Basic Neuroanatomy, Physiology, and Chemistry for Neuropathologists

Society of Toxicologic Pathology – India (STP-I)
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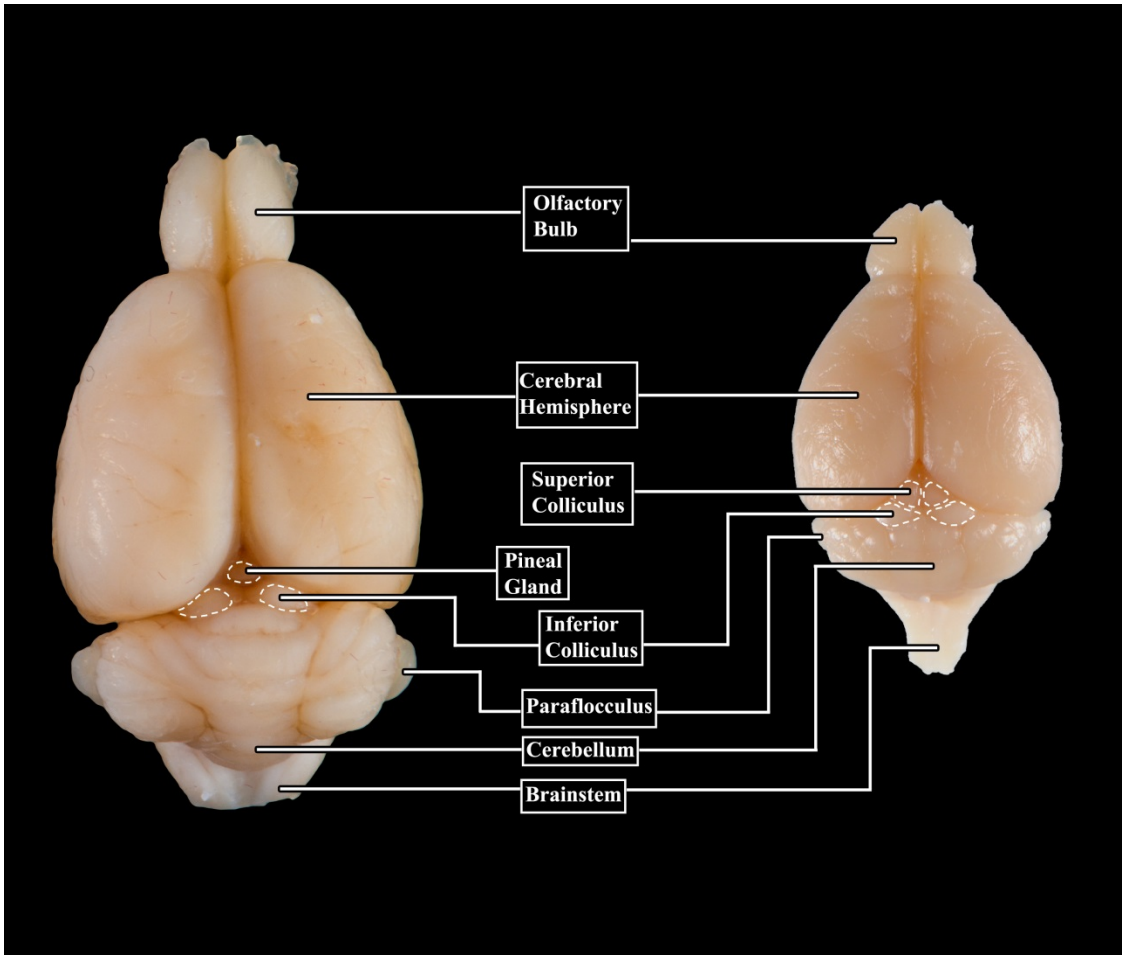
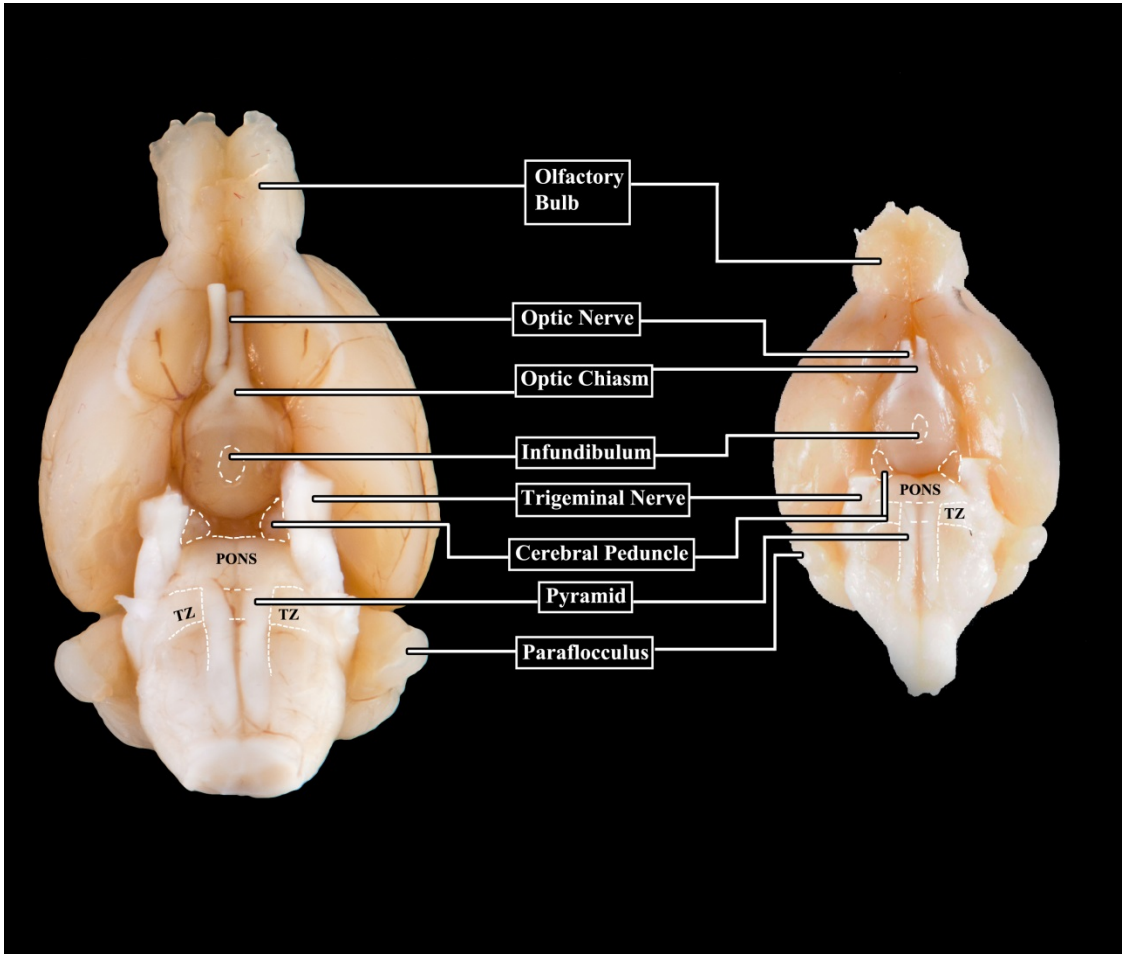
US Food and Drug Administration/CDER
Division of Psychiatric Products

Disclaimer

The opinions expressed in this presentation are my own and do not reflect official support or endorsement by the Food and Drug Administration


Olfactory Bulb
Cerebral Hemisphere
Superior Colliculus
Pineal Gland
Inferior Colliculus
Paraflocculus
Cerebellum
Brainstem


Olfactory Bulb
Optic Nerve
Optic Chiasm
Infundibulum
Trigeminal Nerve
Cerebral Peduncle
Pyramid
Parafloccculus
PONS
TZ
TZ
PONS
TZ

j. **Seven** cross-sections of the brain **taken at levels (brain matrix molds may be used) shown in Figure 5a (rat) and 5b (mouse)** shall include: (1) **olfactory bulb (mid-level); (2) fronto-parietal** cortex **including** basal ganglia **(1-2 mm cranial to the optic chiasma)**; **(3) mid-**parietal cortex and thalamus **(mid-point of the infundibulum); (4) mid-brain with substantia nigra and red nucleus (mid-point of anterior colliculus); (5) posterior colliculi (mid-point of posterior calliculus); (6) mid-cerebellum including cranial nerve VIII; and (7) posterior medulla through the area postrema (2-3 mm anterior to termination of the cerebellum). If small brains preclude obtaining seven quality sections, a minimum of five sections shall be obtained to include sections 1-4 and 6 corresponding to Figure 5b below. Sections 'b' through 'h' shall be placed in the cassette (large cassette for thick sections) with rostral surface down for sectioning.** If any lesions are observed after sectioning, they shall be noted on the IANR.

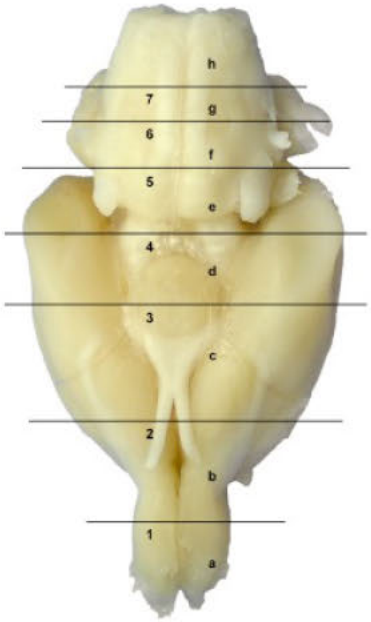


Figure 5a

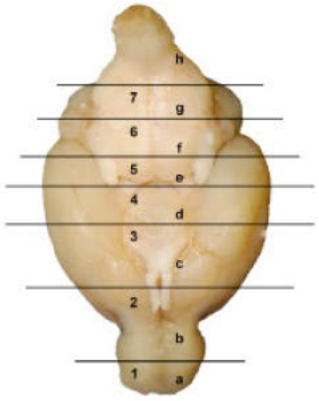
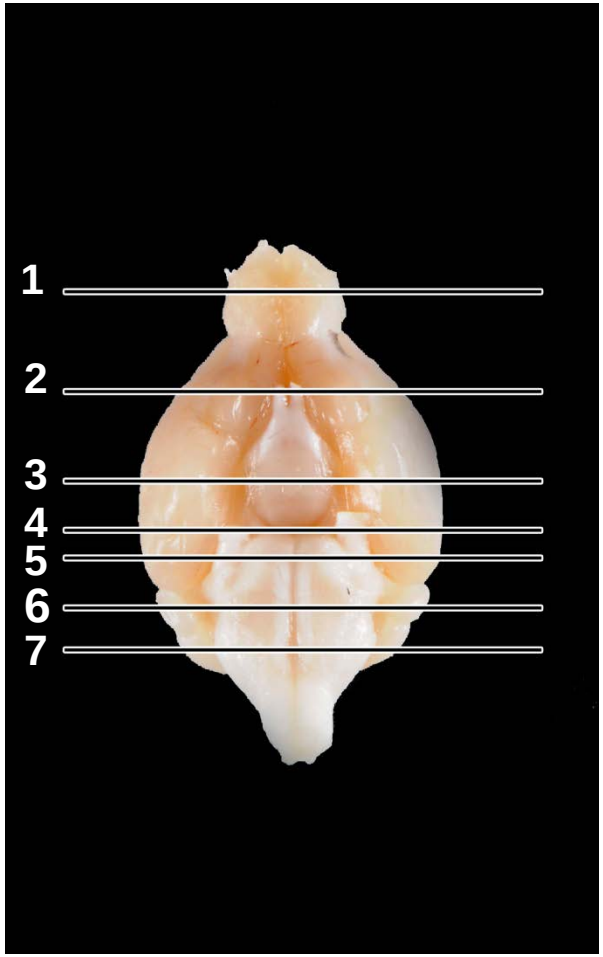


Figure 5b

B6C3F1 Mouse

SPECIFICATIONS
FOR THE CONDUCT OF STUDIES
TO EVALUATE THE TOXIC AND CARCINOGENIC POTENTIAL
OF CHEMICAL, BIOLOGICAL AND PHYSICAL AGENTS
IN LABORATORY ANIMALS
FOR THE NATIONAL TOXICOLOGY PROGRAM (NTP)


1
2
3
4
5
6
7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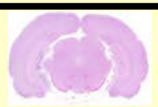
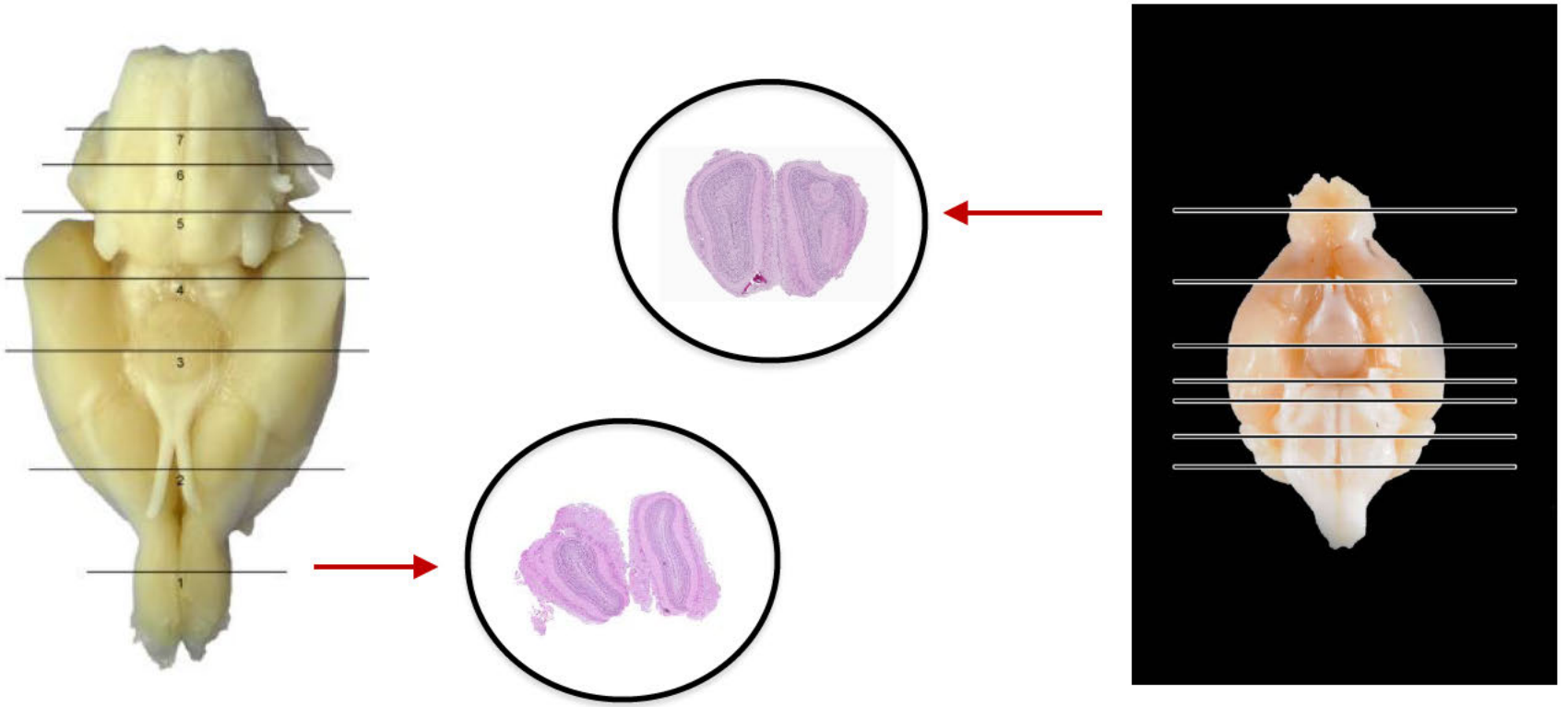
Neuroanatomic subsites

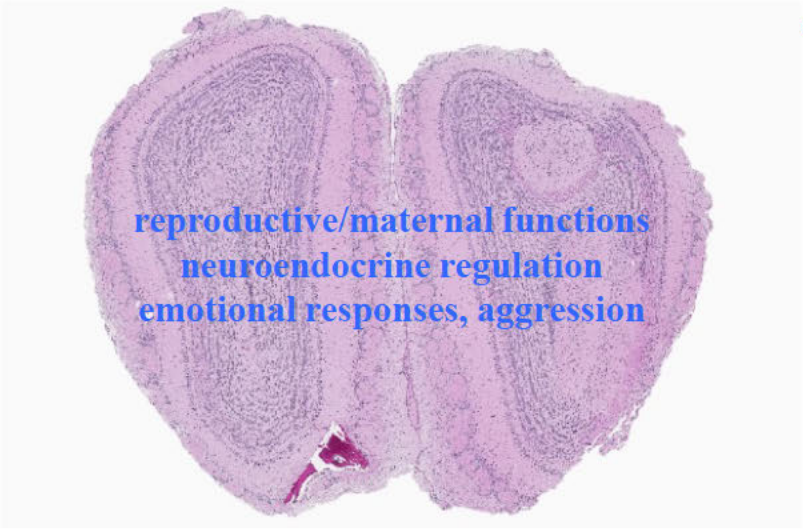
NEUROANATOMIC SUBSITES		
	**NTP-7 Level 1**	olfactory bulb (olfactory nerve layer, glomerular layer, external and internal plexiform layers, mitral cell layer, and granule cell layer)
	**NTP-7 Level 2**	fronto-parietal cortex, cingulate cortex, corpus callosum, caudate-putamen, (internal capsule, globus pallidus), septal nuclei, anterior commissure, accumbens nucleus, piriform cortex, optic chiasm or nerve, lateral olfactory tract
	**NTP-7 Level 3**	fronto-parietal cortex, retrosplenial cortex, auditory (temporal) cortex, amygdaloid nuclei, hippocampus (CA regions - 1,2,3, dentate gyrus), habenular nucleus, thalamus, hypothalamus, internal capsule, (globus pallidus)
	**NTP-7 Level 4**	visual (occipital) cortex, auditory (temporal) cortex, entorhinal cortex, superior colliculus, periaqueductal gray, medial geniculate body, red nucleus, raphe nuclei, cerebral peduncle, substantia nigra
	**NTP-7 Level 5**	inferior colliculus, locus coeruleus, mesencephalic trigeminal nucleus, principal sensory nucleus of CN V, motor trigeminal nucleus, superior olivary nucleus, pyramidal tracts
	**NTP-7 Level 6**	cerebellar lobules (vermis, ansiform, paraflocculus, lingula), facial (CN VII) nucleus, spinal trigeminal tract, vestibular nucleus, cochlear nucleus, raphe nuclei, pyramidal tracts
	**NTP-7 Level 7**	area postrema, solitary tract nucleus, vagal (CV X) nucleus, hypoglossal (CN XII) nucleus, reticular formation, raphe nuclei, inferior olivary nucleus, pyramidal tracts, spinal trigeminal tract

