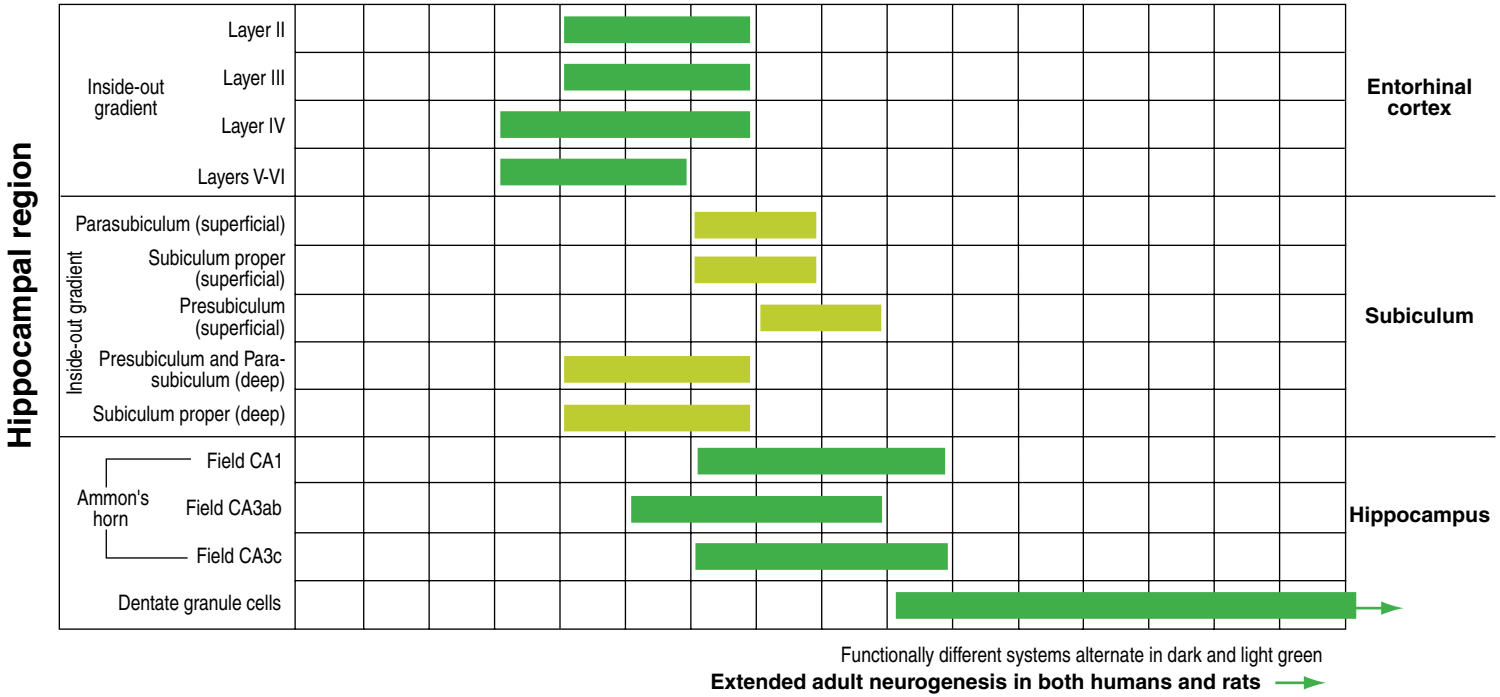

Timespans of Neurogenesis
Experimentally determined data in rats (in days)
E11
E12
E13
E14
E15
E16
E17
E18
E19
E20
E21 E22
P1 P3
P4 P7
P8 P11
P12 P15
P16 P19
Estimated time of development in humans in weeks (GW)
3.0 3.2
3.5 4.0
4.5 5.5
5.5 6.5
6.5 7.0
7.0 7.5
8.0 8.5
8.5 9.5
9.5 10
10.5 11
11.5 12
No equivalence during the second and third trimesters
Cerebellum
Deep nuclei
Purkinje cells
Golgi cells
Basket cells
Stellate cells
Granule cells
Precerebellar nuclei
Inferior olive
Lateral reticular nucleus
Reticular tegmental nucleus
Pontine gray
Functionally different systems alternate in dark and light green
Extended neurogenesis in humans

TABLE 7

Timespans of Neurogenesis	Experimentally determined data in rats (in days)															
	E11	E12	E13	E14	E15	E16	E17	E18	E19	E20	E21 E22	P1 P3	P4 P7	P8 P11	P12 P15	P16 P19
	Estimated time of development in humans in weeks (GW)															
	3.0 3.2	**3.5 4.0**	**4.5 5.5**	**5.5 6.5**	**6.5 7.0**	**7.0 7.5**	**8.0 8.5**	**8.5 9.5**	**9.5 10**	**10.5 11**	**11.5 12**	**No equivalence during the second and third trimesters**				



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GLOSSARY

An asterisk in front of a term indicates that it is a separate entry in the Glossary with additional information.

A

Abducens nucleus (VI) – An aggregate of cranial nerve motor neurons situated beneath the fourth ventricle in the *pons. The nucleus receives input from the *vestibular nuclear complex and is the source of motor fibers of cranial *nerve VI that innervate the lateral rectus muscle of the eye.

Ammonic NEP – Subdivision of the *hippocampal NEP, the putative source of the pyramidal cells of Ammon's horn.

Amygdaloid NEP – Neuroepithelium lining the posteroventral *telencephalic superventricle, the presumptive site of origin of neurons and glia of the amygdala. It is continuous rostrally with the posterior *striatal NEP, laterally with the temporal NEP, and medially with the ventral *hippocampal NEP.

Anterior extramural migratory stream – Large stream of young neurons that migrate from the *precerebellar NEP to the *pontine gray and the *reticular tegmental nucleus. The stream forms during the latter part of the late first trimester, after the settling of inferior olivary neurons that migrate in the *posterior intramural migratory stream.

Anterior neuropore – The unfused *neural tube in the early *prosencephalon. It closes between GW3.2 and GW3.8.

Anterior pituitary gland (embryonic) – The anterior lobe of the pituitary gland, also known as the adenohypophysis. It is derived from the invaginating *Rathke's pouch, a midline portion of the *cephalic placode.

Anterior precerebellar NEP – Neuroepithelial source of neurons of the *pontine gray and *reticular tegmental nucleus associated with the lower *rhombic lip. The neurons migrate to their target structures by way of the *anterior extramural migratory stream.

Aqueduct (embryonic) – *See* **Mesencephalic superventricle.**

Auditory-Vestibular NEP – *See* **Rhombomeric NEPs**

B

Basal ganglia – Large nuclear (subcortical) component of the telencephalon, including the *septum, the *striatum, the *nucleus accumbens, and the *globus pallidus.

Basal ganglionic NEP and SVZ – Initially a single ventral telencephalic protuberance, the basal ganglionic NEP is partitioned into three large hillocks or eminences – the anterolateral, the anteromedial, and the posterior – protruding into the *telencephalic superventricle and produce the neuroepithelial and subventricular progenitor cells that furnish neurons and neuroglia to the *basal ganglia. A fourth component is the corticoganglionic NEP/SVZ that may generate cortical neurons. The SVZ is far more prominent in the basal ganglia than in the developing *cerebral cortex.

Basal telencephalic NEP – Putative source of neurons and neuroglia of the basal nucleus of Meynert and the substantia innominata.

Branchial arches – Mesenchymal pouches – including the mandibular arch (I), the hyoid arch (II), and the pharyngeal (post-oral, visceral) arches III-IV – that contribute to the formation of the mandible, the hyoid bone, parts of the ear, the thyroid cartilage, and some visceral structures. The branchial arches are believed to be phylogenetically derived from the gills of protochordates and lower vertebrates.

Branchial placodes – Distinguished from the rostral *cephalic placodes, the caudal branchial placodes cover portions of the *branchial arches, the oral cavity, and the gullet. The pluripotent progenitor cells of the branchial placodes are the source of neurons of the cranial nerve ganglia, and may contribute the somatosensory elements of the head region, the gustatory system, and the acoustico-vestibular system.

Boundary cap – A thin ring of proliferative cells surrounding the spinal and cranial nerves at the site they enter the CNS. It is presumed to be a source of Schwann cells of peripheral nerves.

C

Cajal-Retzius cells – Unique neurons with perikarya oriented parallel to the pial surface in the *primordial plexiform layer of the developing *cerebral cortex.

Central canal (embryonic) – Portion of the ventricular system continuous with the *rhombencephalic superventricle. It extends from the cervical to the sacral segments of the spinal cord. During embryonic development, the proliferative NEP matrix lining this canal is the source of neurons and neuroglia of the spinal cord. After the cessation of neurogenesis, the shrunken central canal is lined by the *ependyma.

Cephalic placodes – Distinguished from the *branchial placodes, part of the *preplacode, that will become subdivided into the *olfactory placode, the *optic (lens) placode, and the *pituitary placode (*Rathke's pouch). The cephalic placode, composed of pluripotent progenitor cells, is continuous with the *prosencephalic NEP before it fuses.

Cephalic vesicles – NEP divisions of the head region, initially composed of the *prosencephalon, *mesencephalon, and *rhombencephalon. Early during embryonic development, the prosencephalon becomes divided into the bilateral telencephalon and the medial diencephalon.

Cerebellar cortex (embryonic) – Begins to form after the spreading *external germinal layer (EGL) forms a canopy over the surface of the cerebellum and the *Purkinje cells begin to line up beneath the EGL. The embryonic cerebellar cortex is devoid of microneurons (granule, basket, and stellate cells) and lacks a differentiated granular and molecular layer.

Cerebellar deep nuclei – Three pairs of ganglionic structures beneath the *cerebellar cortex: the medial *fastigial nucleus; the intermediate *interpositus nucleus, and the lateral *dentate nucleus. The efferent fibers of cerebellar *Purkinje cells synapse with the neurons of the cerebellar deep nuclei which, in turn, are the source of cerebellofugal fibers that terminate in structures outside the cerebellum. The early-generated deep nuclei neurons initially sojourn superficially in the *nuclear transitional zone of the formative cerebellum.

Cerebellar hemisphere – Portion of the cerebellum flanking the medial *vermis. It is particularly large in higher mammals and humans.

Cerebellar NEP – An extensive neuroepithelial matrix that initially forms the upper *rhombic lip. It is the direct source of the neurons of the *cerebellar deep nuclei and the *Purkinje cells, and an indirect source of the basket, stellate, and granule cells, which are produced by a secondary proliferative matrix, the *external germinal layer.

Cerebellar transitional field (CTF) – Transient cellular and fibrous layers, composed of migrating deep neurons and Purkinje cells, and of exiting and entering fiber tracts, prior to the formation of the *cerebellar cortex.

Cerebellar vermis – Medial portion of the cerebellum. It is relatively small in higher mammals and man.

Cerebral cortex (embryonic) – The expanding and differentiating bilateral brain region covering the lateral, dorsal, and medial aspects of the *telencephalic superventricles. It has three major components, the *neocortex, the *limbic cortex, and the *primary olfactory cortex. The neurons generated by the cortical NEPs initially form the *stratified transitional field and the *cortical plate.

Choroid plexus (embryonic) – Glycogen-rich epithelial tissue that forms during the early first trimester and begins to expand during the late first trimester in the *rhombencephalic superventricle and the *telencephalic superventricle. It is formed by proliferative stem cells associated with the cerebellar *germinal trigone and an analogous germinal site in the *hippocampus. The fetal choroid plexus may play a role in the anaerobic metabolism of the early developing brain. During late-fetal development, it becomes gradually transformed into the mature choroid plexus of the shrunken lateral and fourth ventricles, with a different cellular composition and presumably a different function.

Cingulate NEP – Extensive neuroepithelial matrix in the *limbic cortex along the medial wall of the *telencephalic superventricle above the *septum and *hippocampus. It generates the neurons and neuroglia of the cingulate cortex.

Cochlear NEP – Neuroepithelial matrix in the vicinity of the lower *rhombic lip, the putative source of neurons and neuroglia of the ventral and dorsal *cochlear nuclei.

Cortical NEP – An extensive and continuous neuroepithelial matrix lining of the lateral, dorsal, and medial banks of the *telencephalic superventricle; major subdivisions are the *neocortical NEP, *limbic cortical NEP, and the *primary olfactory cortical NEP. It is the sole constituent of the *cerebral cortex during the early embryonic period. Following a strict timetable and spatial gradient, it expands and then shrinks as classes of differentiating neurons and glia leave it to enter the *stratified transitional field and migrate to the *cortical plate. The cortical NEP is also the source of a secondary proliferative matrix, the *subventricular zone, of fate-restricted *glioepithelia and

neurons, and the cells that line the enduring *ependyma of the lateral ventricles.

Cortical plate – The densely packed cellular band in the embryonic and fetal *cerebral cortex that later becomes the stratified *gray matter of cortical layers II-VI. It is situated between the *primordial plexiform layer (future layer I) and the subplate (future layer VII).

Cortical transition zone (cerebellum) – Deep sojourn zone of young *Purkinje cells before they begin their ascent toward the surface to form the cerebellar cortex.

Corticofugal fibers (embryonic) – Collective term for the efferent fiber system (the traditional pyramidal tract) that originates in the cerebral cortex and terminates in subcortical structures. It is known by different names along its path from rostral to caudal: *internal capsule, cerebral peduncle, *transpontine corticofugal tract, and corticospinal tract. The corticofugal tract begins to form during the end of the late first trimester but its fibers do not reach the spinal cord until the end of the second trimester.

D

Dentate gyrus – Component of the *hippocampus, composed of granule cells and interlocked with the large-celled *Ammon's horn. Although the *dentate migration is recognizable by the end of the first trimester, the blades of the dentate gyrus do not form until the second trimester.

Dentate migration – Precursors of granule cells of the *dentate gyrus that leave the *dentate NEP to form what will later become the secondary germinal matrix of the hippocampus, the *subgranular zone.

Dentate NEP – Division of the *hippocampal NEP that is the source of the progenitor cells of the *dentate migration and the *subgranular zone.

Dentate nucleus (embryonic) – The lobulated and largest of the *cerebellar deep nuclei in the core of the *cerebellar hemisphere, it is the principal source of efferent fibers of the superior cerebellar peduncle. In the embryonic cerebellum, the early-generated neurons of the dentate nucleus are situated superficially and do not descend until after the late-generated *Purkinje cells migrate toward the surface to form the cerebellar cortex.

Diencephalic NEP – An extensive neuroepithelial matrix lining the midline *diencephalic superventricle. Its different mosaic components, distinguished by bilaterally symmetrical evaginations or invaginations and variable cell-depth, are the source of neurons and neuroglia of the different nuclei of the *diencephalon.