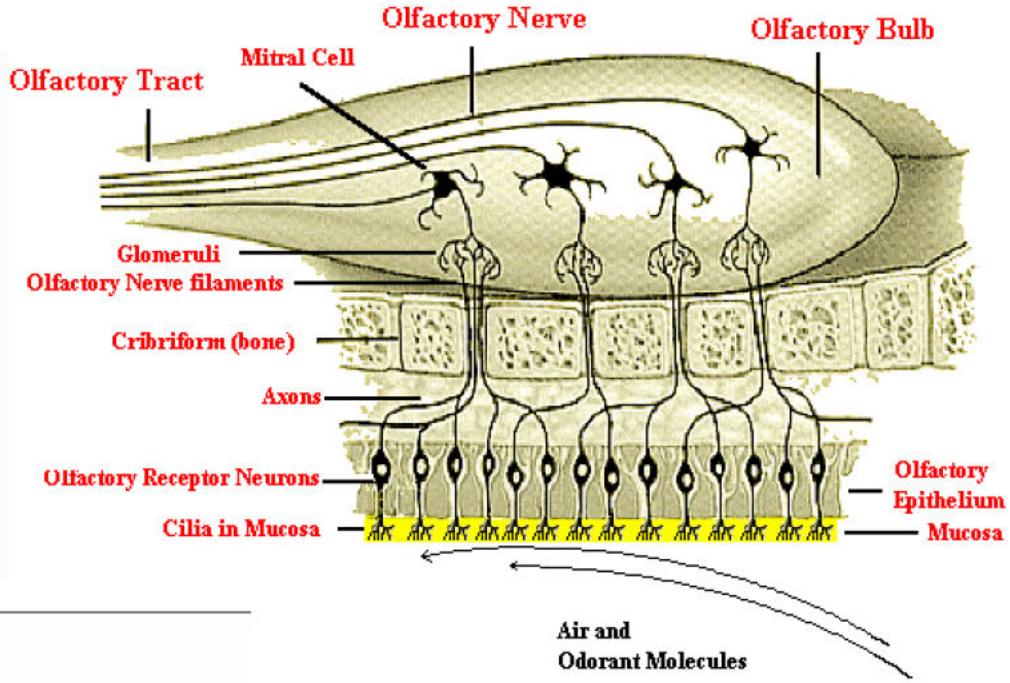
Level 1: mid-olfactory bulb



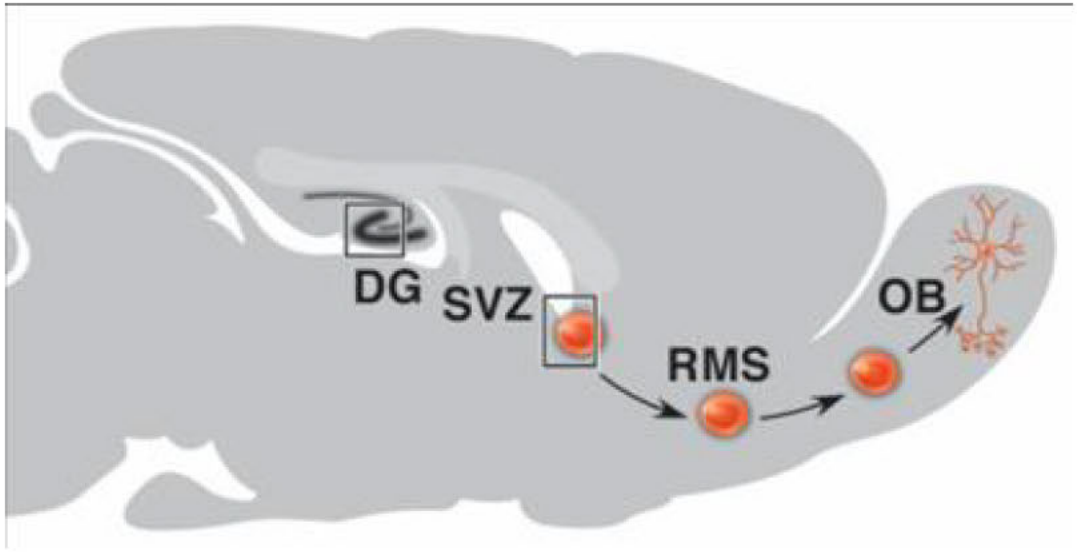
	**NTP-7 Level 1**	olfactory nerve layer, glomerular layer, external and internal plexiform layers, mitral cell layer, and granule cell layer

Level 1





humanphysiologywiki2011.wikispaces.com



http://neuro.dept.med.gunma-u.ac.jp

FDA notice on 6/16/2009

FDA Advises Consumers Not To Use Certain Zicam Cold Remedies
Intranasal Zinc Product Linked to Loss of Sense of Smell

The U.S. Food and Drug Administration today advised consumers to stop using three products marketed over-the-counter as cold remedies because they are associated with the loss of sense of smell (anosmia). Anosmia may be long-lasting or permanent.

The products are:
--Zicam Cold Remedy Nasal Gel
--Zicam Cold Remedy Nasal Swabs
--Zicam Cold Remedy Swabs, Kids Size (a discontinued product)

The FDA has received more than 130 reports of loss of sense of smell associated with the use of these three Zicam products. In these reports, many people who experienced a loss of smell said the condition occurred with the first dose; others reported a loss of the sense of smell after multiple uses of the products.

"Loss of sense of smell is a serious risk for people who use these products for relief from cold symptoms," said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research (CDER). "We are concerned that consumers may unknowingly use a product that could cause serious harm, and therefore we are advising them not to use these products for any reason."

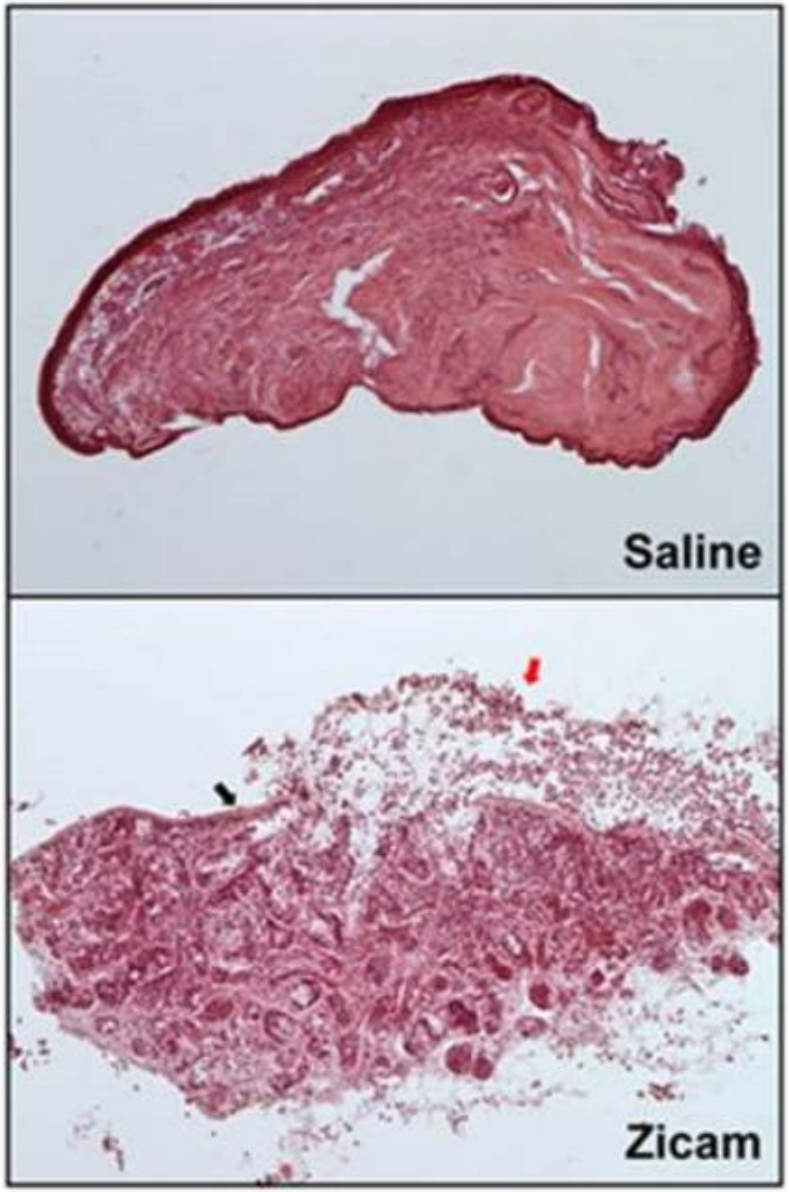
People who have experienced a loss of sense of smell or other problems after use of the affected Zicam products should contact their health care professional. The loss of sense of smell can adversely affect a person's quality of life, and can limit the ability to detect the smell of gas or smoke or other signs of danger in the environment.

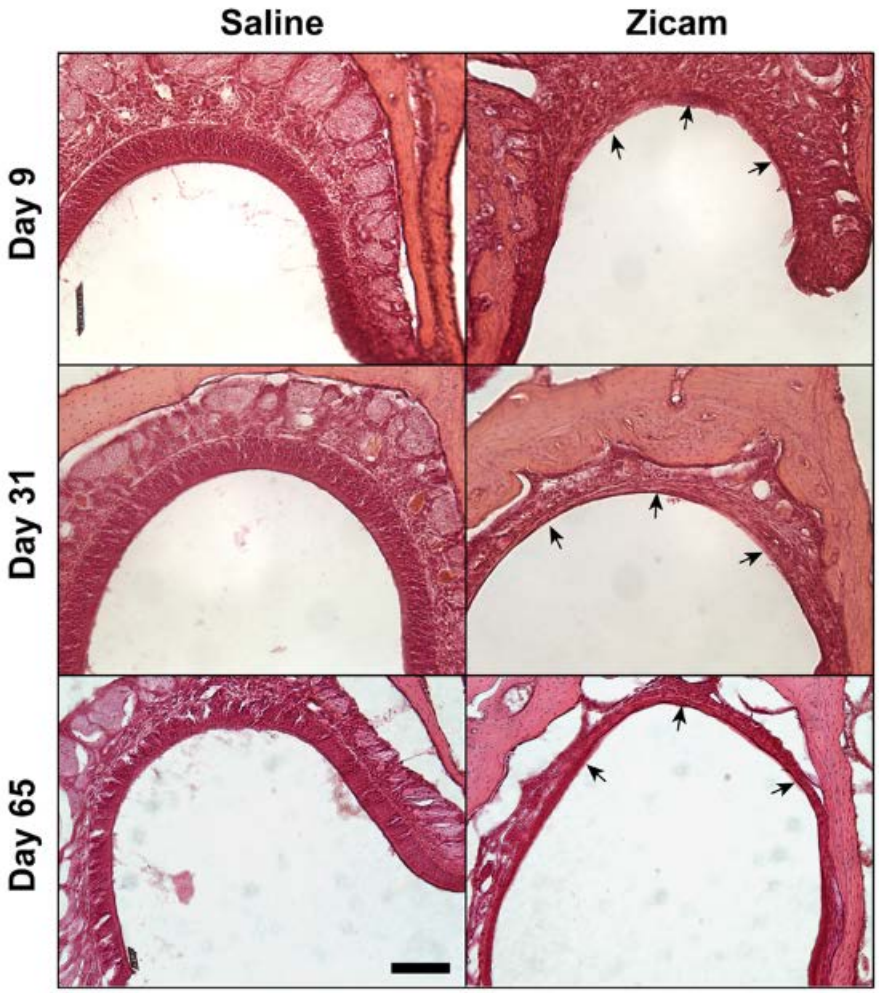
The FDA has issued Matrixx Initiatives, maker of these Zicam products, a warning letter telling it that these products cannot be marketed without FDA approval.

"Companies have an obligation to the public to demonstrate to the FDA that their products are safe, particularly when there is evidence they may be causing serious adverse events, and they are marketed for minor, self-limiting conditions like the common cold," said Deborah M. Autor, director of CDER's Office of Compliance.

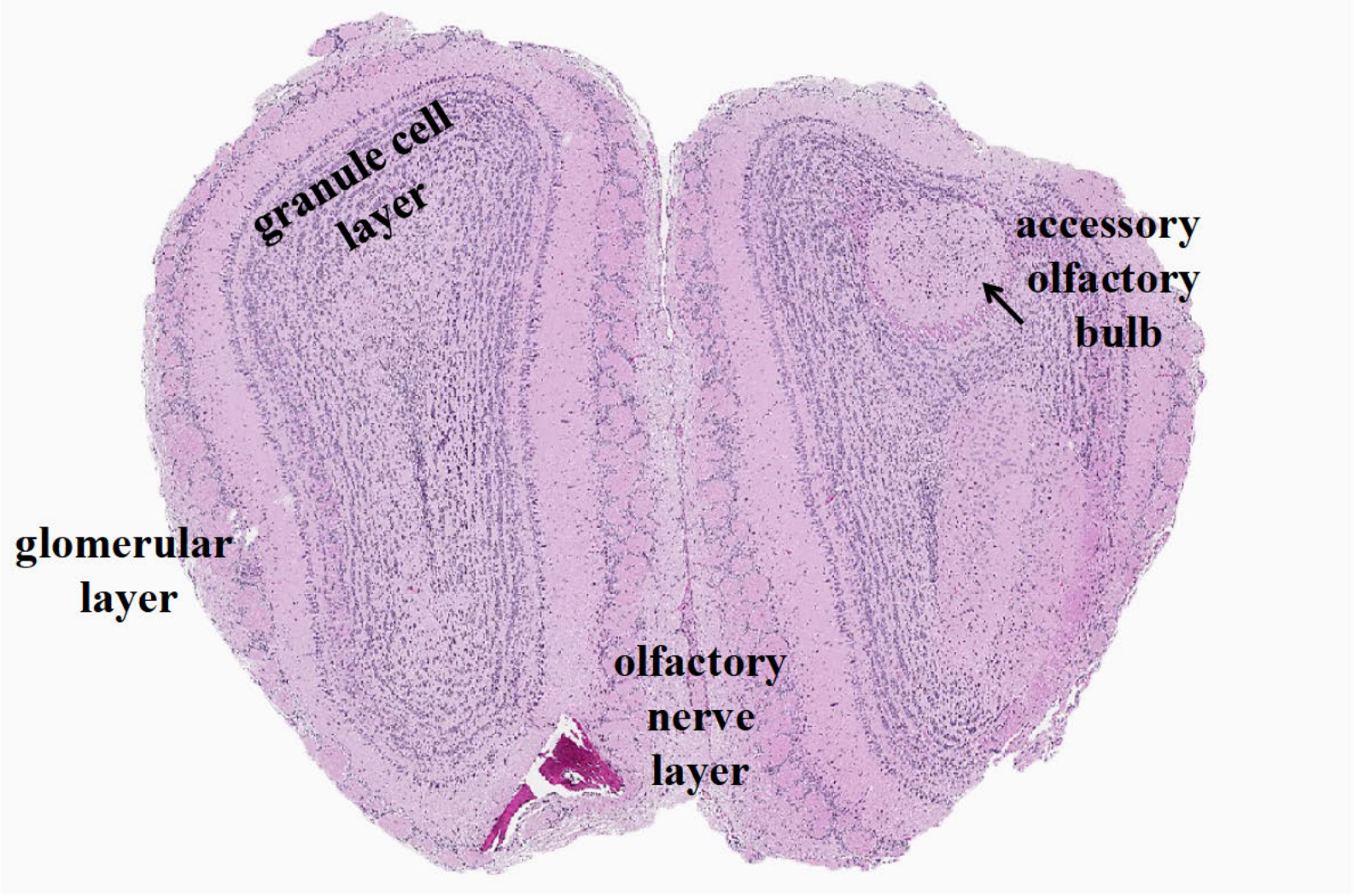
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm167065.htm

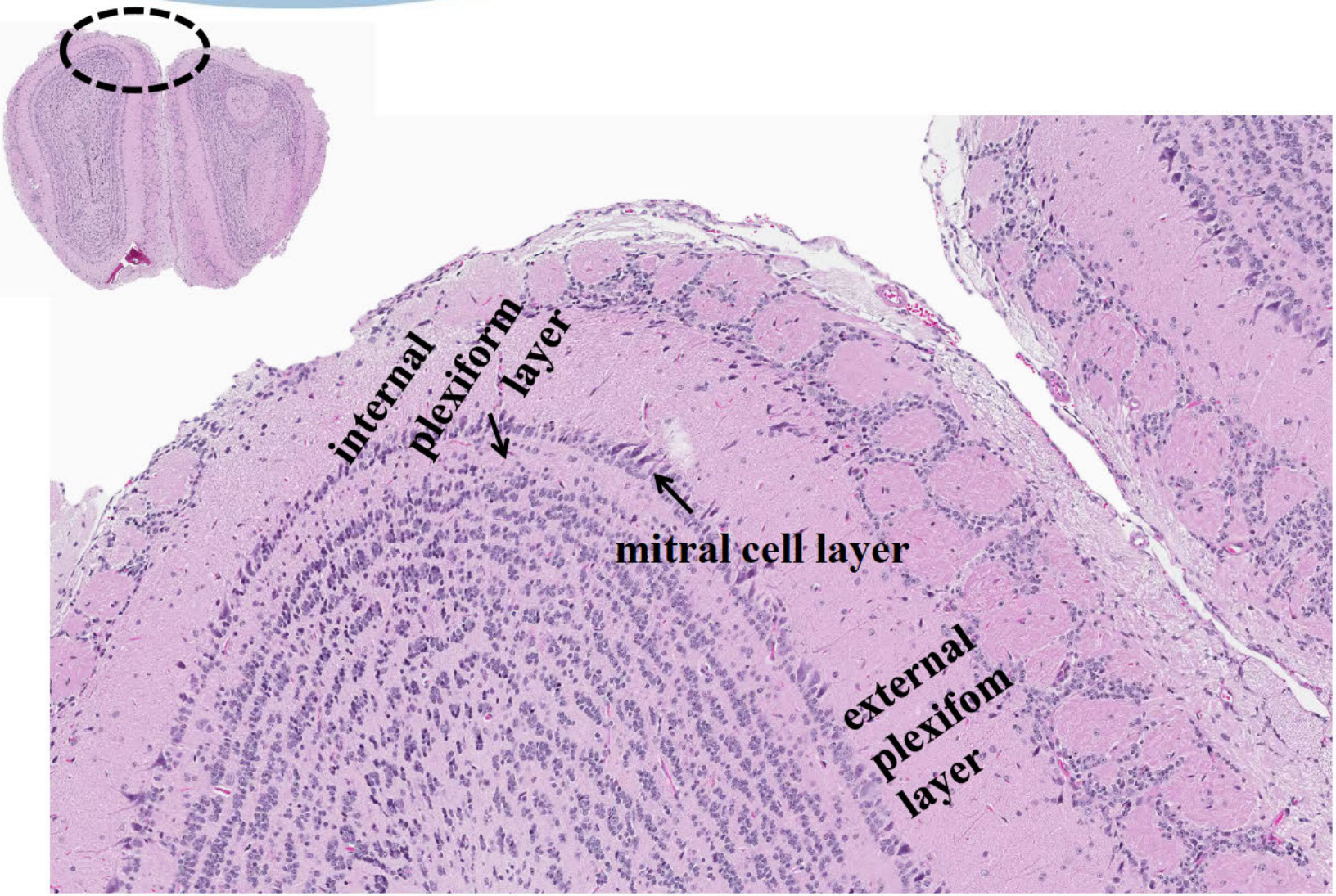
Slide Courtesy: Drs. Patel and Whittaker, FDA-CDER



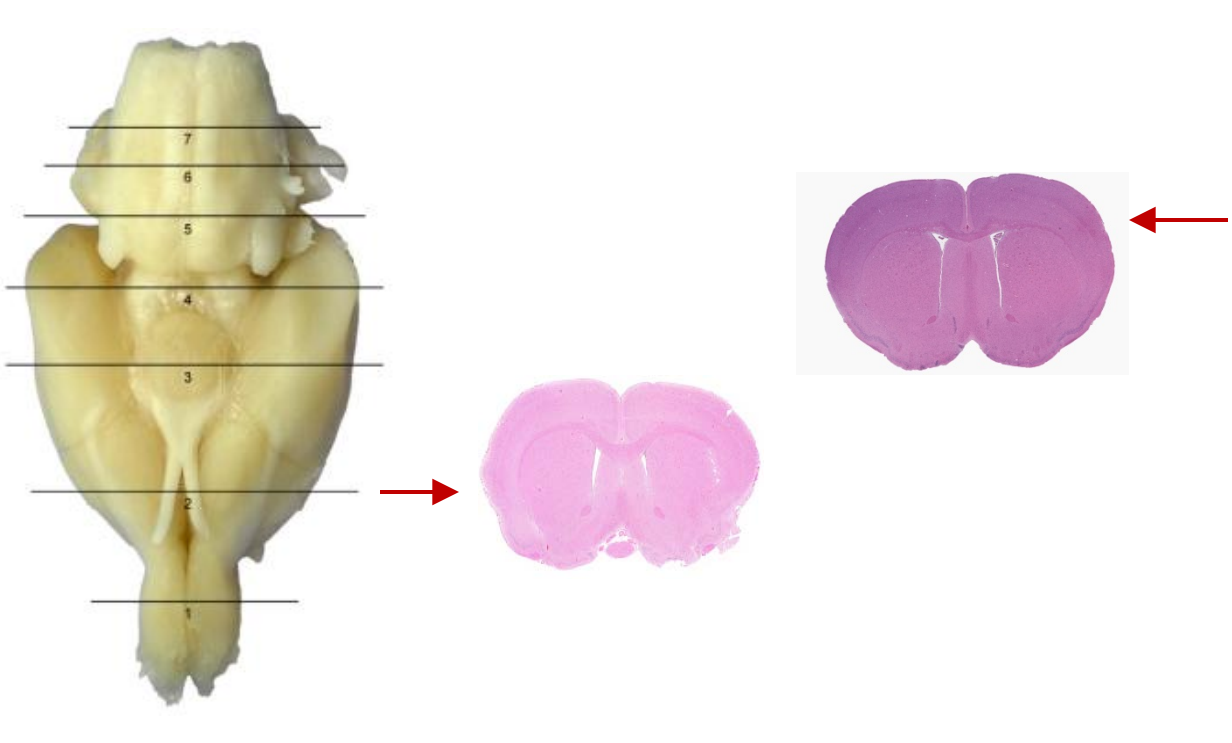


Lim et al, 2009

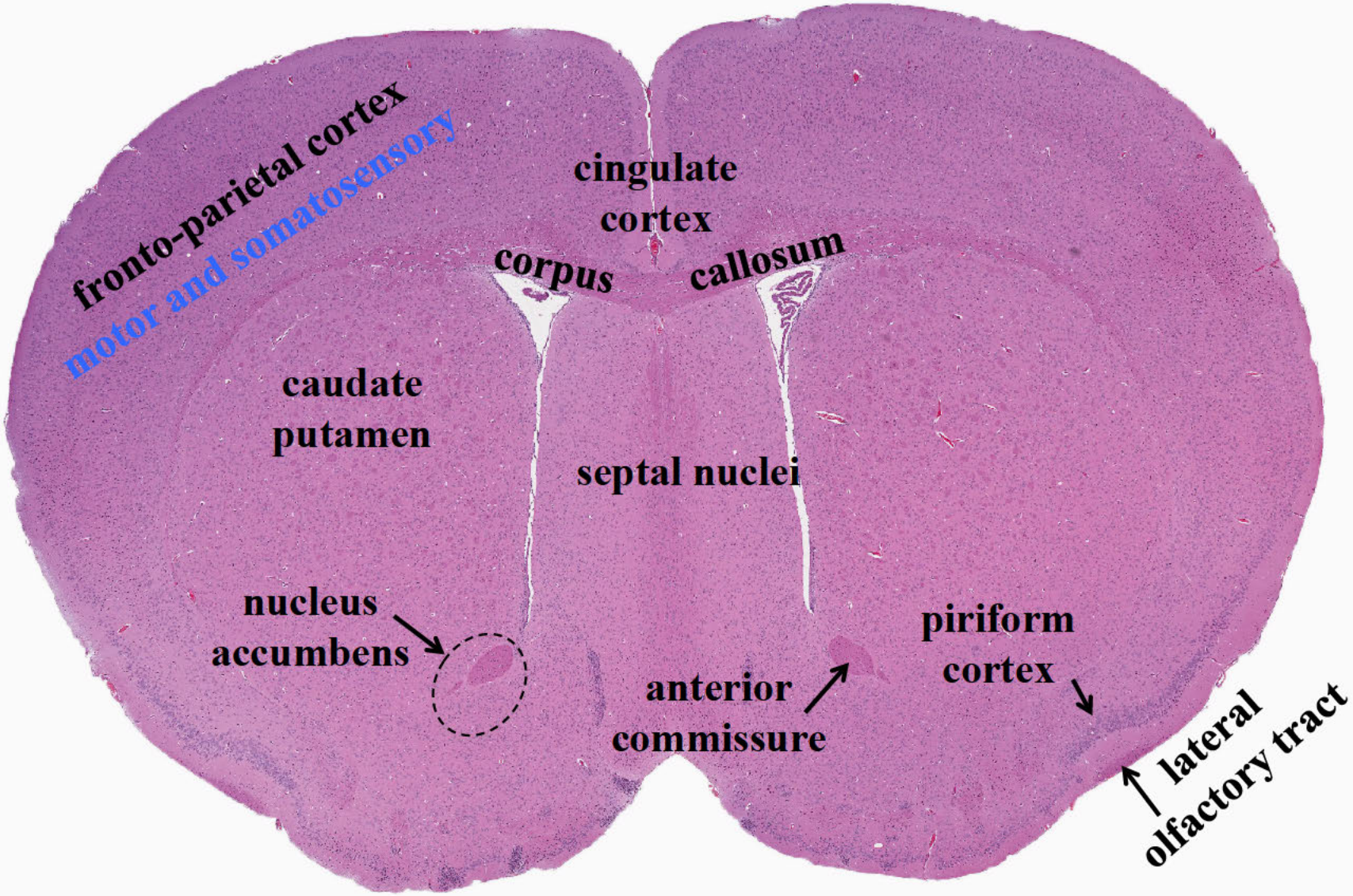

granule cell layer
accessory olfactory bulb
glomerular layer
olfactory nerve layer

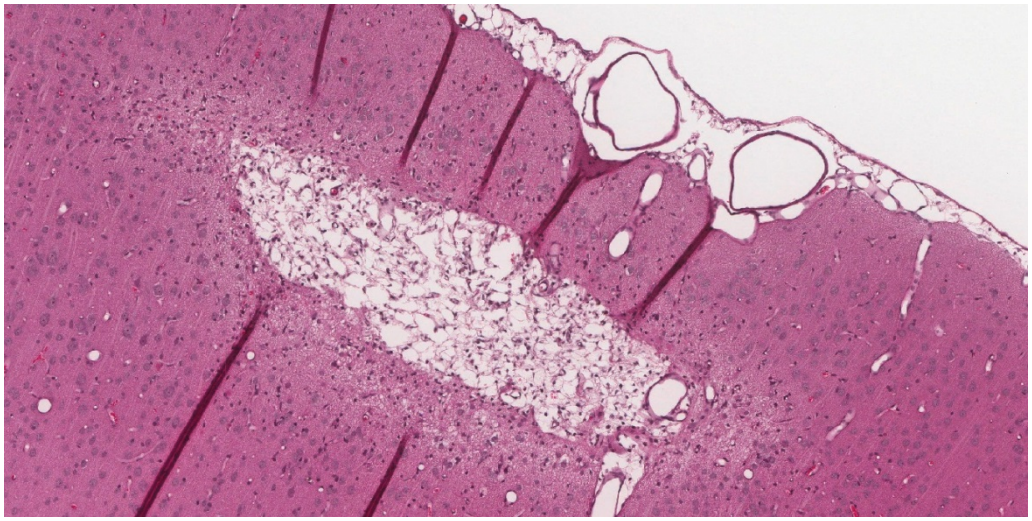

internal plexiform layer
mitral cell layer
external plexifom layer

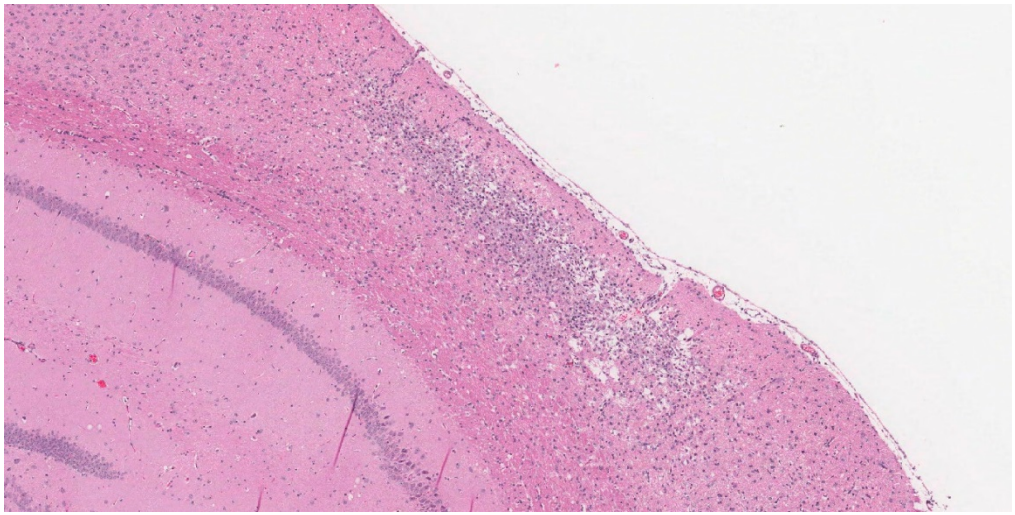
Level 2: 1-2 mm cranial to the optic chiasm

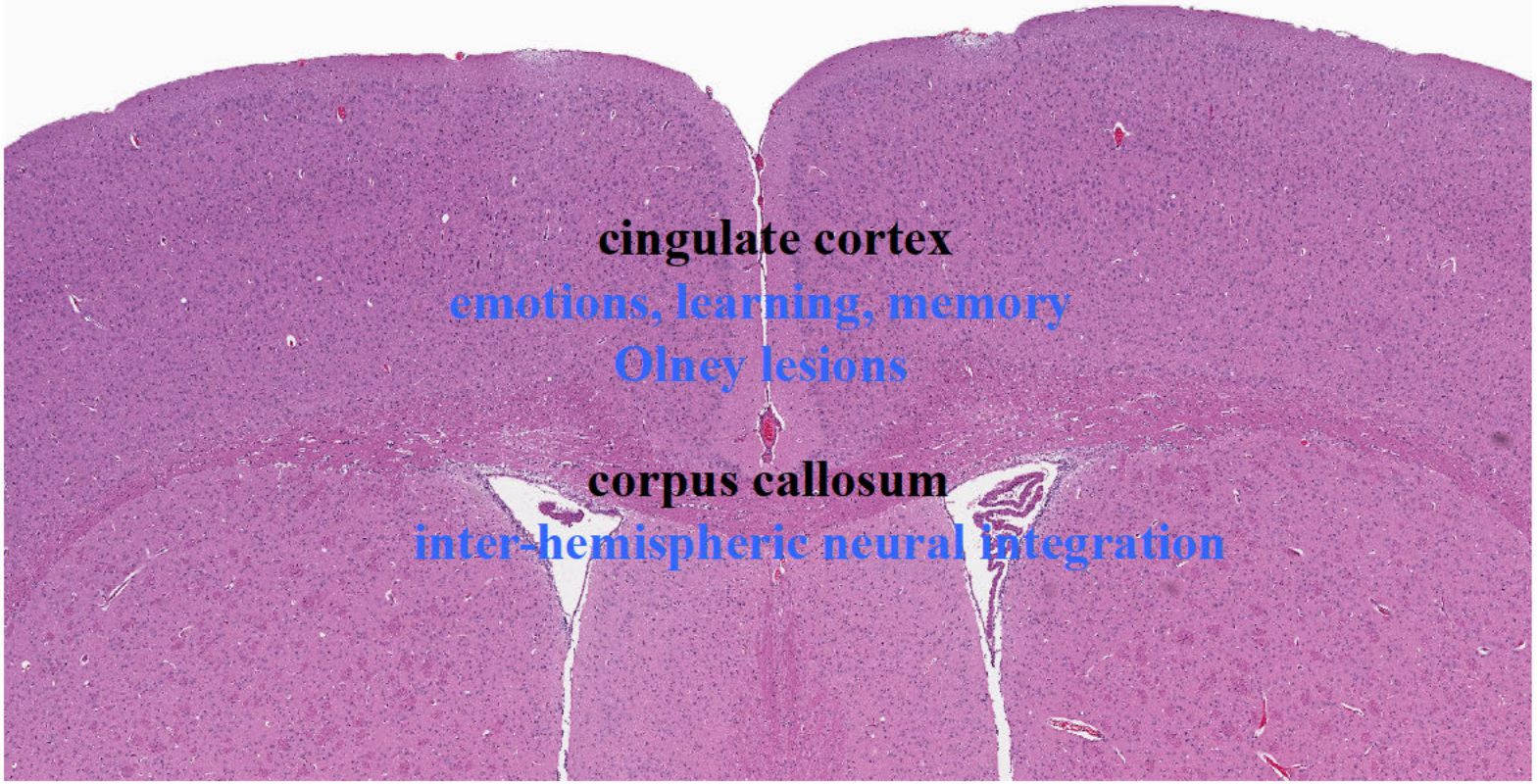


	**NTP-7 Level 2**	fronto-parietal cortex, cingulate cortex, corpus callosum, caudate-putamen, (internal capsule, globus pallidus), septal nuclei, anterior commissure, accumbens nucleus, piriform cortex, optic chiasm or nerve, lateral olfactory tract