Diencephalic superventricle – Large midline component of the embryonic ventricular system that is later reduced to the narrow third ventricle. It is confluent laterally, by way of the foramen of Monro, with the *telencephalic superventricle, and caudally with the *mesencephalic superventricle. Its lining, the *diencephalic NEP, is the source of all the neurons and neuroglia of the *diencephalon.

Diencephalon (embryonic) – Extensive forebrain region flanked laterally by the telencephalon and continuous caudally with the mesencephalon. Among its larger components are the *epithalamus and the *thalamus dorsally; the *optic vesicle, the *preoptic area, the *hypothalamus, and the *subthalamus ventrally. Its parenchymal development precedes that of the dorsal *telencephalon.

Dorsal rhombic lip – *see* **Rhombic lip, upper.**

E

Ependyma – Layer of cuboidal cells that line the lumen of the permanent brain *ventricles and *central canal after dissolution of the proliferative *neuroepithelium.

Epithalamic NEP – Neuroepithelial division of the *diencephalic NEP, the putative source of neurons and neuroglia of the *epithalamus.

Epithalamus – Collective term for the region of the dorsal diencephalon consisting of the habenular nuclei, the stria medullaris, and the habenulo-interpeduncular tract.

External germinal layer (EGL) – Subpial, secondary germinal matrix of the cerebellar cortex, the source of its late-differentiating granule, stellate, and basket cells. It begins to form during GW8 and persists as a source of neurons over the surface of the human cerebellar cortex until the end of the second year of postnatal life.

F

Facial ganglion – A small clump of peripheral sensory neurons located in the hyoid arch slightly below and anterior to the large vestibulocochlear ganglion. It is the source of the sensory axons in nerve VII that carry taste information from the anterior tongue and enter the brain in the posterior rhombomere 3. These neurons are presumably generated by the neural crest and

by germinal cells in a branchial placode in the hyoid arch.

Facial motor nucleus – A large aggregate of somatic motor neurons in the posterior pons and anterior medulla. It is the source of the motor fibers of *nerve VII that innervate the facial mimetic muscles.

Facial NEP – *See* **Rhombomeric NEPs.**

Fastigial nucleus (cerebellum) – A deep nucleus of the *cerebellum, also known as the medial cerebellar nucleus. It is the target of Purkinje cell axons that originate in the *vermis. Its axons contribute to the large efferent system that leaves the cerebellum.

Foramen of Monro (embryonic) – Bilateral channels that connect the paired *telencephalic superventricles with the midline * diencephalic superventricle.

Fornical GEP – Fate-restricted germinal extension of the hippocampal NEP, the *glioepithelium that surrounds the fornix. It may be the germinal source of the oligodendrocytes of the fornix.

Fornix – An early forming fiber tract of the *hippocampus that distributes fibers in the mature brain to the septum and the anterior thalamic nuclei, and terminates in the mammillary body.

Fourth ventricle (embryonic) – *See* **Rhombencephalic superventricle.**

G

Germinal trigone (cerebellum) – Proliferative germinal matrix of the upper *rhombic lip with three prongs: the *cerebellar NEP, the *external germinal layer, and the stem cells of the rhombencephalic *choroid plexus.

Glioepithelium (GEP) – Fate-restricted transient germinal matrix in the developing CNS, the presumed source of astrocytes and oligodendroglia. There are two types of glioepithelia, the *perifascicular GEP that surrounds fiber tracts, such as the *fornical GEP, and another that covers the surface of the brain, the *subpial granular layer. Glioepithelia are easiest to recognize without special glial markers at sites of considerable distance from neuronal aggregates or their migratory routes.

Glioepithelium/Ependyma (G/EP) – Transient proliferative lining of the ventricle that endures into adulthood and gives rise to both neuroglia and cells of the *ependyma.

Glossopharyngeal ganglia – Superior and inferior clumps of peripheral sensory neurons located in arch III and behind the otic vesicle. These ganglia are the source of nerve IX sensory axons that enter the brain at rhombomere 6 carrying taste and visceral sensory information. These neurons are presumably generated by cells in the neural crest and by a placode in arch III.

Glossopharyngeal NEP – *See* **Rhombomeric NEPs.**

Gray matter – General term for the component of the mature CNS with a high concentration of neuronal cell bodies and nerve processes but few myelinated fibers.

H

Hippocampal NEP – Medial matrix of the *cortical NEP, the putative neuroepithelial source of the neurons and neuroglia of the hippocampus. It has three distinctive parts, the *Ammonic NEP, the *dentate NEP, and the *fornical GEP.

Hippocampal region – An inclusive term (also called the hippocampal formation) that includes not only the *hippocampus proper but also the *subicular complex and other components of the parahippocampal cortex.

Hippocampus – A distinctive allocortical (oligolaminar) region formed by the interlocking *dentate gyrus and Ammon's horn. The principal afferents of the hippocampus travel in the alveolar and perforant paths; its efferents leave by way of the *fornix.

Honeycomb matrix – A layer in the *stratified transitional field, composed of radially oriented fibers surrounded by concentrically arranged cells. It is prominent in the sensory areas of the developing *cerebral cortex, and may also be present in the *superior colliculus. The fibers are hypothesized to be topographically organized.

Hook bundle (embryonic) – Intracerebellar commissural tract that originates in the *cerebellar deep nuclei and is presumed to leave the crebellum contralaterally as the uncinate fasciculus. A prominent fibrous region identified at the base of the cerebellum in GW8-GW9 specimens may be the sprouting fibers of this tract.

Hypothalamic NEP – Ventral division of the *diencephalic NEP, situated posterior to the preoptic NEP. It is the source of neurons and neuroglia of the nuclei of the *hypothalamus.

Hypothalamus (embryonic) – Early-differentiating, large diencephalic region that surrounds the ventral division of *diencephalic superventricle. It is continuous anteriorly with the *preoptic area and merges caudally with the midbrain *tegmentum. The hypothalamus contains a large number of discrete nuclei that link the forebrain with the autonomic nervous system and the endocrine system.

I

Inferior collicular NEP – Distinctive neuroepithelial division of the *tectal NEP surrounding the posterior pool of the *mesencephalic superventricle, and the source of neurons of the *inferior colliculus.

Inferior colliculus – Paired posterior hillocks of the midbrain *tectum that receive primary, secondary, and higher order auditory afferents. The output of the inferior colliculus is mainly to the *medial geniculate nucleus in the thalamus.

Inferior olive (embryonic) – A compact cell aggregate in the lower *medulla, formed by neurons of the *posterior intramural migratory stream during the late first trimester. Its lamination does not begin until the end of the second trimester.

Infundibular recess – Small recess of the third ventricle that evaginates into the *infundibulum and is closely associated with the *pituitary placode (Rathke's pouch).

Infundibulum – Stalk extending from the ventral *hypothalamus that forms a link with the pituitary gland.

Insular cortex – Early maturing part of the lateral limbic cortex located above the neocortex of the future temporal lobe. This area of cortex is the first to have a cortical plate that appears on GW7.5. Early thalamocortical fibers and other pioneer cortical afferents invade the cortex here.

Interhemispheric fissure – Longitudinal cleft that separates the two cerebral hemispheres. The corpus callosum that traverses it in the maturing brain starts to form at the beginning of the second trimester.

Intermediate zone – *See* **Stratified transitional field**.

Internal capsule (embryonic) – Massive fiber tract between the thalamus and cortex, composed of *thalamocortical fibers and *corticofugal fibers. It is beginning to form at about GW8 as the earliest thalamocortical fibers cross into the telencephalon.