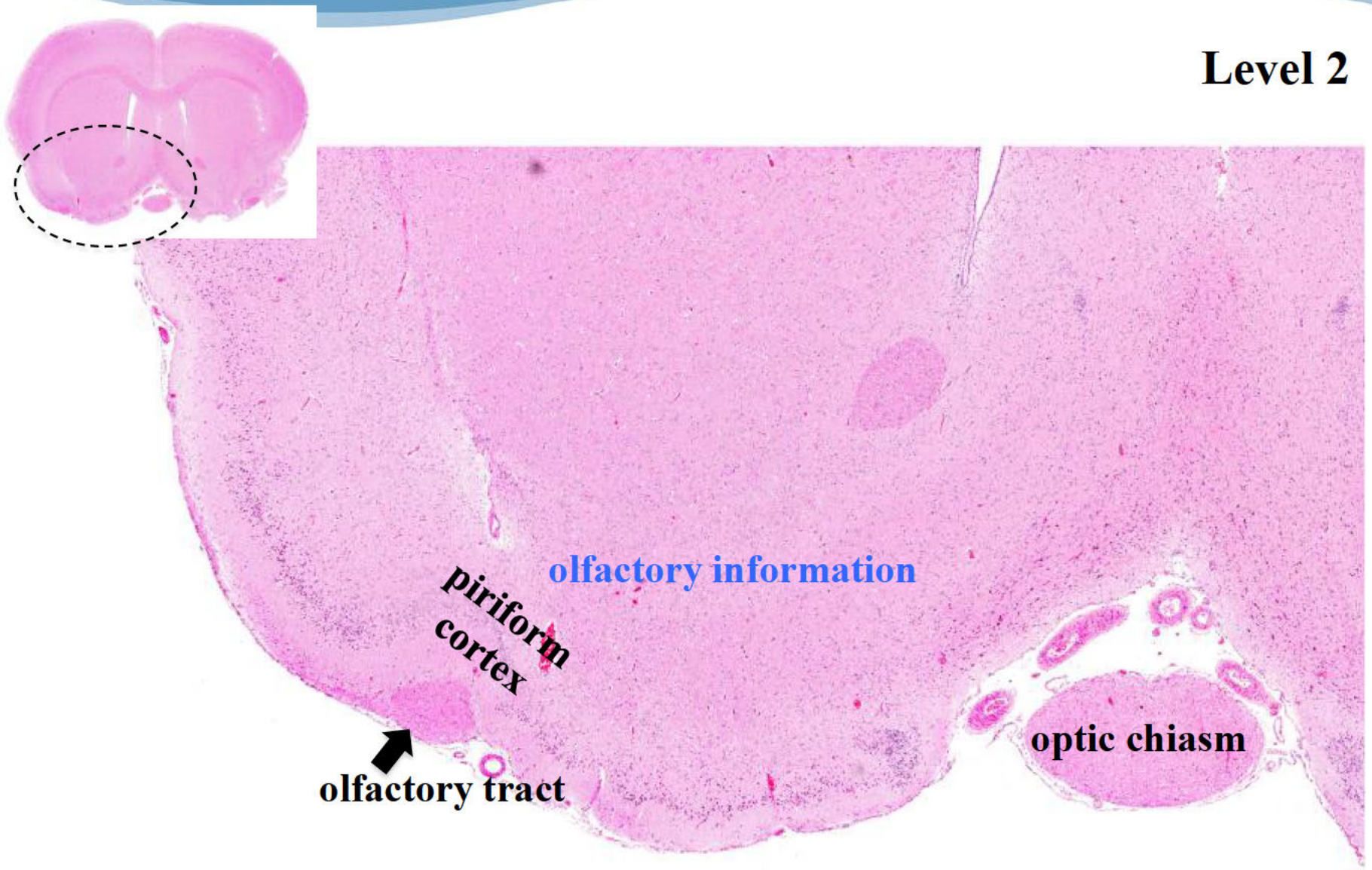

fronto-parietal cortex
motor and somatosensory
cingulate
cortex
corpus
callosum
caudate
putamen
septal nuclei
nucleus
accumbens
anterior
commissure
piriform
cortex
lateral
olfactory tract



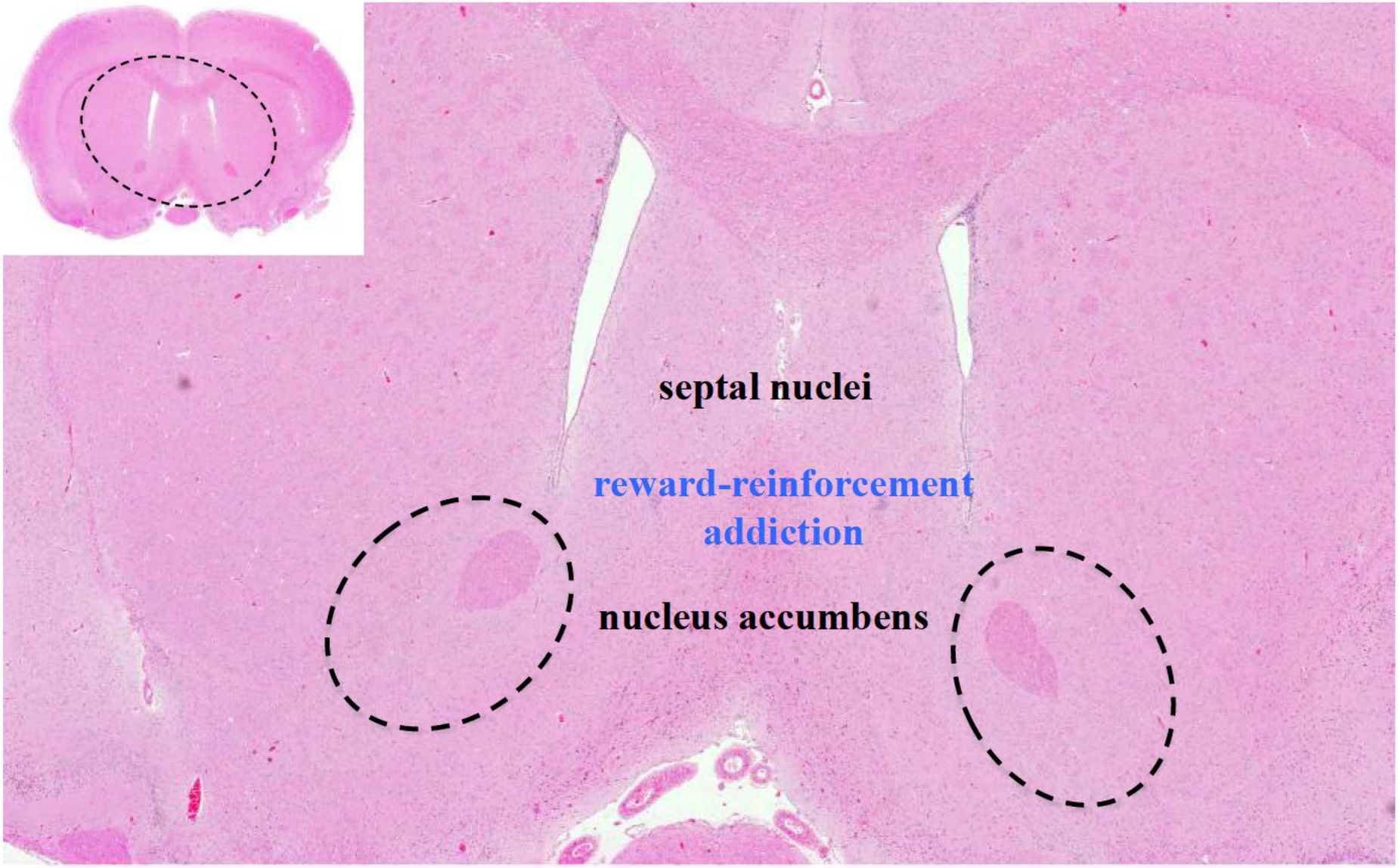



cingulate cortex
emotions, learning, memory
Olney lesions
corpus callosum
inter-hemispheric neural integration

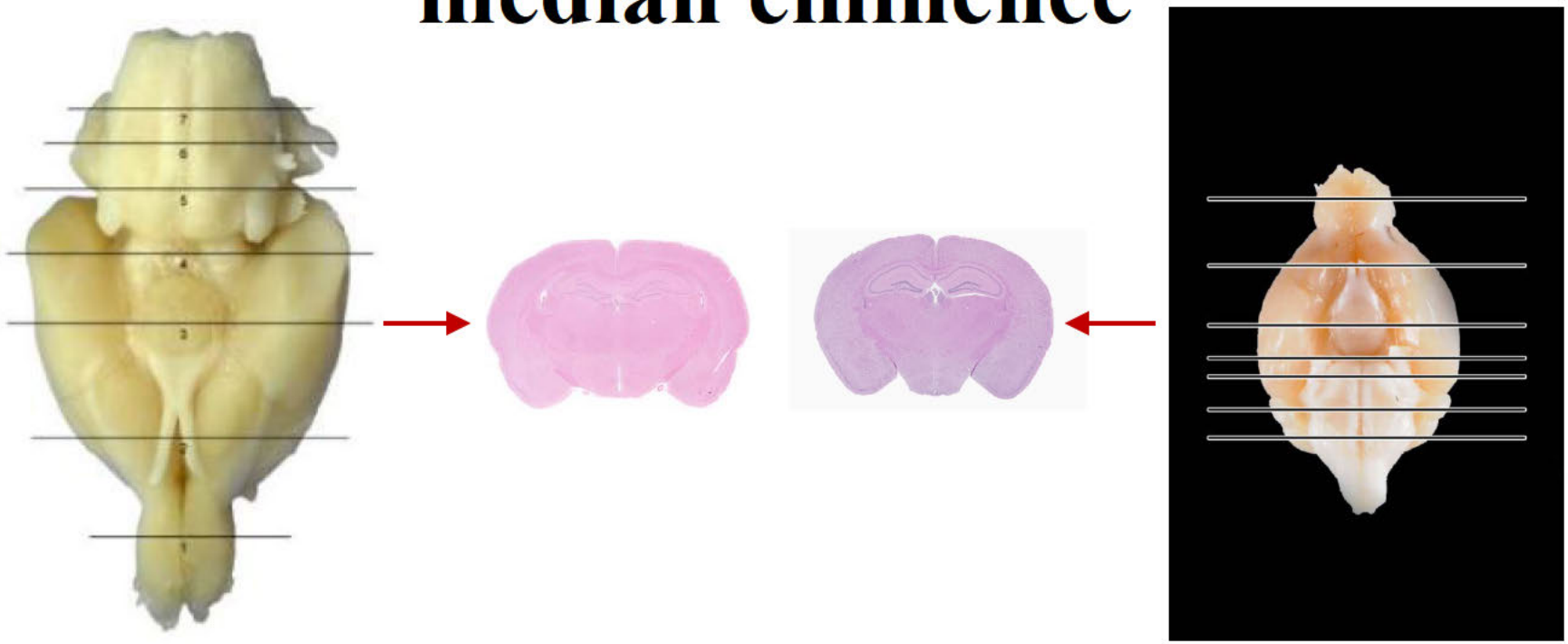
Level 2


olfactory information
piriform cortex
olfactory tract
optic chiasm

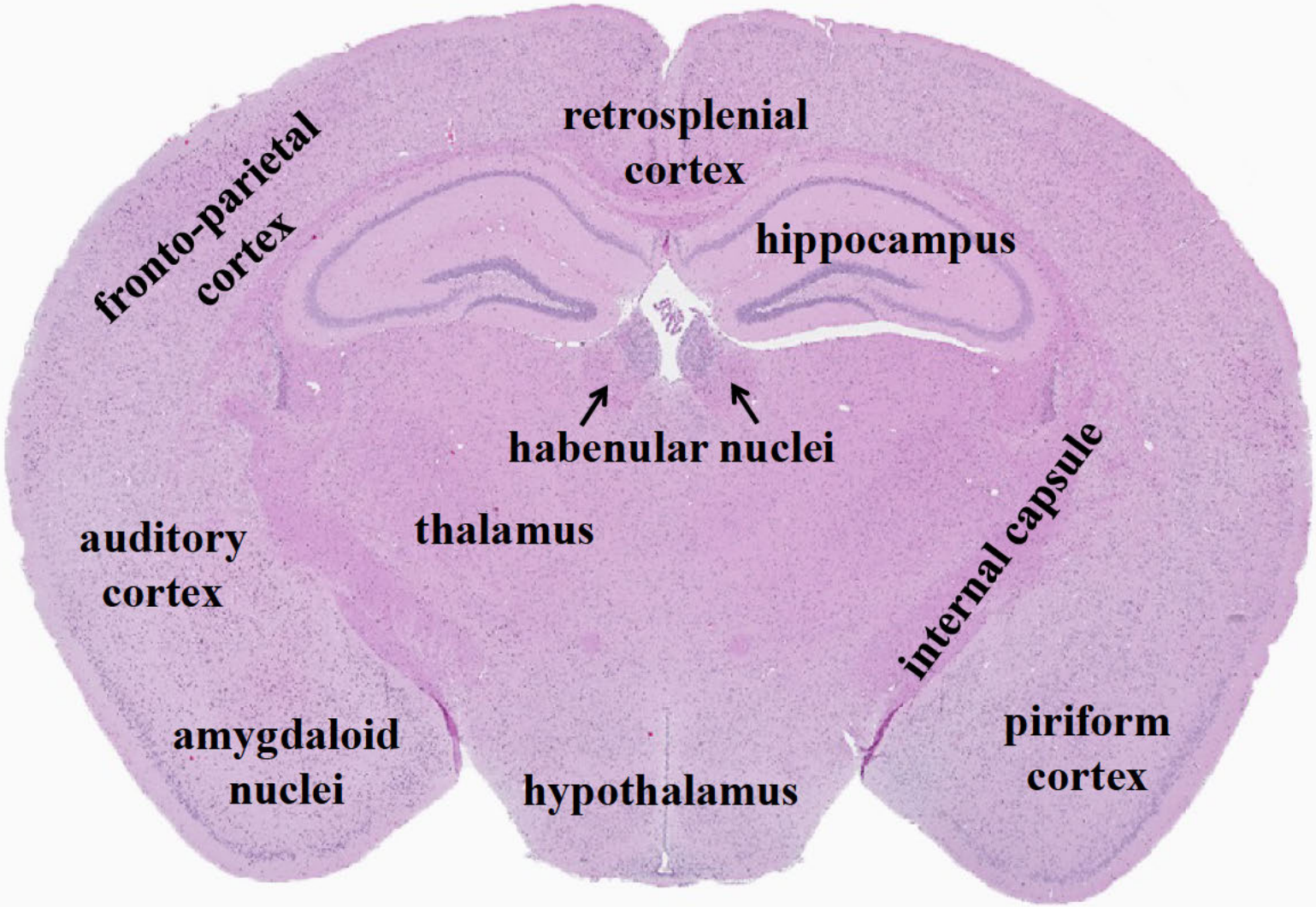
Level 2

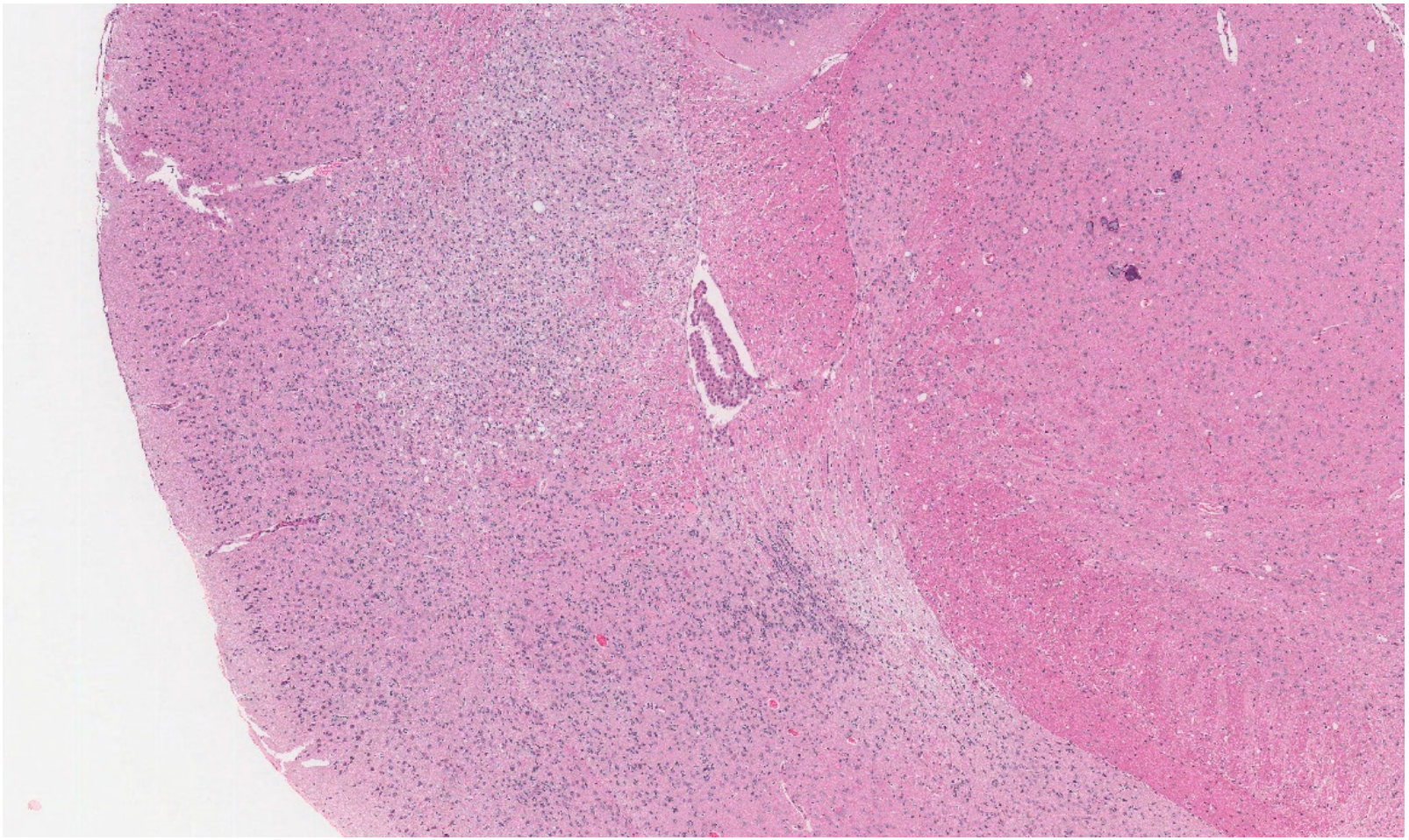

septal nuclei
reward-reinforcement
addiction
nucleus accumbens

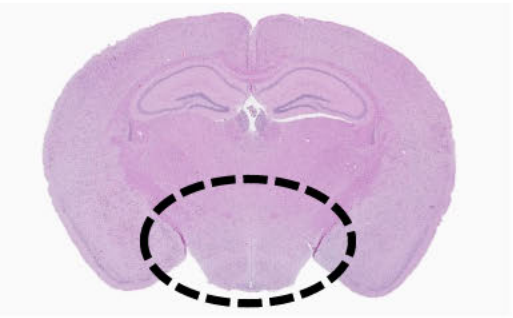
Level 3: infundibulum or median eminence

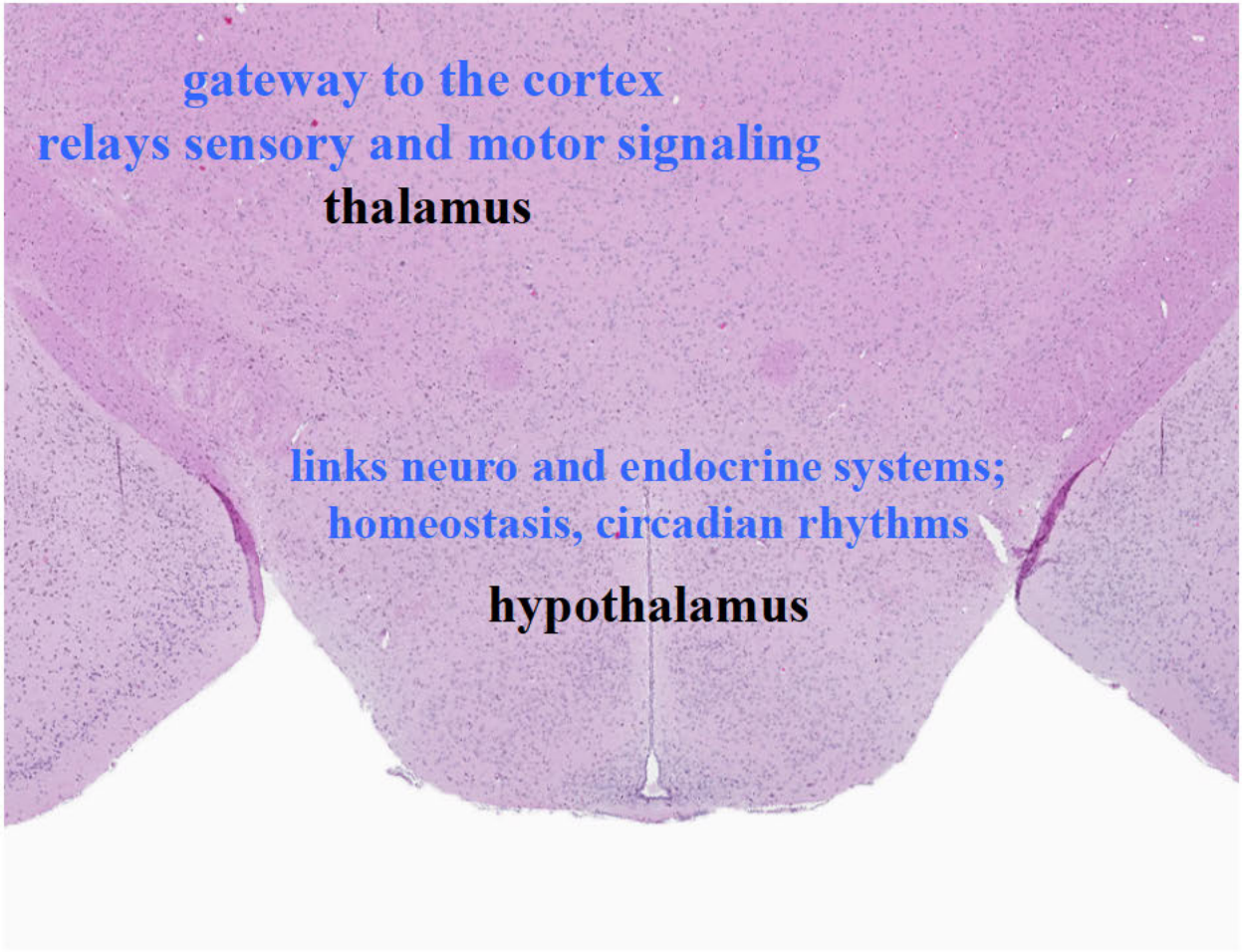


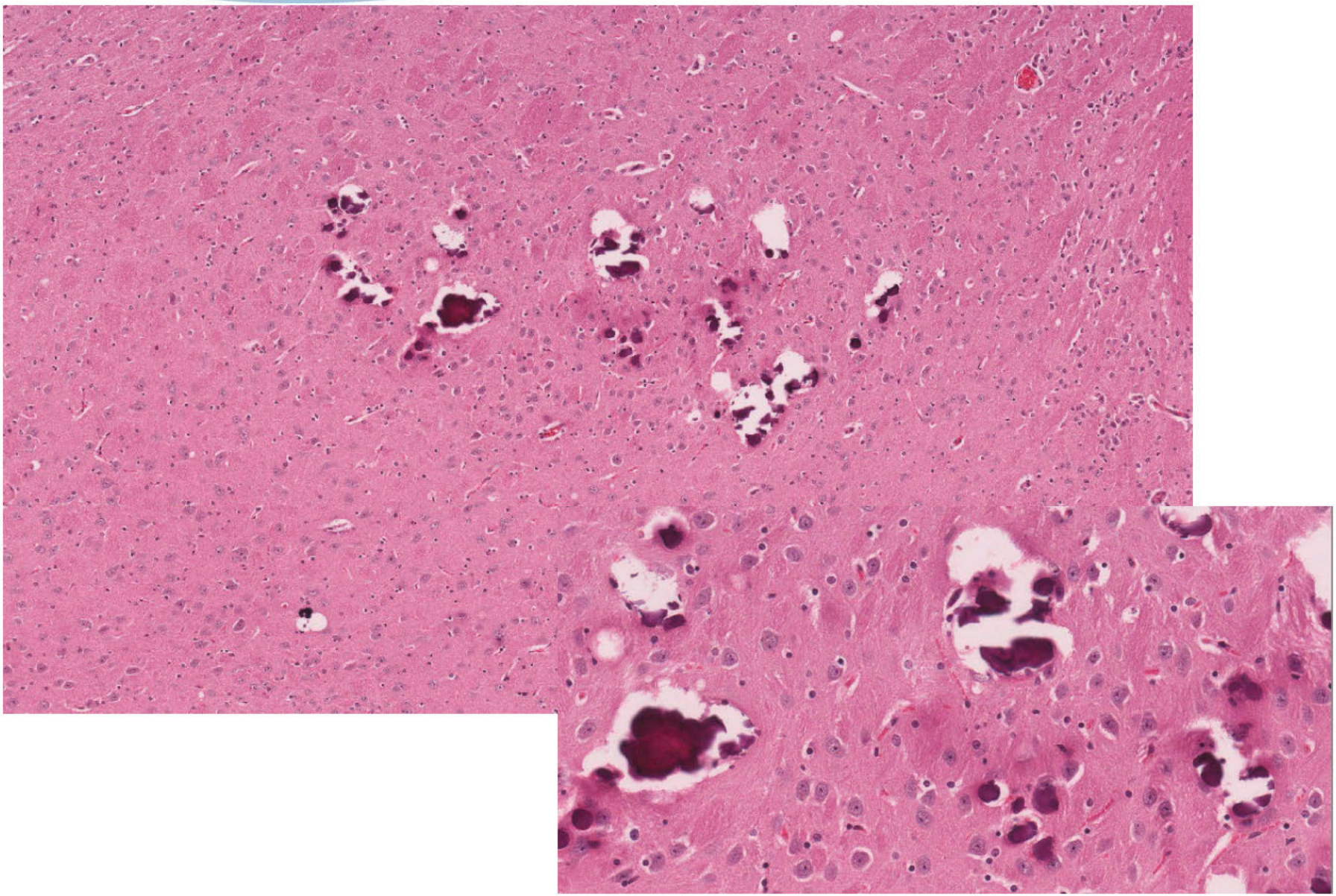
	**NTP-7 Level 3**	fronto-parietal cortex, retrosplenial cortex, auditory (temporal) cortex, amygdaloid nuclei, hippocampus (CA regions - 1,2,3, dentate gyrus), habenular nucleus, thalamus, hypothalamus, internal capsule, (globus pallidus)


retrosplenial cortex
fronto-parietal cortex
hippocampus
habenular nuclei
auditory cortex
thalamus
internal capsule
amygdaloid nuclei
hypothalamus
piriform cortex

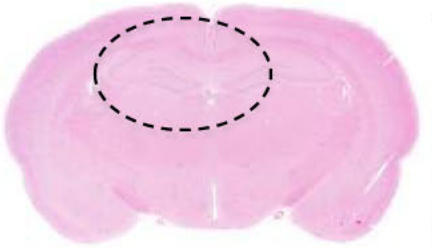


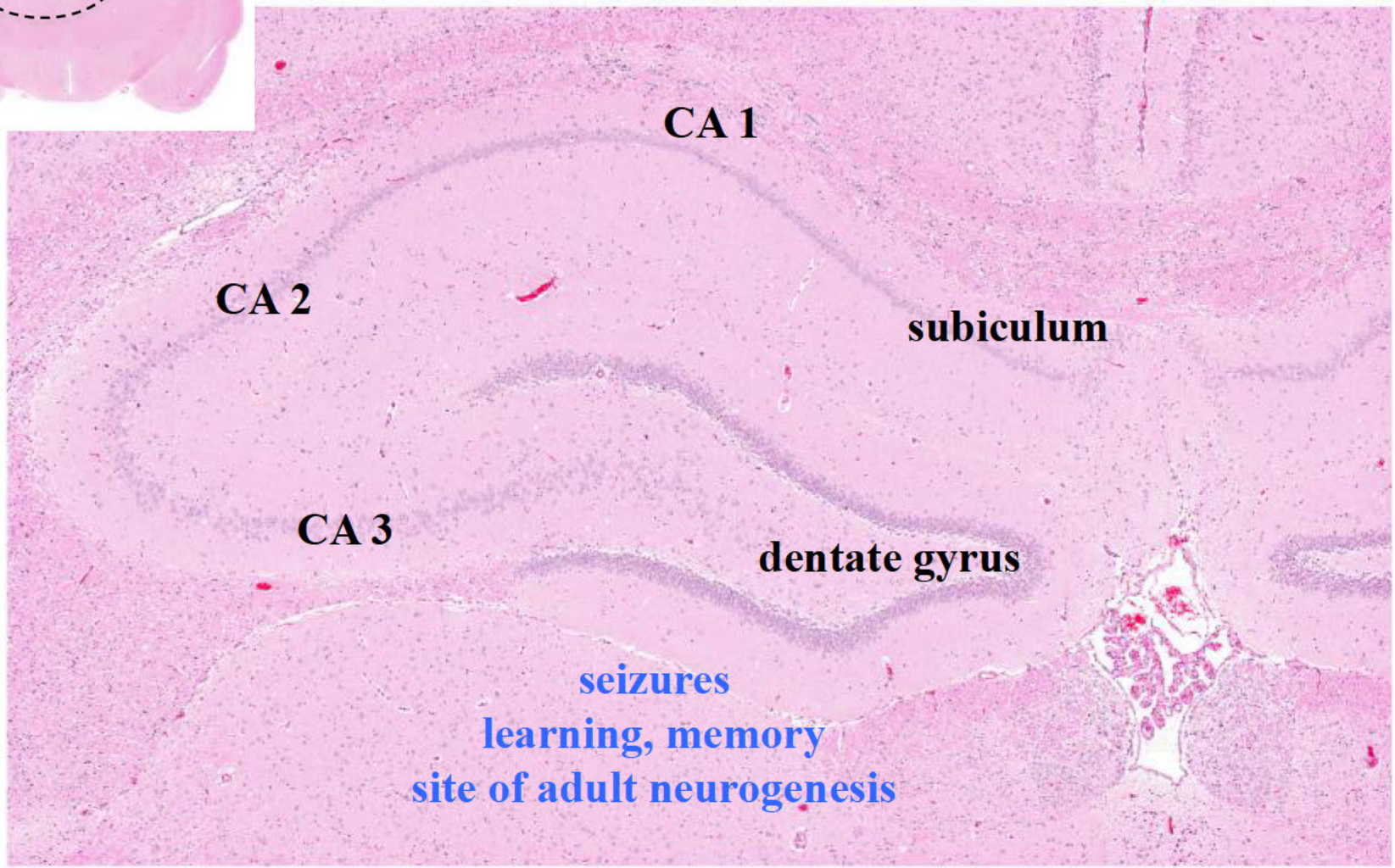



gateway to the cortex
relays sensory and motor signaling
thalamus
links neuro and endocrine systems;
homeostasis, circadian rhythms
hypothalamus



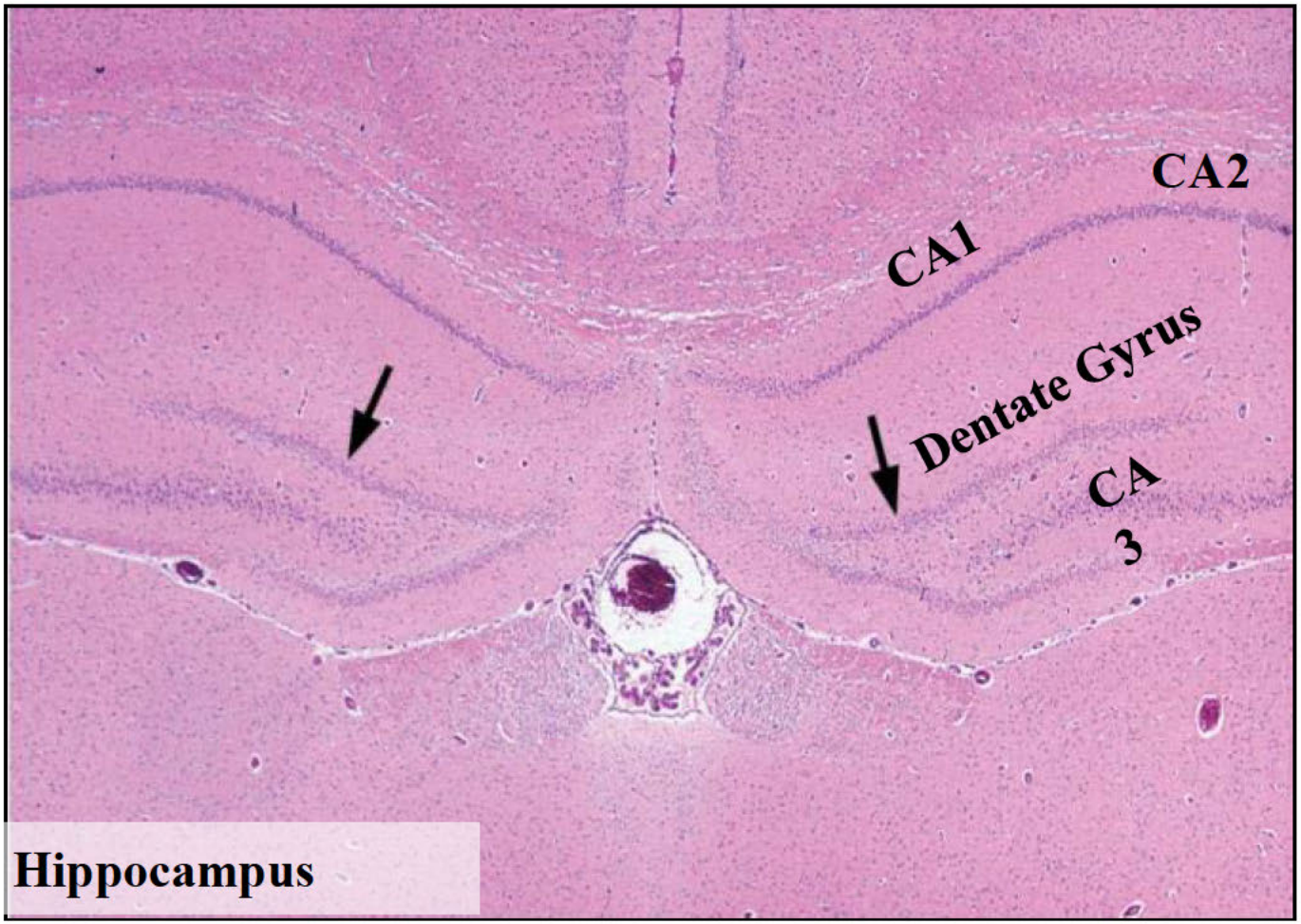
Level 3




CA 1
CA 2
subiculum
CA 3
dentate gyrus
seizures
learning, memory
site of adult neurogenesis