Interpositus nucleus (cerebellum) – A deep cerebellar nucleus located between the *dentate nucleus and the *fastigial nucleus.

Isthmal canal – Channel that interconnects the *mesencephalic superventricle and the *rhombencephalic superventricle.

Isthmal NEP – The putative source of neurons and neuroglia of the transient *isthmus region.

Isthmus – Transient mesencephalic region that surrounds the isthmal canal, situated caudal to the tectum and tegmentum, and rostral to the rhombencephalon. Most of the neurons generated at this site migrate to other, as yet undetermined, regions of the pons and midbrain.

L

Lateral geniculate nucleus (embryonic) – The neurons of this prominent thalamic nucleus appear to be generated dorsally in a distinct neuroepithelial locus and migrate ventrolaterally where they meet the fibers of the incoming *optic tract.

Lateral hypothalamic area – An ill-defined fibrous region of the *hypothalamus with scattered neurons medial to the cerebral peduncle. It is traversed by many fiber tracts, including the *medial forebrain bundle.

Lateral lemniscus – The fiber tract on the lateral surface of the *pons that contains secondary auditory fibers from the dorsal and ventral cochlear nuclei and higher-order auditory fibers from the superior olivary complex.

Lateral migratory stream (**cortical**) – Tangentially migrating neurons and glia in the developing *cerebral cortex that leave dorsal *cortical NEP and migrate laterally and ventrally to the insula, the *temporal lobe, and other telencephalic structures that lack a nearby germinal matrix. The bulk of the lateral migratory stream follows a trajectory outlined by the receding *subventricular zone between the basal ganglia and the lateral cortex.

Lateral ventricles – *See* **Rhombencephalic superventricle**

Layer I, cortical (embryonic) – *See* **Primordial plexiform layer.**

Lens placode – Fate-restricted portion of the *cephalic placode whose progenitor cells will produce the crystalline lens of the eye.

Limbic cortex – Portion of the cerebral hemispheres that, in contrast to the *neocortex, contains fewer than six definite cellular layers. Among prominent limbic regions are the cingulate gyrus, hippocampus, entorhinal cortex, and insula.

Limbic cortical NEP – Portion of the *cortical NEP that generates neurons in the *cingulate gyrus, *hippocampus, *entorhinal cortex, and *insular cortex. This part of the cortical NEP forms a lateral and medial border around the *neocortical NEP.

Luysiian migration – The intramural migratory stream of subthalamic nuclear neurons (corpus Luysii) has been traced from the region of the formative mammillary body medially to the subthalamus dorsolaterally.

M

Maxillary process – A swelling in the embryonic head located behind the invaginating olfactory placode that contains the primordium of the maxilla.

Medial forebrain bundle – A diffuse fiber tract that extends from the olfactory region, through the *lateral hypothalamic area, to the *substantia nigra in the midbrain *tegmentum.

Medial geniculate nucleus – Principal thalamic relay station in the auditory pathway to the *cerebral cortex. Its afferents originate in the *trapezoid body, the *superior olivary complex, the *nuclei of the lateral lemniscus, and the *inferior colliculus. Its efferents form the auditory radiation that terminates in the *temporal lobe.

Medial lemniscus – Large fiber bundle conveying tactile and other somatosensory input to the thalamus. It originates in the gracile and cuneate nuclei in the *medulla, crosses to the opposite side, ascends through the *pons and the *mesencephalon, and terminates in the somatosensory relay nuclei of the thalamus (ventral complex).

Medial lemniscus (decussation) – Also known as the arcuate decussation, it is composed of ascending somatosensory fibers of the medial lemniscus that cross to the opposite side in the medulla.

Medial longitudinal fasciculus – A dorsomedial tract in the *mesencephalon, *pons, and *medulla that contains ascending and descending vestibular fibers coursing in the medial tegmentum and pons, turns ventrally in the posterior *medulla and extends into the ventral funiculus of the cervical spinal cord.

Medulla (embryonic) – Early-generated region of the brain that is continuous with the spinal cord, also known as the medulla oblongata. This extremely heterogeneous region surrounds the posteroventral *rhombencephalic superventricle and contains sensory, somatomotor, and visceromotor nuclei as well as several ascending, descending, and decussating fiber tracts.

Medullary NEP – Extensive neuroepithelial matrix that lines the variegated caudal bank of the *rhombencephalic superventricle. Its several subdivisions are the source of neurons and neuroglia of the different sensory, relay, and motor nuclei of the *medulla.

Medullary velum – Membranous roof of the *rhombencephalic superventricle that extends from the upper to the lower *rhombic lips. It is the only site in the CNS where the neural tube fails to fuse. A portion of its inner surface contains stem cells for the rhombencephalic choroid plexus.

Mesencephalic NEP – The extensive neuroepithelium that lines the large *mesencephalic superventricle. Its major divisions are, from rostral to caudal, the *pretectal NEP, the *tectal NEP, the *tegmental NEP, and the *isthmal NEP. Subdivisions of the tectal NEP are the NEPs of the *superior colliculus and *inferior colliculus. Subdivisions of the tegmental NEP are the NEPs of the *oculomotor nucleus, the *red nucleus, and other structures of the *tegmentum.

Mesencephalic superventricle – Greatly inflated lumen of the embryonic *mesencephalon, situated between the *diencephalic superventricle rostrally and the *rhombencephalic superventricle caudally. The connection with the latter is by way of the *isthmal canal. It shrinks in the maturing brain into the small and narrow aqueduct.

Mesencephalon (embryonic) – Region of the brainstem that surrounds the *mesencephalic superventricle and forms a bridge between the *pons and the *diencephalon. Among its early-differentiating components are the pretectum with the *posterior commissure, the *oculomotor nucleus and the *trochlear nucleus, and neurons of the *reticular formation.

Meyer's loop – Part of the *visual radiation that takes a sharp curve in the *temporal lobe as it proceeds to the occipital lobe. It is recognizable by GW11.

Microneurons – Late-generated small neurons ("granule cells") with locally arborizing axons that form discrete layers in several cortical structures or become embedded within nuclear structures. Microneurons are produced by *secondary germinal matrices, such

as the *subventricular zone of the cerebral cortex and striatum, the *subgranular zone of the hippocampus, and the *external germinal layer of the cerebellum. A high proportion of cerebellar granule cells are generated during the first years of life, and the granule cells of the olfactory bulb and the dentate gyrus are generated from fetal stages through adulthood.

Midbrain – *See* **Mesencephalon.**

N

Neocortex (embryonic) – Portion of the cerebral hemispheres that develops into a "six-layered" cortical *gray matter. Neocortical development begins with the expansion of the primordial *cortical NEP devoid of differentiated neurons. Next comes the formation of the *primordial plexiform layer. Then the *cortical plate appears along with different layers in the *stratified transitional field (*intermediate zone), and the *subventricular zone. The principal divisions of the neocortex are the frontal lobe, the paracentral lobule, the parietal lobe, the temporal lobe, and the occipital lobe.

Neocortical NEP – Extensive neuroepithelium that lines the lateral and dorsal aspects of the *telencephalic superventricles. The proliferating neocortical NEP cells are the source of neurons and neuroglia that migrate to the *cortical plate by way of the *stratified transitional field. Some of its cells may move to more distant sites by way of the *lateral migratory stream. It is bordered medially and laterally by the *limbic cortical NEP.