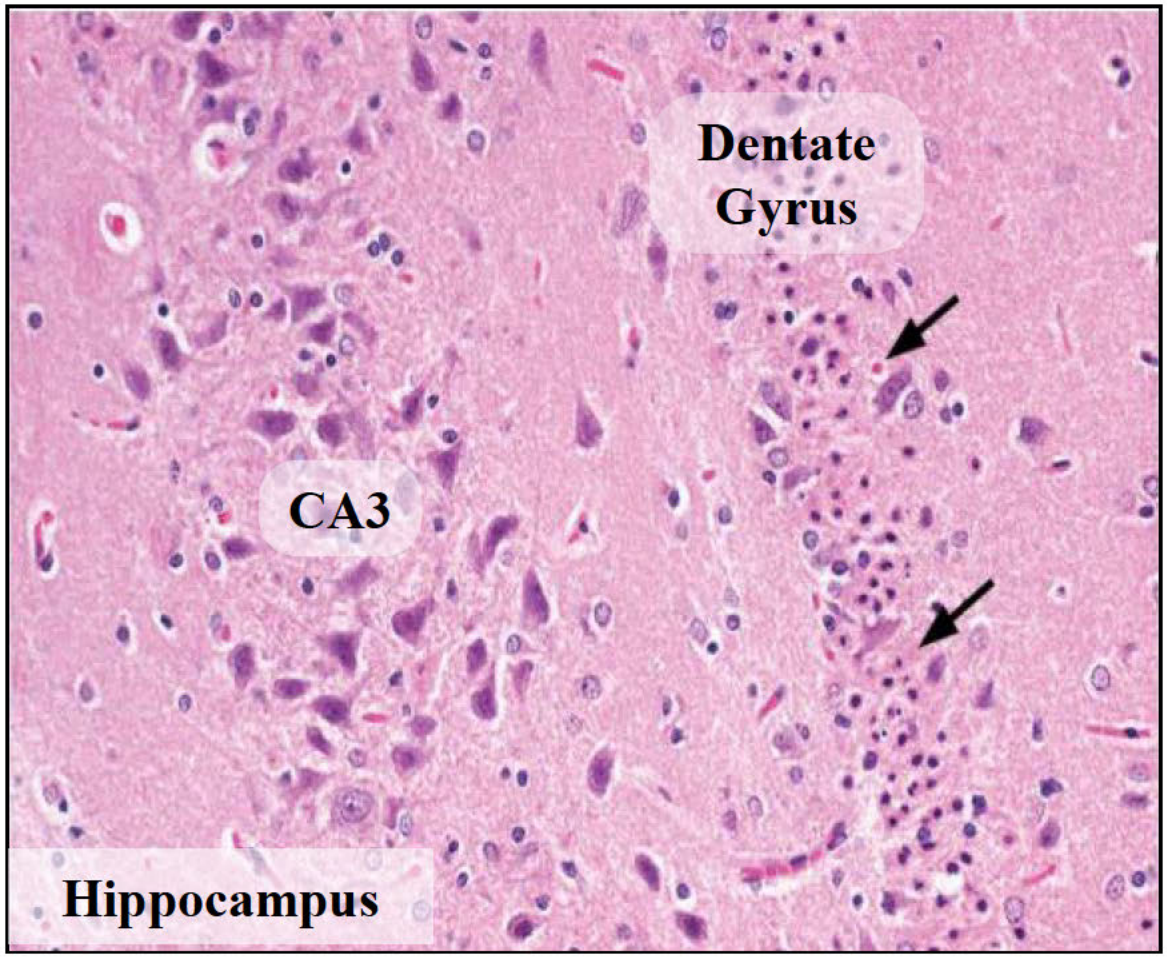
Hippocampal Lesions

Level 3

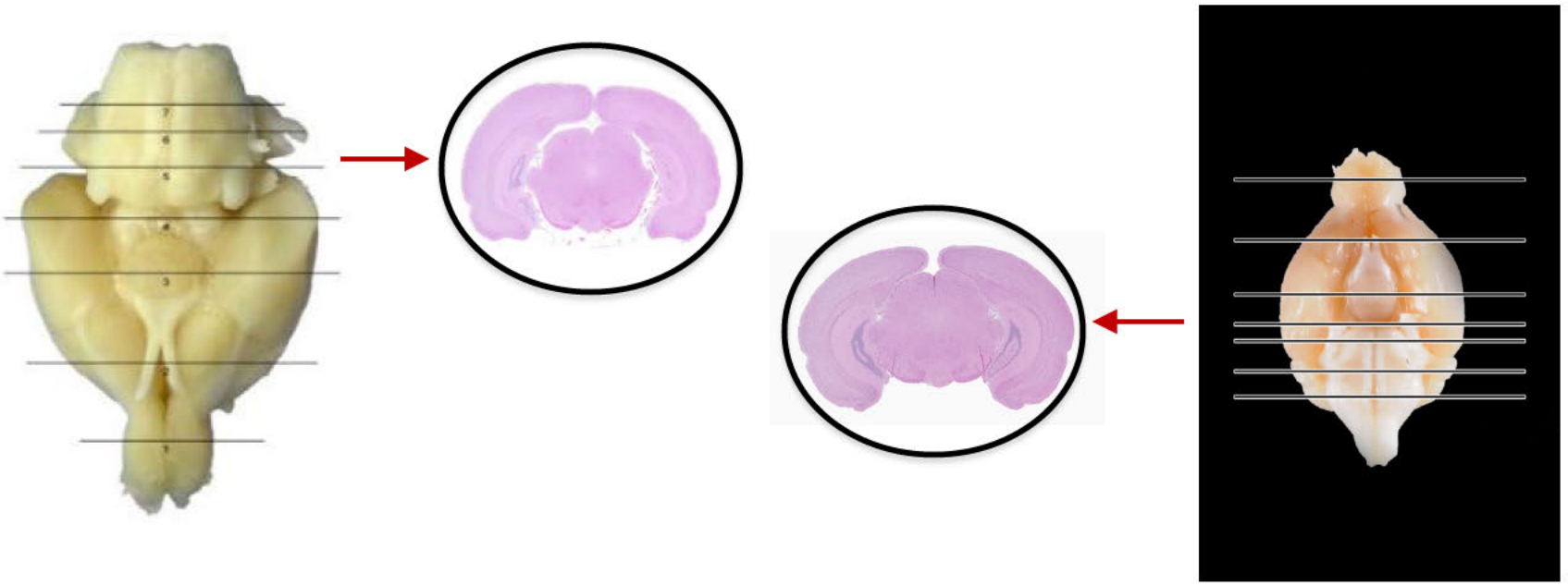


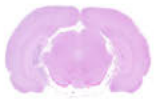
Hippocampal Lesions

Level 3

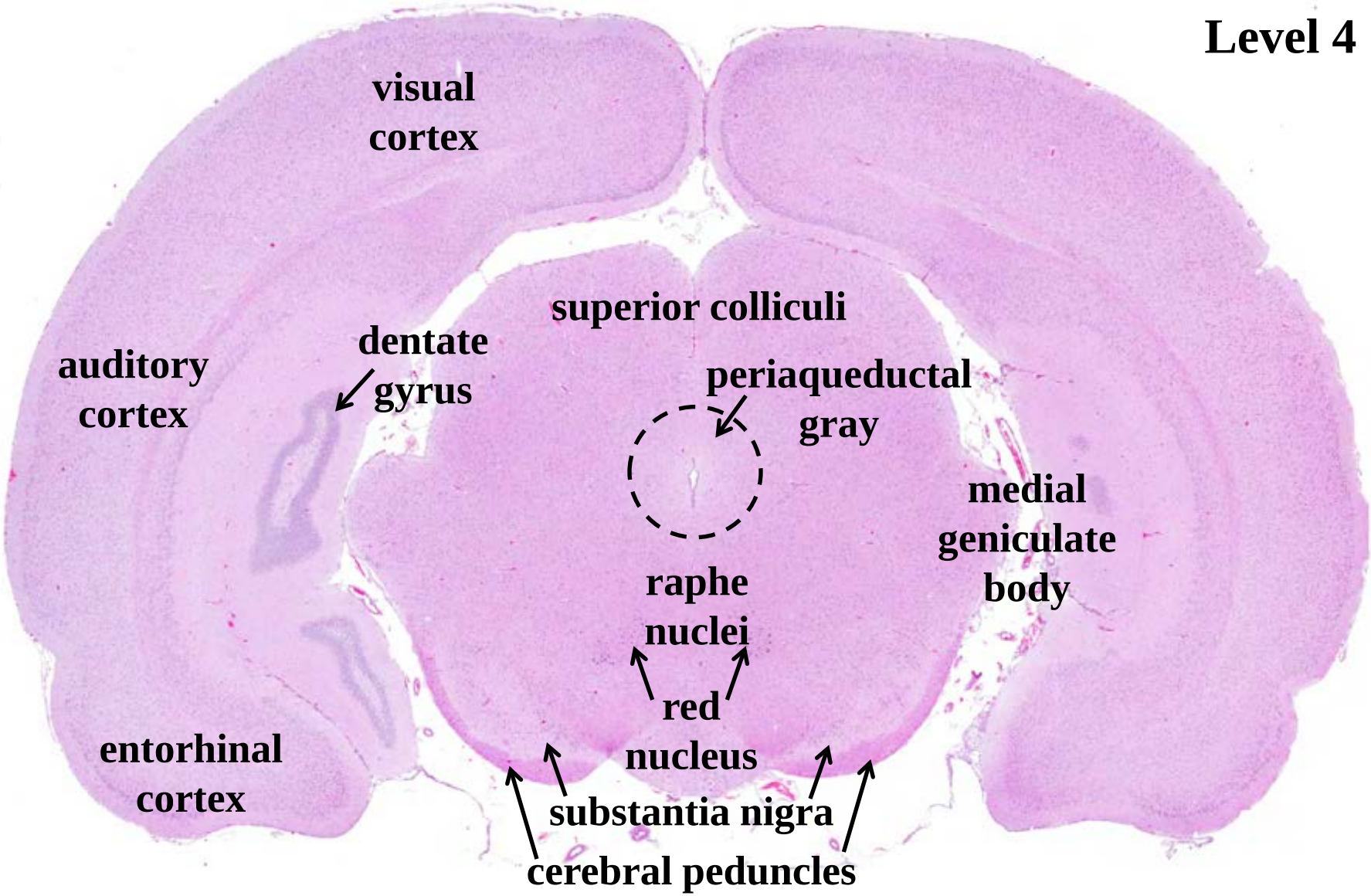


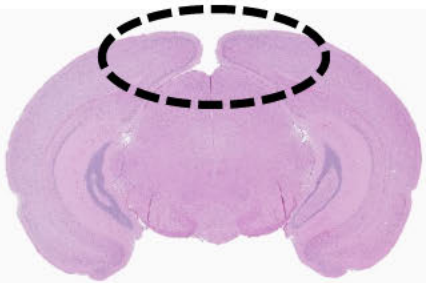
Level 4: superior colliculi

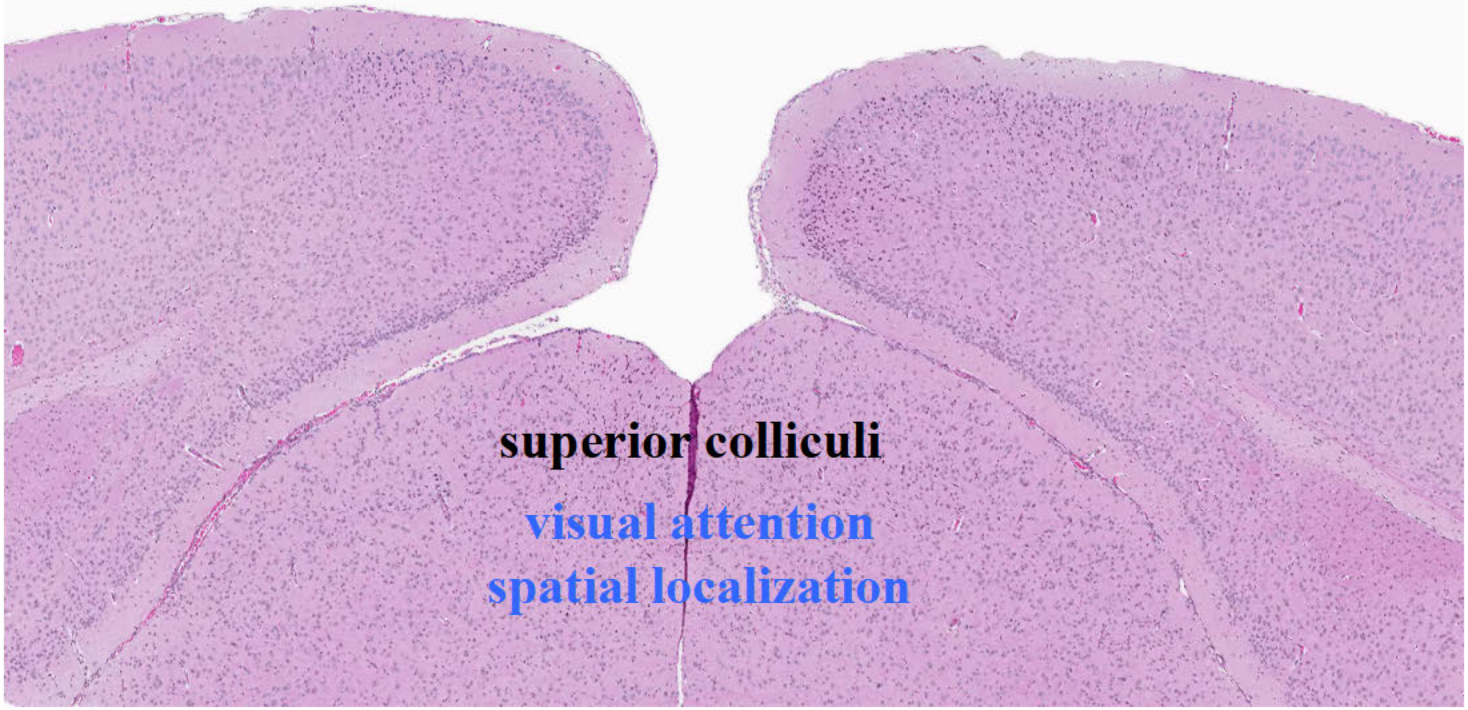


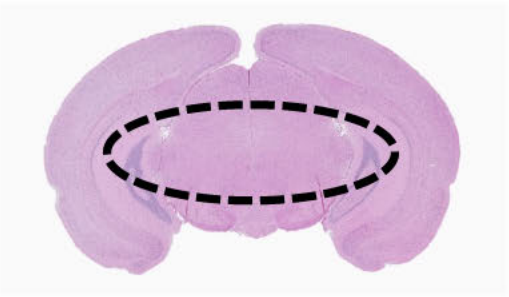
	**NTP-7 Level 4**	visual (occipital) cortex, auditory (temporal) cortex, entorhinal cortex, superior colliculus, periaqueductal gray, medial geniculate body, red nucleus, raphe nuclei, cerebral peduncle, substantia nigra

Level 4


visual cortex
superior colliculi
dentate gyrus
auditory cortex
periaqueductal gray
medial geniculate body
raphe nuclei
red nucleus
entorhinal cortex
substantia nigra
cerebral peduncles