Nerve I – *See* **Olfactory nerve.**

Nerve II – *See* **Optic nerve.**

Nerve III (oculomotor) – Cranial motor nerve originating in the *oculomotor nucleus. It innervates all the extraocular muscles (except the lateral rectus and superior oblique), the skeletal muscles of the eyelid, the smooth sphincter muscles of the iris, and the ciliary muscles of the lens.

Nerve IV (trochlear) – Cranial motor nerve composed of axons of the *trochlear nucleus that innervates the superior oblique muscle of the eye. This nerve is unique because it exits from the dorsal surface of the *mesencephalon beneath the *inferior colliculus.

Nerve V (trigeminal)– A mixed sensory and motor cranial nerve that has three peripheral branches: the ophthalmic, the maxillary, and the mandibular. All three branches contain peripheral sensory fibers from the *trigeminal ganglion that terminate in the trigeminal principal sensory nucleus, the *trigeminal spinal nucleus, and the substantia gelatinosa in upper cervical segments of the spinal cord. A bundle of fibers in the mandibular branch, originating in the *trigeminal motor nucleus, innervates the muscles of mastication.

Nerve VI (abducens) – Cranial motor nerve that originates in the abducens nucleus and emerges near the midline at the caudal border of the pons. The fibers innervate the lateral rectus muscle of the eye.

Nerve VII (facial) – A mixed sensory and motor nerve, the facial nerve has three components. Primary sensory gustatory fibers from the geniculate ganglion enter the solitary tract and nucleus. Somatic motor fibers from the *facial motor nucleus innervate the mimetic muscles. Visceral motor (parasympathetic) fibers from preganglionic neurons of the salivatory nucleus target the pterygopalatine and submandibular ganglia.

Nerve VIII (vestibulo-cochlear) – A sensory cranial nerve that contains primary auditory afferents from the spiral ganglion in the cochlea and primary vestibular afferents from the vestibular (Scarpa's) ganglion. Embryonically, both of these ganglia form the large *vestibulo-cochlear ganglion adjacent to the *otic vesicle. The auditory afferents terminate in the dorsal and ventral cochlear nuclei; the vestibular afferents terminate in the nuclei of the vestibular nuclear complex and some reach the cerebellum.

Nerve IX (glossopharyngeal) – A mixed sensory and motor cranial nerve. The sensory part originates in the superior and inferior *glossopharyngeal ganglia, and relays gustatory input from the posterior third of the tongue and visceral sensory input from the tonsils, the Eustachian tube, and the carotid sinus. These fibers enter the solitary tract and terminate in the solitary nucleus. The somatic motor part of nerve IX originates in the nucleus ambiguus and innervates the pharyngeal and laryngeal muscles. The visceral motor fibers from parasympathetic preganglionic neurons in the salivatory nucleus terminate in the otic ganglion.

Nerve X (vagus) – A mixed sensory and motor cranial nerve, with some somatic and many visceral afferents and efferents associated with the craniosacral parasympathetic ganglia. The sensory fibers originate peripherally in the superior and inferior ganglia and are widely distributed throughout the body, including the pharynx, larynx, trachea, esophagus, and all the thoracic and abdominal viscera. They terminate centrally in the solitary nucleus and at other medullary sites. Most of its preganglionic motor neurons are located in the dorsal motor nucleus of X.

Nerve XI (accessory) – This motor nerve has a cranial and a spinal component. The cranial fibers originate in the nucleus ambiguus and innervate the muscles of the larynx and pharynx. The spinal motor fibers originate in a motor column of the cervical spinal cord and innervate the sternocleidomastoid and upper trapezius muscles. Early in embryonic life this nerve is seen along the superficial border of the superior *vagal ganglion.

Nerve XII (hypoglossal) – A somatic motor cranial nerve that originates in the *hypoglossal nucleus and innervates the intrinsic and extrinsic muscles of the tongue.

Neural plate – Matrix of pluripotent stem cells of the early embryo that gives rise to neural crest cells and the *neuroepithelium.

Neuroepithelium (NEP) – Pseudostratified matrix of neural stem cells, the source of all neurons and neuroglia of the developing CNS. The NEP matrix begins its developmental career as the *neural plate. The neural plate folds dorsally and fuses to form, caudally, the neural tube (future spinal cord) and, rostrally, the *cephalic vesicles (the future brain). After closure, the lumen of the cephalic vesicles expands enormously to form the *rhombencephalic, *mesencephalic, *diencephalic, and *telencephalic superventricles. This expansion provides the space for the mitotic division of NEP cell nuclei that must shuttle to the fluid-filled lumen to undergo mitosis. Two NEP matrices are distinguished, the early-phase *stock-building NEP that only produces proliferative daughter cells, and the later-phase NEP that produces daughter cells that leave the NEP matrix. The continuous but variegated cephalic NEP matrix lining the ventricles have a mosaic organization, being composed of bilaterally symmetrical long stretches, and of intermediate or shorter patches that give rise to neurons and neuroglia of different brain regions, distinct brain structures, and specific cell types. Examples of long stretches are the *cortical NEP and the *cerebellar NEP. Examples of intermediate patches are the *thalamic NEP and the *hypothalamic NEP of the inclusive *diencephalic NEP. Examples of short patches are the *Ammonic NEP and *dentate NEP of the inclusive *hippocampal NEP. The primary NEP matrix is also the source of several *secondary germinal matrices that generate *microneurons with locally arborizing axons. Finally, as neurogenesis winds down, the pluripotential NEP is transformed at many sites into a *glioepithelium, such as the *fornical GEP, or into the *ependyma that lines the enduring ventricles.

Nuclear transition zone (cerebellum) – Superficial sojourn site in young embryos, composed of the early-generated deep nuclear neurons. These neurons migrate to a deep position within the cerebellum as the later-generated Purkinje cells that sojourn in the *cortical transition zone migrate toward the surface to form a monolayer there.

Nucleus accumbens – Ganglionic component of the ventral telencephalon ventromedial to the striatum. It is distinguished from the striatum by its cellular organization, molecular composition, and intimate connections with the hypothalamus, amygdala, and other regions of the limbic system.

O

Occipital NEP – Putative neuroepithelial division of the neurons and neuroglia of the occipital lobe. It is the target of *visual radiation fibers from the *lateral geniculate nucleus.

Oculomotor nerve – *See* **Nerve III**.

Oculomotor nucleus – Early-forming medial structure in the anterior mesencephalic tegmentum that is the source of the fibers of cranial *nerve III.

Olfactory bulb – Laminated brain structure where the first-order fibers of the *olfactory nerve terminate and the second-order fibers of the olfactory tract originate. It is composed of three classes of neurons: the early-generated large mitral cells, the intermediate tufted cells, and the late-generated small granule cells.

Olfactory bulb NEP – This NEP evaginates into the telencephalic area that is contacted by olfactory nerve axons, forming the olfactory recess. It generates some of the neurons in the olfactory bulb; the later-generated granule cells are supplied by the *rostral migratory stream.

Olfactory cortical NEP – This NEP is located near the *olfactory bulb NEP anterolateral to the basal telencephalic NEP. It generates some of the neurons in the *primary olfactory cortex.

Olfactory nerve (embryonic) – Composed of the fine axons of bipolar neurons in the olfactory epithelium that terminate in the *olfactory bulb. The sprouting nerve is recognizable as early as GW4.

Olfactory placode – Fate-restricted portion of the *cephalic placode whose progenitor cells will produce the olfactory epithelium and the olfactory bipolar neurons. The olfactory placode may exert an inductive influence on the diversification of the olfactory NEP.