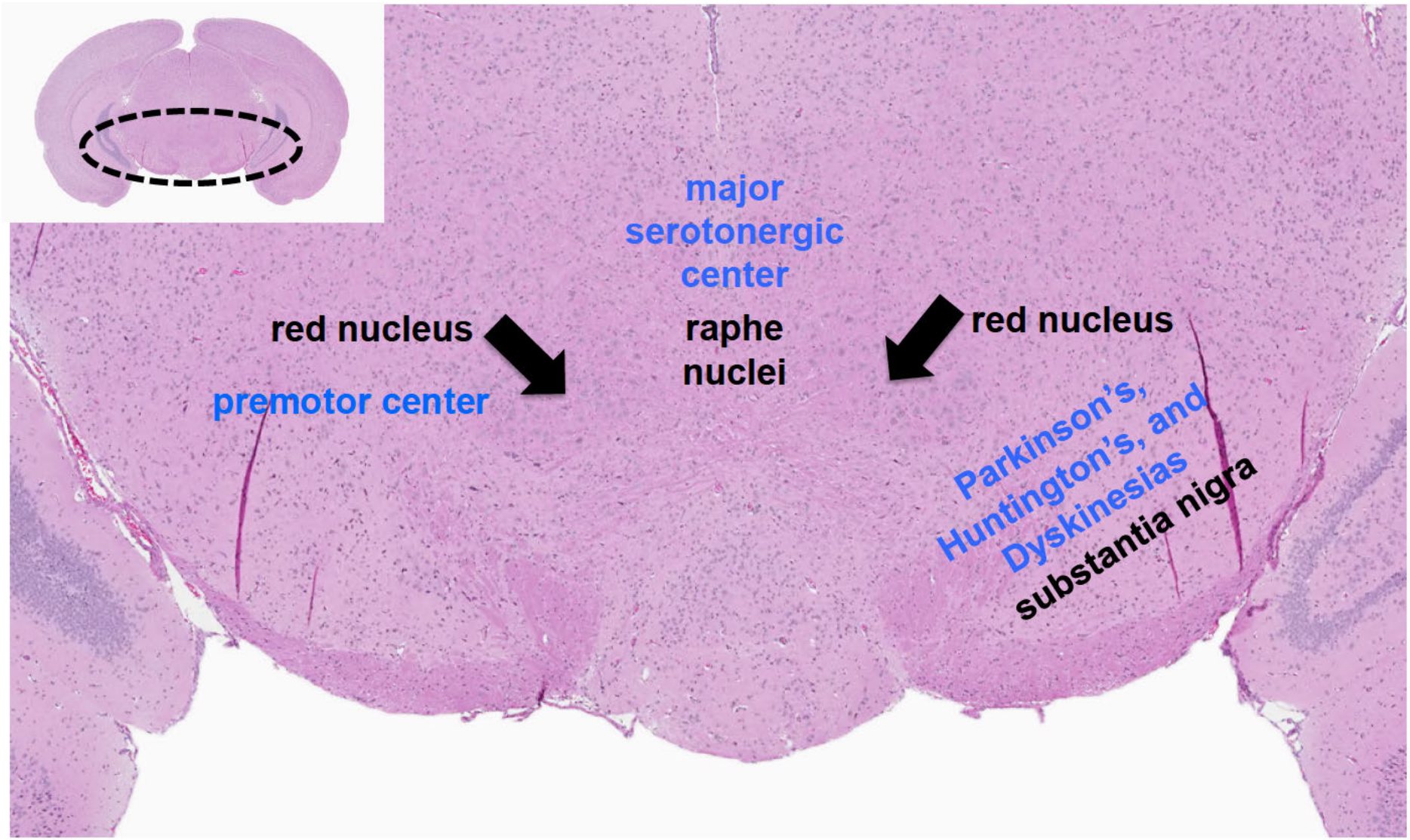

superior colliculi
visual attention
spatial localization



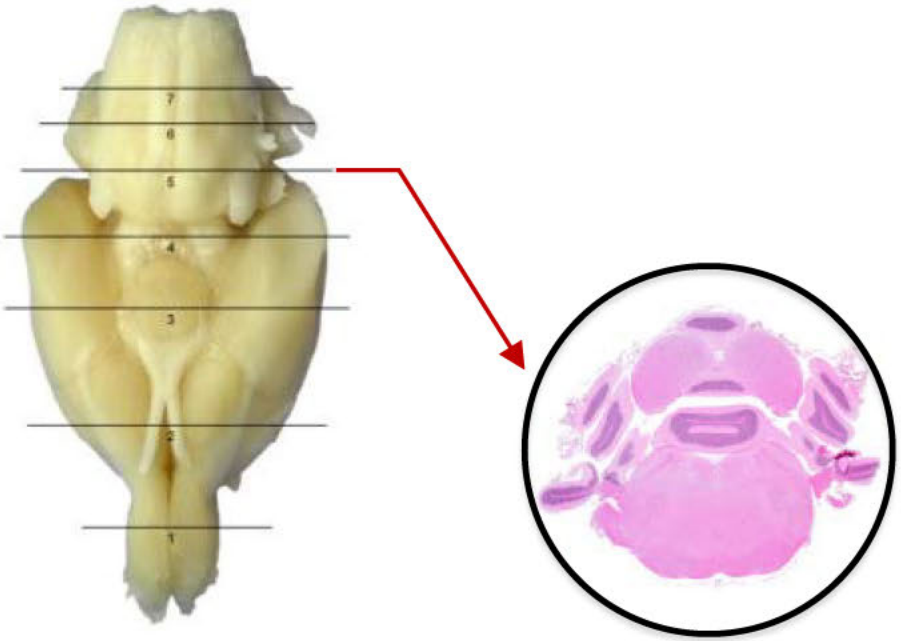
auditory processing

medial geniculate body

medial geniculate body

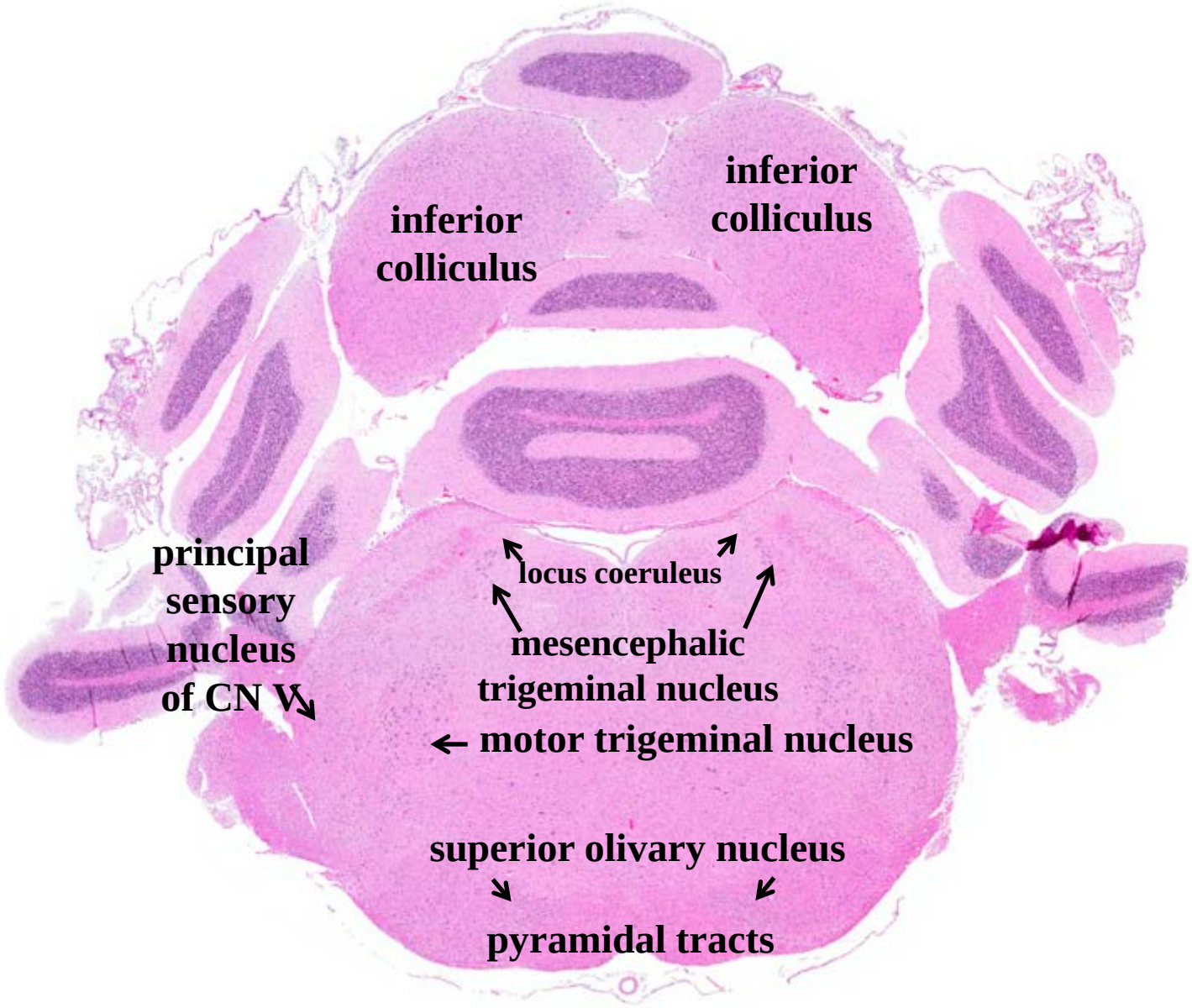

major serotonergic center
raphe nuclei
red nucleus
premotor center
red nucleus
Parkinson's, Huntington's, and Dyskinesias
substantia nigra

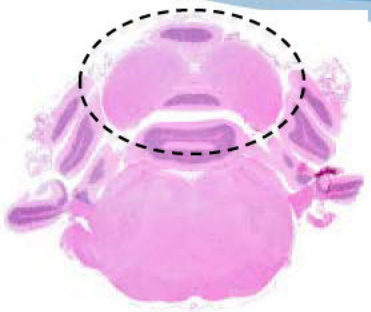
Level 5: inferior colliculi



	**NTP-7 Level 5**	inferior colliculus, locus coeruleus, mesencephalic trigeminal nucleus, principal sensory nucleus of CN V, motor trigeminal nucleus, superior olivary nucleus, pyramidal tracts

Level 5

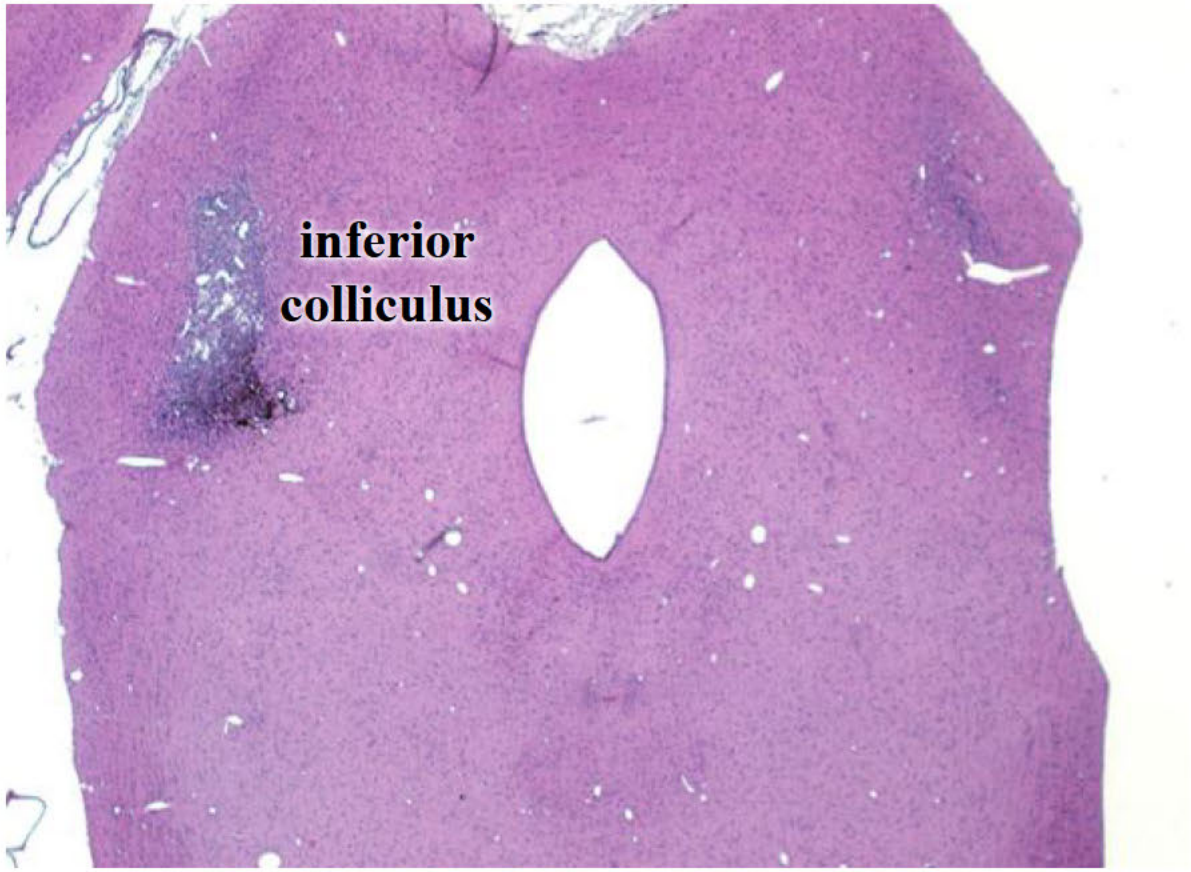

inferior colliculus
inferior colliculus
principal sensory nucleus of CN V
locus coeruleus
mesencephalic trigeminal nucleus
motor trigeminal nucleus
superior olivary nucleus
pyramidal tracts



Level 5

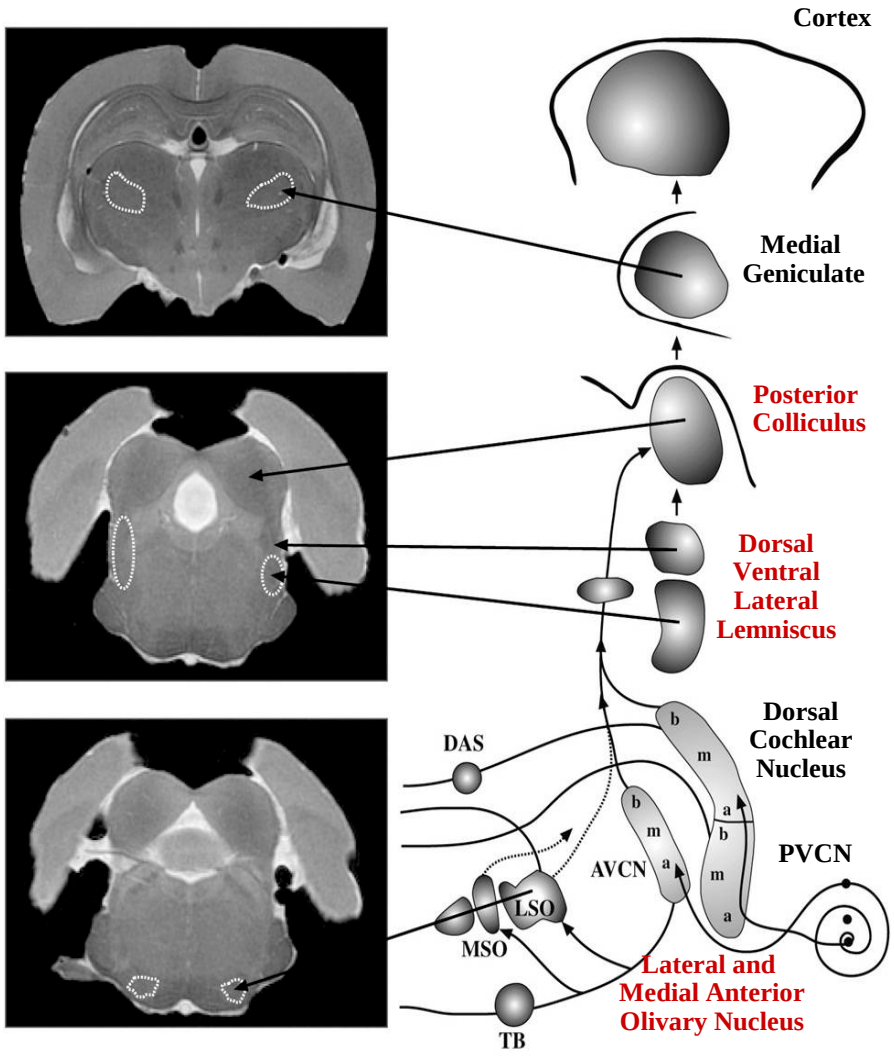
inferior colliculus
auditory pathway
metabolically active site
vulnerable to toxicants
inferior colliculus

Necrosis and Microgliosis detected in Inferior Colliculus



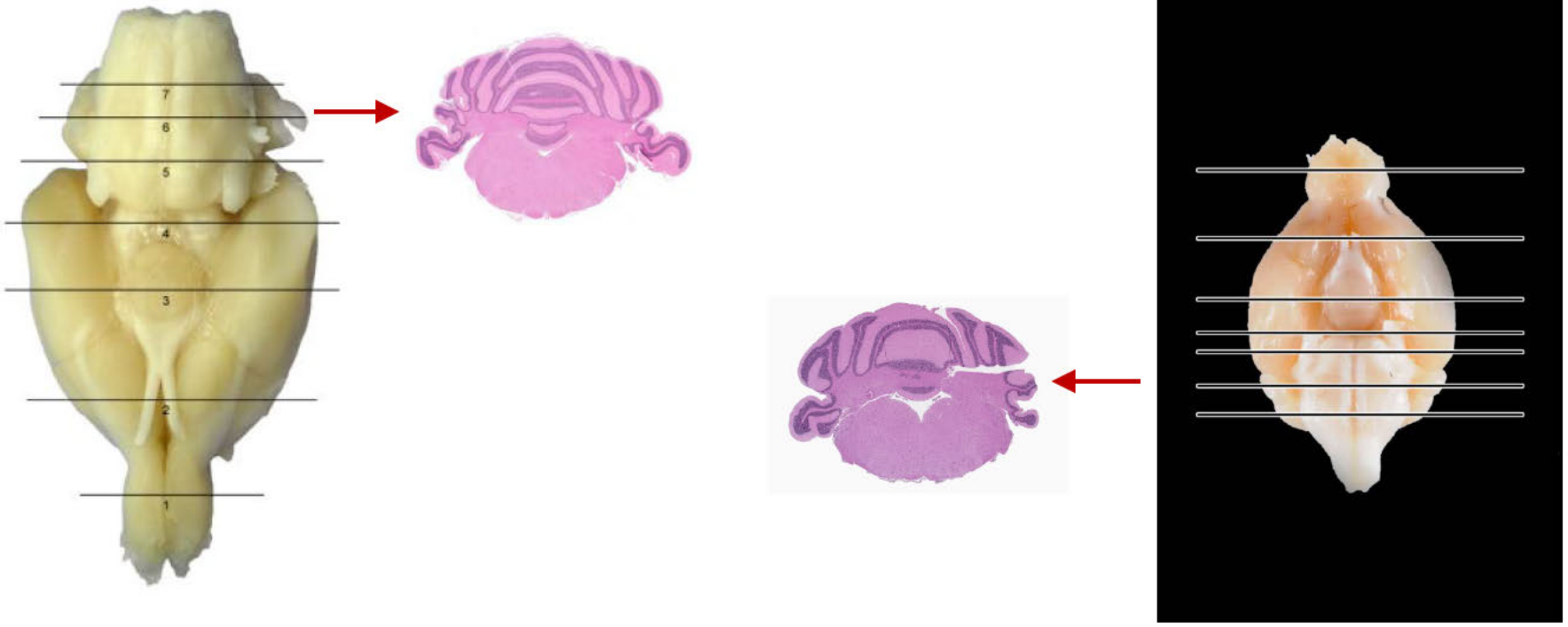
Sills et al Toxicol Pathol 2004; 32: 501-510