Optic chiasm (embryonic) – Site of crossing of fibers of the *optic nerve. Fibers from the nasal half of each retina cross here to the opposite side while those from the temporal half proceed uncrossed. The earliest crossing fibers are seen in GW7.5 specimens.

Optic nerve – Large fiber tract composed of the axons of retinal ganglion cells. Traditionally, the portion of the tract between the eye and the *optic chiasm is referred to as cranial nerve II.

Optic (lens) placode – Fate-restricted portion of the *cephalic placode whose progenitor cells will produce the crystalline lens of the eye.

Optic tract – Large bundle of crossed and uncrossed retinal afferent fibers. In the human brain the majority of the fibers terminate in the *lateral geniculate body; others proceed to the *superior colliculus and some other diencephalic and mesencephalic structures.

Optic vesicle – Early diversifying component of the *prosencephalon that will become the source of the *retinal NEP, the *retinal pigment epithelium, and the neuroglia of the *optic nerve and the *optic chiasm. This part of the prosencephalon is already evaginated before closure of the *anterior neuropore.

Orbitofrontal NEP – Putative source of neurons and glia of the orbitofrontal cortex.

Otic placode – Fate-restricted segregated portion of the *cephalic placode located above the hyoid arch; it begins to evaginate prior to neural tube closure and is nearly completely invaginated by GW3.2.

Otic vesicle – The fully invaginated and fused *otic placode that is no longer attached to the head surface and is surrounded by the primordium of the petrous temporal bone. The otic epithelium is the source of neurons in the vestibular and spiral ganglia (*vestibulocochlear ganglion), the cochlea, the semicircular canals, the utricule, and the saccule. Its epithelium touches the brain surface at rhombomere 5.

P

Paracentral NEP – Putative neuroepithelium of the paracentral lobule (pre- and postcentral gyri) in the developing neocortex. It is flanked by the paracentral *subventricular zone and the distinctive paracentral *stratified transitional field.

Parahippocampal NEP – Putative source of the neurons and neuroglia of the subicular complex and the entorhinal cortex. It is flanked by the parahippocampal *subventricular zone and the parahippocampal *stratified transitional field.

Parietal lobe or **cortex** (**embryonic**) – Region of the developing neocortex bounded anteriorly by the *paracentral lobule and posteriorly by the *occipital lobe.

Parietal NEP – Long stretch of the cortical neuroepithelium containing the neural progenitor cells of the *parietal lobe. It is flanked by the parietal *subventricular zone and *stratified transitional field.

Perifascicular GEP – Fate-restricted glioepithelium, the presumed source of oligodendrocytes that surround a fiber tract, such as the *fornical GEP.

Pineal gland – Midline endocrine gland connected by its stalk to the pineal recess of the dorsal *diencephalic superventricle. It secretes melatonin and other indoleamines. It is believed to receive indirect visual input from the retina.

Pituitary gland – *See* **Anterior pituitary gland**; **Posterior pituitary gland.**

Pituitary placode – Fate-restricted portion of the *cephalic placode whose progenitor cells form Rathke's pouch that later becomes the *anterior pituitary gland. The pituitary placode may exert inductive influence on the *hypothalamic NEP to form the *posterior pituitary gland and to generate neurons that produce releasing factors and neurohormones.

Placode – *See* **Preplacode.**

Pons (embryonic) – Developing brainstem region, situated between the *isthmus and the *medulla, that surrounds the anteroventral part of the *rhombencephalic superventricle. It contains some early ascending, descending, and decussating fiber tracts, the sensory and motor nuclei of some of the cranial nerves, and the *reticular formation.

Pontine gray (embryonic) – This massive basal region of the *pons is just beginning to form during the late first trimester as neurons of the *anterior extramural migratory stream start to settle and the earliest descending *corticofugal fibers reach the site. Corticofugal axons that collateralize here are the principal afferents of the pontine gray neurons that are, in turn, the source of the pontocerebellar fibers of the *middle cerebellar peduncle.

Posterior commissure (embryonic) – Early-forming decussating fiber tract that interconnects some early generated nuclei of the pretectum.

Posterior extramural migratory stream – Subpial stream of young neurons that originate in the *precerebellar NEP. These neurons cross the midline ventrally, and settle on the opposite side to form two precerebellar nuclei contralaterally, the external cuneate nucleus and the lateral reticular nucleus.

Posterior intramural migratory stream – Stream of young neurons generated in the *precerebellar NEP that migrate inside the parenchyma to form the *inferior olive in the ventral medulla.

Posterior pituitary gland – The posterior lobe of the pituitary gland, also known as the neurohypophysis, is an evagination of the *hypothalamic NEP into posterior Rathke's pouch. Presumably, it is a glioepithelium that generates the highly specialized pituicytes that surround the axons of the paraventricular and supraoptic nuclei that are the source of oxytocin and vasopressin.

Precerebellar NEP – Dorsally situated neuroepithelium that lines the *rhombencephalic superventrticle in the vicinity of the lower rhombic lip and is the source of neurons of the *precerebellar nuclei. Neurons of its rostral division migrate in the *anterior extramural migratory stream and settle in the *pontine gray and the *reticular tegmental nucleus. Neurons of its posterior division form two migratory streams, the *posterior intramural migratory stream that forms the *inferior olive, and the *posterior extramural migratory stream that crosses to the opposite side and forms the *lateral reticular nucleus and the *external cuneate nucleus.

Preoptic area (embryonic) – Early developing region surrounding the preoptic recess of the *diencephalic superventricle. It is contiguous anteriorly with the basal telencephalon and blends posteriorly with the anterior *hypothalamus. It is implicated in the regulation of sexual behavior and other reproductive functions.

Preplacode – Unique peripheral germinal matrix on the surface of the head and neck that is closely associated with the *neural plate and *neural tube. It is composed of pluripotent – neurogenic and non-neurogenic – progenitor cells that generate diverse specialized components of the head. Its two distinct derivatives are the *cephalic placodes and the *branchial placodes.

Pretectal NEP – Germinal matrix anterior to the tectal NEP, the source of pretectal neurons that are the source of the early sprouting fibers of the posterior commissure.

Primary olfactory cortex – That part of the cerebral cortex that gets direct input from the olfactory bulb via the lateral olfactory tract. This cortex contains two cellular layers, a thin cell-dense layer II and a thick layer III of medium cell density. Many neurons appear to migrate into this part of the cortex from the *lateral migratory stream.

Primordial plexiform layer – The cell-sparse layer beneath the pia in the early developing *cerebral cortex. This is the first cortical layer to develop and contains the earliest generated *Cajal-Retzius cells, the subplate neurons, and some pioneer cortical afferent axons. A portion of this layer persists as layer I of the mature cortex.

Prosencephalon – Primordial vesicle of the forebrain that becomes divided into the paired lateral *telencephalon surrounding the telencephalic superventricles and the medial *diencephalon surrounding the diencephalic superventricle.

Purkinje cells (embryonic) – These neurons, which form a monolayer in the maturing cerebellar cortex, are generated in the *cerebellar NEP toward the end of the first trimester, after the production of the *cerebellar deep nuclear neurons. Hence, they are initially situated in the *cortical transition zone (cerebellar transitional field 6), adjacent to the cerebellar NEP, beneath the layers of deep neurons. Later they migrate toward the surface of the formative cerebellar cortex to settle beneath the *external germinal layer.

R

Rathke's pouch – The infolding *pituitary placode that, after fusion, forms the *anterior pituitary gland.

Red nucleus (embryonic) – A prominent nucleus in the maturing brain with a small-celled (parvocellular) and a large-celled (magnocellular) component. It is recognizable during the first trimester in the vicinity of the putative *rubral NEP.

Reticular formation – A large collection of early-developing neurons, enmeshed in a complex network of fibers in the core of the *medulla, the *pons, and the *mesencephalon.

Reticular tegmental nucleus (embryonic) – Situated dorsal to the *pontine gray, this precerebellar nucleus, also known as the nucleus reticularis tegmenti pontis, begins to form toward the end of the first trimester before the pontine gray forms.

Reticular nucleus (thalamus, embryonic) – An early-forming, thin belt of cells and fibers between the

parenchyma of the thalamus and the *internal capsule. Virtually all thalamocortical fibers traverse the thalamic reticular nucleus.

Retinal NEP – Component of the *optic vesicle germinal matrix that will generate the neurons of the retina.

Retinal pigment epithelium – Component of the *optic vesicle germinal matrix that will generate the non-neural pigment epithelium of the eye.

Rhombencephalic superventricle – The greatly expanded NEP-lined lumen of the embryonic *rhombencephalon, situated between the *isthmal canal rostrally and the *central canal caudally, and covered dorsally by the *medullary velum. Among NEP divisions lining the rhombencephalic superventricles are the *cerebellar NEP, the *precerebellar NEP, and the *rhombomere NEPs. The shrunken rhombencephalic superventricle becomes the enduring, *ependyma-lined fourth ventricle.

Rhombencephalon (embryonic) – An extremely heterogeneous hindbrain region lining the *rhombencephalic superventricle, that includes the developing cerebellum, pons, and medulla.

Rhombic lip, lower – NEP matrix that forms the posterior bridgehead of the medullary velum covering the *rhombencephalic superventricle. It is the source of precerebellar neurons that migrate in the *posterior intramural migratory stream and the *posterior extramural migratory stream.

Rhombic lip, upper – NEP matrix that forms the anterior bridgehead of the medullary velum covering the *rhombencephalic superventricle. It is a component of the cerebellar NEP. Following the formation of the *external germinal layer by the end of the first trimester, it is identified as the *germinal trigone of the cerebellum.

Rhombomeric NEPs – Prominent neuroepithelial evaginations (bulges) that line the lateral *rhombencephalic superventricle and are morphogenetically related to the *branchial arches and the *branchial placodes. Traditionally, the rhombomeres are distinguished by numbers, as R1 to R7. However, only R2 to R7 have shared characteristics; others identify R1 as the *cerebellar NEP which is very different from the other rhombomeres. We propose the following rhombomeric classification: R2-trigeminal NEP; R3-facial NEP; R4+R5-auditory-vestibular NEP; R6-glossopharyngeal NEP; and R7-vagal NEP.

Rostral migratory stream – A large stream of mitotic and postmitotic cells in the forebrain extending from the *subventricular zone of the cerebral cortex to the olfactory bulb. It is a source of late-generated olfactory granule cells and it persists through adulthood.

Rubral NEP – A distinctive neuroepithelial patch lining the *mesencephalic superventricle, situated between the *tectal NEP and the *tegmental NEP. It is the putative source of neurons of the early generated neurons of the *red nucleus.

S

Secondary germinal matrix – Layer or field of proliferative progenitors of neurons and neuroglia generated by the receding primary *neuroepithelium. Examples of secondary germinal matrices are the *external germinal layer of the cerebellum, the *subgranular zone of the hippocampal dentate gyrus, and the *subventricular zone of the cerebral cortex and the striatum. Typically, the secondary germinal matrices are the source of late-generated *microneurons.

Septal NEP – Midline telencephalic neuroepithelium that produces the neurons and neuroglia of the septal nuclei and Broca's area.

Sojourn zones – Transient cellular layers formed by young neurons that halt their migration for varying periods before they proceed to their final destination. Prominent sojourn zones are present in the *stratified transitional field of the cerebral cortex and in the *cerebellar transitional field. It is hypothesized that the sojourn zones are transient sites where connections are established between translocating neurons and ingrowing fiber tracts, as the first step in the formation of the gross circuitry of the CNS.

Stockbuilding NEP –Very few or no differentiating (postmitotic) cells surround the NEP matrix for some time during the early phase of its expansion. The absence of accumulating parenchymal cells indicates that during this period the sole function of NEP cell proliferation is the building of the stock of progenitor cells. Stockbuilding proliferation is referred to as symmetric cell division. This is followed by the asymmetric division of NEP cells, when one daughter cell exits the NEP matrix and starts to differentiate.

Stratified transitional field (STF) – As the *cortical plate begins to form, the field situated between it and the NEP matrix becomes stratified. This transient stratified field initially consists of a cell-dense ("cellular") and a cell-sparse ("fibrous") layer, STF5 and STF1, respectively. As development proceeds, several other layers emerge (STF2, STF3, STF4, STF6), with pronounced variations in their cellular and fiber composition in motor and sensory regions of the neocortex.

Invading *thalamocortical fibers mingle with *corticofugal fibers and with sojourning and migrating neurons in the STF to set up local and extracortical circuitry. A unique feature of the future sensory areas is the *honeycomb matrix. We hypothesize that the STF is a site where unspecified young neurons become specified and where the establishment of interconnections among them commences. This area is also known as the *intermediate zone in some cortical developmental studies.

Striatal NEP – Primary germinal source of neurons of the caudate nucleus, putamen, and globus pallidus. It has a large anterolateral and anteromedial division, also known as the lateral and medial eminences, and a small posterior division that generates the neurons of the tail of the caudate nucleus. The posterior striatal NEP is continuous with the *amygdaloid NEP.

Striatal subventricular zone (SVZ) – A massive *secondary germinal matrix beneath the striatal NEP. It generates the bulk of the neurons of the *striatum. It may also be the source of some cortical neurons.

Striatum – Large component of the *basal ganglia in the ventral telencephalon, consisting of the caudate nucleus, the putamen, and the pallidum (globus pallidus).

Strionuclear GEP – Fate-restricted glioepithelium, the putative source of the neuroglia of the stria terminalis, stria medullaris, and possibly other nearby fiber tracts.

Strionuclear NEP – Putative neuroepithelial source of the neurons of the bed nucleus of the stria terminalis. It is situated beneath the *striatal NEP in a notch near the *foramen of Monro.

Subgranular zone (hippocampus) – *Secondary germinal matrix beneath the granular layer of the hippocampal *dentate gyrus, the source of late generated dentate granule cells. It is recognizable in incipient form by the end of the first trimester and persists into adulthood.

Subpial granular layer – Transient cellular layer between the pia and cortical layer I in some regions of the developing *cerebral cortex. It may be a source of cortical astrocytes.

Substantia nigra (embryonic) – An early-generated pigmented region in the *tegmentum abutting the future cerebral peduncle. It has two components, the dopaminergic pars compacta and the GABAergic pars reticulata.

Subthalamic NEP – Neuroepithelial division between the *thalamic NEP and the *hypothalamic NEP that generates neurons in Forel's fields and the zona incerta.

Subthalamus (embryonic) – Diencephalic region situated between the *thalamus dorsally and the *hypothalamus ventrally. Its major components, the *zona incerta and Forel's fields, are recognizable in late first trimester fetuses.

Subthalamic nuclear NEP – *See* **Luysiian NEP**

Subventricular zone (SVZ) – Secondary germinal matrix, derived from the primary *neuroepithelium. The SVZ flanks the NEP during early development and then abuts the ependyma when the NEP dissolves. The nuclei of proliferative SVZ cells, unlike the nuclei of NEP cells, do not shuttle to the lumen of the ventricle during mitosis. Prominent SVZs in the telencephalon are found in the *cerebral cortex and the *striatum. The cells of the *rostral migratory stream derive from the anterior telencephalic SVZ.

Superarachnoid reticulum – Expanding and then shrinking cell-sparse tissue between the early-forming pia and the formative dura. This fluid-filled and spongy meningeal tissue provides expansion space for the developing parenchyma and may contain trophic factors to promote that expansion.

Superior colliculus (embryonic) – Anterior component of the *tectum (known in lower vertebrates as the optic lobe) is a direct target of optic nerve fibers. Several waves of migrating cells suggest its imminent lamination by the end of the first trimester. There are indications that the entering optic fibers form a *honeycomb matrix superficially, similar to that found in the occipital lobe.

Superventricles – The hypertrophied fluid-filled ventricles of the embryonic and early-fetal brain, the superventricles are lined by the expanding *neuroepithelium. Four large components are distinguished: the *telencephalic, *diencephalic, *mesencephalic, and *rhombencephalic superventricles. The initial expansion of the lumen of the superventricles antedates the "flowering" of the embryonic *choroid plexus. However, the sustained inflation of the telencephalic and rhombencephalic superventricles is correlated with the great expansion of the embryonic choroid plexus at these sites. The expanded shorelines of the superventricles promote *stockbuilding NEP cell division, which is sustained for a long time in the cerebral cortex and the cerebellum of the human brain. The superventricles may contain trophic factors that promote NEP cell division.

T

Tectal NEP – Extensive, smooth-surfaced NEP that lines the dorsal bank of the *mesencephalic superventricle. Its most anterior part generates the neurons and neuroglia of the pretectum, a large central part generates those of the *superior colliculus, and its smaller posterior part generates those of the *inferior colliculus.

Tectum (embryonic) – Dorsal region of the *mesencephalon, consisting of the *pretectum, *superior colliculus, and *inferior colliculus.

Tegmental NEP – The variegated ventral matrix of the *mesencephalic NEP that contains small NEP patches that produce neurons and neuroglia for various nuclei, such as the *red nucleus, the *oculomotor nucleus, the *substantia nigra, and the ventral tegmental area.

Tegmentum (embryonic) – Ventral and ventrolateral region of the *mesencephalon. In addition to several brainstem nuclei, it contains many early-forming ascending, decussating, and descending fiber tracts. Some tegmental nuclei have been implicated in somatomotor and visceromotor functions. The onset of development of some components of the tegmentum precede development of the *tectum.

Telencephalic superventricle – The largest component of the *superventricles, the paired telencephalic superventricle begins to expand during the early first trimester and shrinks considerably during the third trimester. It is lined laterally, dorsally, and dorsomedially by the extensive *cortical NEP, and ventromedially and ventrally by the smaller *olfactory, *septal, *striatal, *hippocampal, and *amygdaloid NEPs. A large portion of its lumen is occupied by the fetal telencephalic *choroid plexus. The shrunken telencephalic superventricle becomes transformed into the enduring lateral ventricle line by *ependyma.

Telencephalon (embryonic) – Extensive forebrain region consisting of both cortical and nuclear (subcortical) components. Among its cortical components are the *cerebral cortex, the *olfactory bulb, and the *hippocampus. Among its nuclear components are the *striatum, *the nucleus accumbens, and the *septum.

Temporal NEP – Putative source of neurons and neuroglia of the future temporal lobe, the lateral and ventral portion of the developing cerebral cortex that will later become separated from much of the cerebral hemisphere by the lateral fissure. The temporal NEP is flanked during fetal development by the *subventricular zone and the *stratified transitional field.

Thalamic NEP – Large division of the *diencephalic NEP, situated above the *subthalamic NEP. Its mosaic divisions are the putative source of neurons and neuroglia of many thalamic nuclei, including the *reticular, *lateral geniculate, and *medial geniculate nuclei.

Thalamocortical fibers (embryonic) – Collective term for the large afferent tracts, including the *visual radiation, that proceed from relay nuclei in the thalamus, by way of the *internal capsule, to the *cerebral cortex. Early thalamocortical fibers reach the base of the developing cerebral cortex by GW8 but may not reach the cortical plate for weeks thereafter.

Third ventricle – *See* **Diencephalic superventricle.**

Transpontine corticofugal tract (embryonic) – Portion of the large descending fiber tract in the maturing brain that traverses the *pontine gray and gives off collaterals there. Pioneering fibers of this tract are present by the end of the first trimester.

Trigeminal ganglion – A large clump of peripheral sensory neurons located lateral to the trigeminal NEP in rhombomere 2. It is the source of the sensory axons in nerve V that carry light touch and pressure information from the face and jaw. These neurons are presumably generated by the neural crest and by germinal cells in a branchial placode at the junction of the *maxillary process and the mandibular arch.

Trigeminal, motor nucleus (embryonic) – Aggregate of trigeminal somatic motor neurons situated medial to the *trigeminal principal sensory nucleus. It is recognizable in late first trimester embryos.

Trigeminal, principal sensory nucleus (embryonic) – The second-order sensory neurons in the trigeminal system located dorsal and lateral to the incoming sensory root of cranial *nerve V. It receives topographic somatosensory input from the face and mouth, and its efferents cross the midline in the pons and proceed to the somatosensory thalamus in close association with the *medial lemniscus. The nucleus is prominent by the late first trimester.

Trigeminal, spinal nucleus (embryonic) – A continuation of the *trigeminal principal sensory nucleus that extends caudally through the *medulla to the second cervical level of the *spinal cord. It is prominent by the late first trimester.

Trigeminal NEP – *See* **Rhombomeric NEPs**

Trochlear nucleus – Aggregate of somatic motor neurons located posterior to the *oculomotor nucleus that

innervate the superior oblique muscle of the eye by way of cranial *nerve IV.

V

Vagal ganglia – Superior and inferior clumps of peripheral sensory neurons located in arch IV and extending posteriorly along rhombomere 7. These ganglia are the source of nerve X sensory axons that enter the brain at rhombomere 7 carrying visceral sensory information. These neurons are presumably generated by cells in the neural crest and by a branchial placode in arch IV.

Vagal NEP – *See* **Rhombomeric NEPs .**

Vermis – *See* **Cerebellum (vermis)**.

Vestibulocochlear ganglion – A large clump of peripheral sensory neurons located adjacent to the otic vesicle that later subdivides into the vestibular ganglion and the spiral ganglion. It is the source of nerve VIII axons that enter the brain at rhombomere 4 carrying vestibular and auditory information. These neurons are presumably generated by cells in the otic vesicle epithelium.

Visual radiation (embryonic) – Thalamocortical fibers that originate in the *lateral geniculate nucleus and terminate in the striate cortex of the *occipital lobe. The identification of *Meyer's loop at GW11 suggests that this tract may reach the occipital lobe by the end of the first trimester.

W

White matter – General term for extensive regions in the brain and spinal cord composed of myelinated fiber tracts but few or no neuronal cell bodies. In histological preparations with myelin stains, the white matter appears black. In laminated brain regions, as in the *cerebral cortex, the white matter is called the medullary layer.

Z

Zona incerta (embryonic) – Region in the *subthalamus with uncertain boundaries with Forel's fields. It is a prominent area in the late first trimester *diencephalon.