Lesion in the Inferior Colliculus reflect lesions in the Auditory Neuronal Circuit



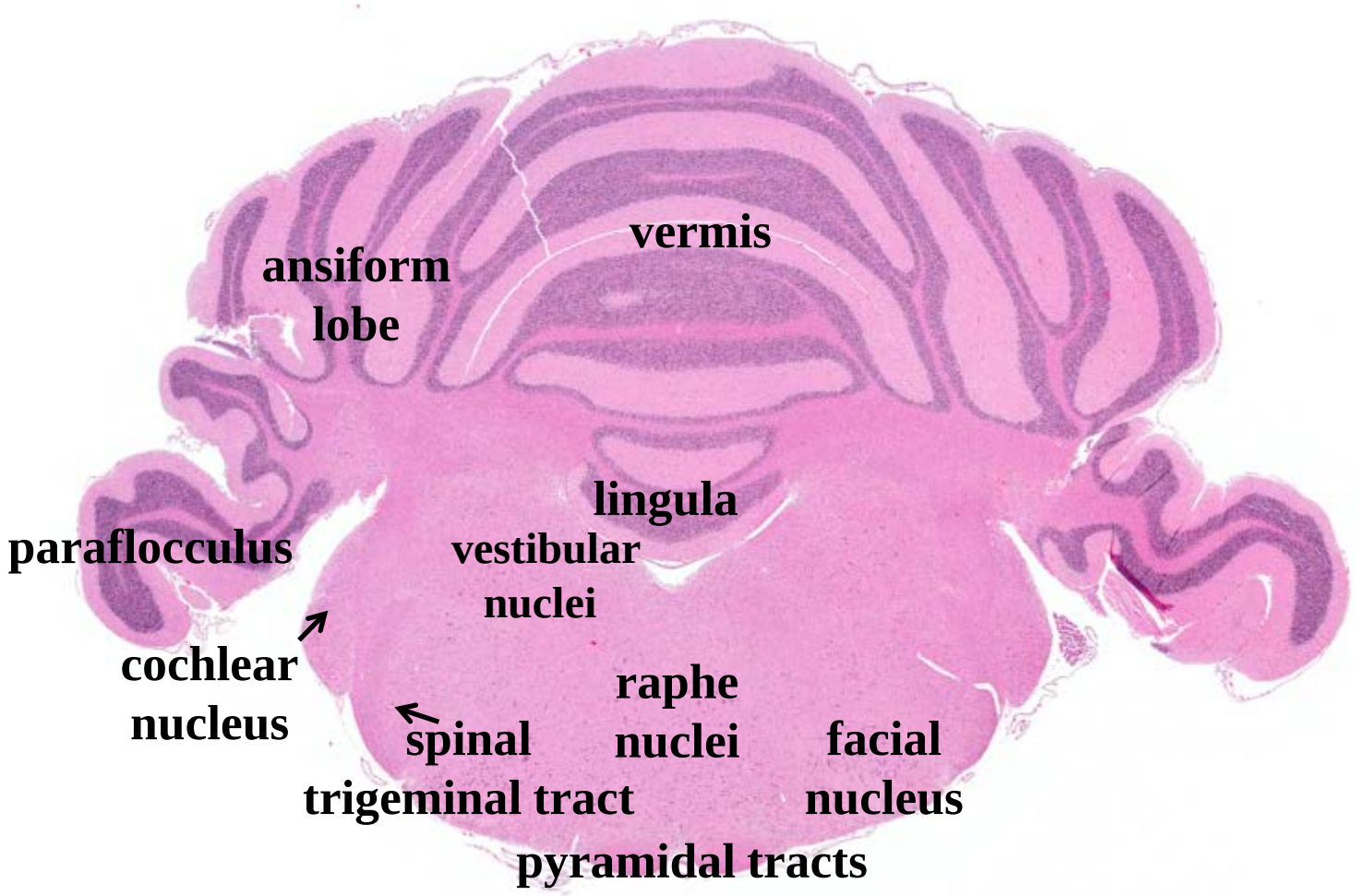
Sills et al Toxicol Pathol 2004; 32: 501-510

Level 6: mid-cerebellum

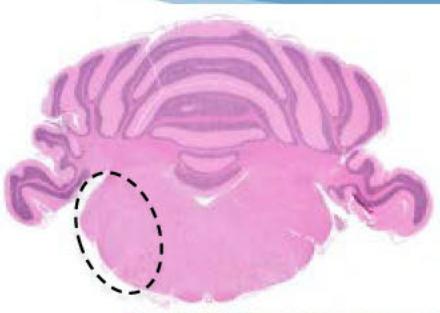


	**NTP-7 Level 6**	cerebellar lobules (vermis, ansiform, paraflocculus, lingula), facial (CN VII) nucleus, spinal trigeminal tract, vestibular nucleus, cochlear nucleus, raphe nuclei, pyramidal tracts

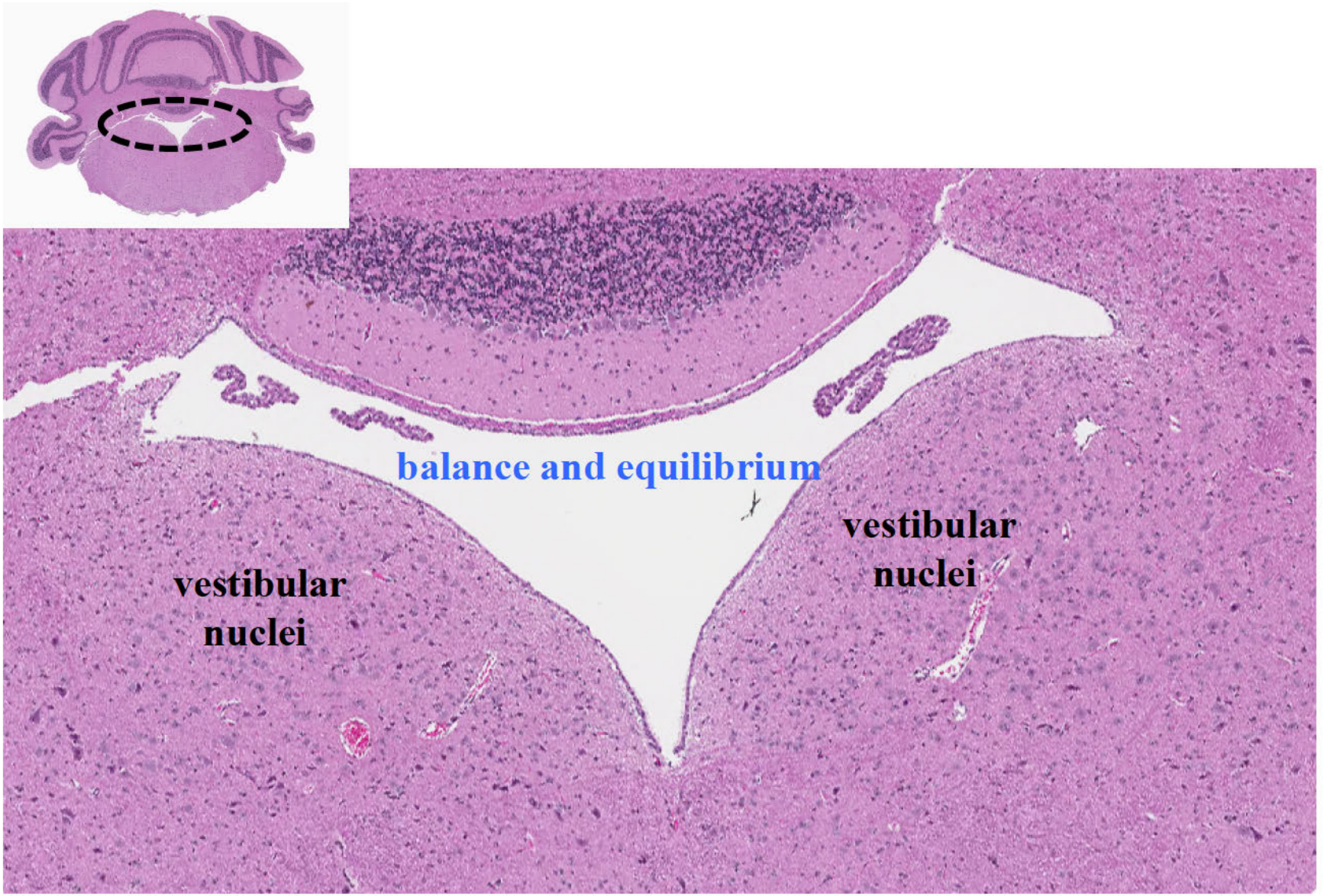
Level 6

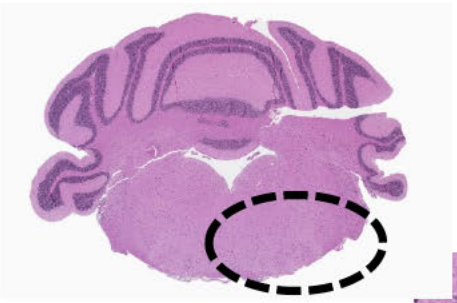

vermis
ansiform lobe
lingula
parafloccul us
vestibular nuclei
cochlear nucleus
raphe nuclei
spinal trigeminal tract
facial nucleus
pyramidal tracts

Level 6



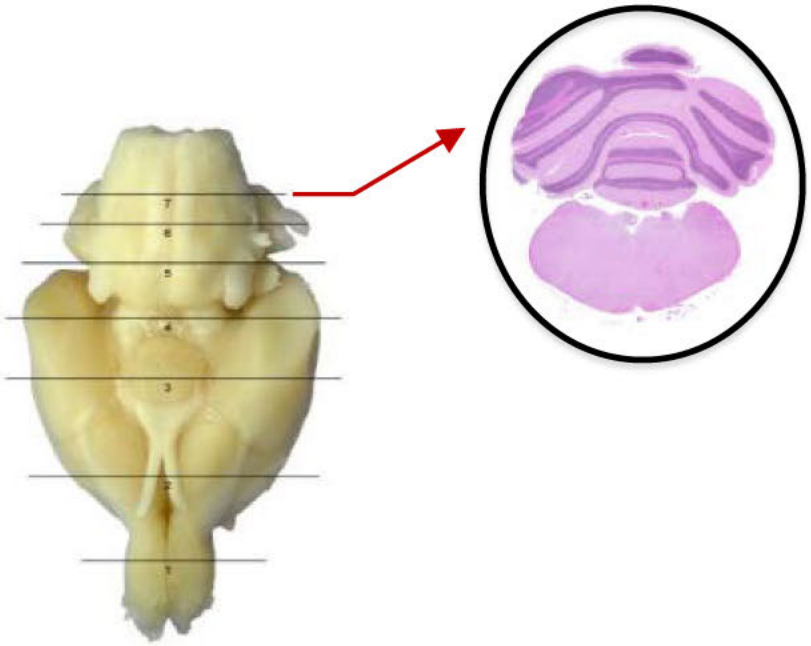
cochlear nucleus
first relay station auditory pathway
spinal trigeminal tract
afferents from CN V


balance and equilibrium
vestibular nuclei
vestibular nuclei



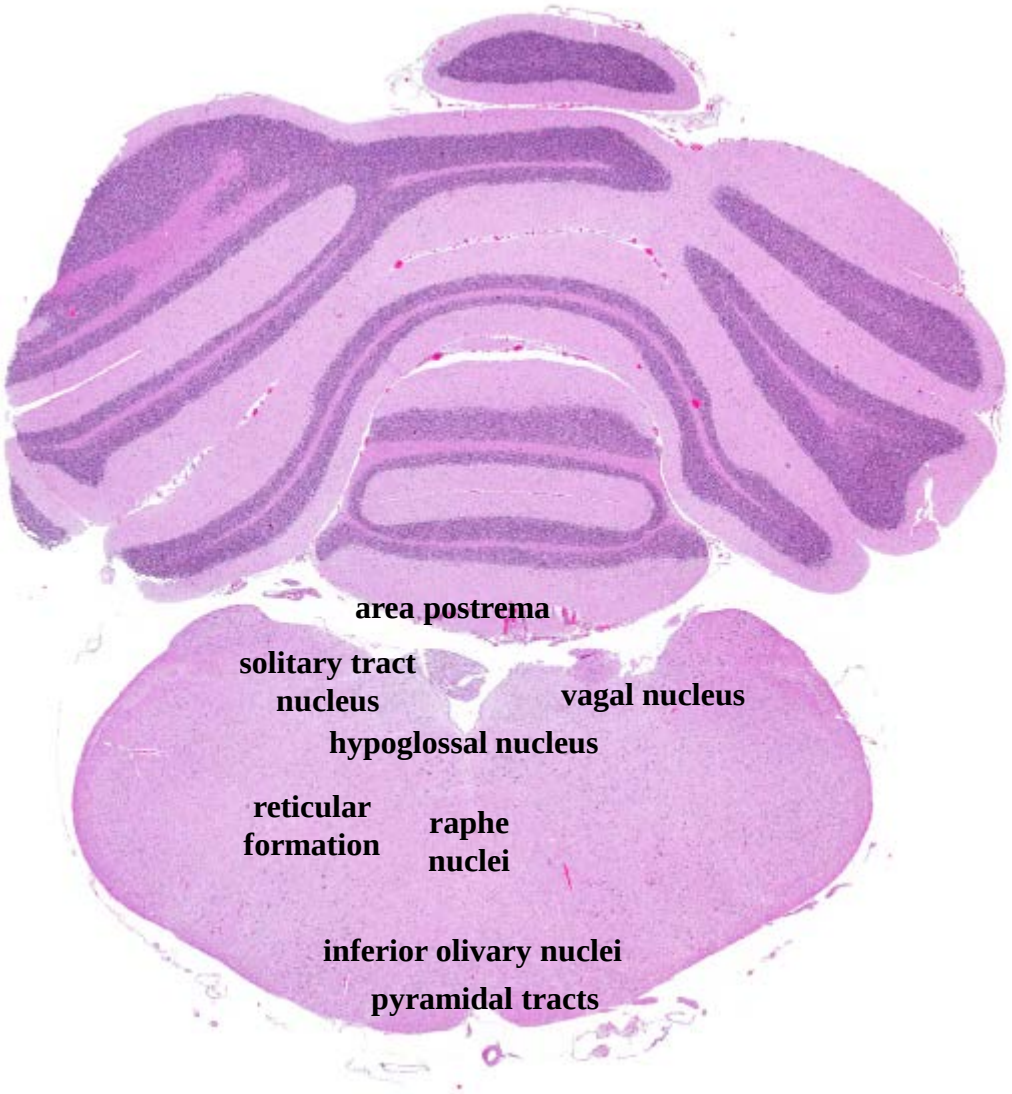

motor neurons
superficial muscles of head and neck
facial
nucleus
voluntary motor activity
pyramidal tract

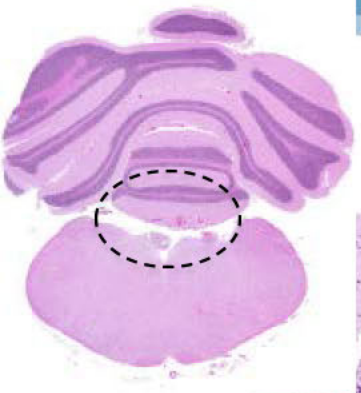
Level 7: 2-3 mm rostral to caudal termination of the cerebellum



	**NTP-7 Level 7**	area postrema, solitary tract nucleus, vagal (CV X) nucleus, hypoglossal (CN XII) nucleus, reticular formation, raphe nuclei, inferior olivary nucleus, pyramidal tracts, spinal trigeminal tract

Level 7


area postrema
solitary tract nucleus
vagal nucleus
hypoglossal nucleus
reticular formation
raphe nuclei
inferior olivary nuclei
pyramidal tracts



Level 7

area postrema

circumventricular organ
trigger zone for emesis

solitary tract
nucleus

vagal nucleus

source of visceral
efferent fibers
for CN X

hypoglossal nucleus

Invited Review

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Subsite Awareness in Neuropathology Evaluation of National Toxicology Program (NTP) Studies: A Review of Select Neuroanatomical Structures with Their Functional Significance in Rodents

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ABSTRACT

This review article is designed to serve as an introductory guide in neuroanatomy for toxicologic pathologists evaluating general toxicity studies. The article provides an overview of approximately 50 neuroanatomical subsites and their functional significance across 7 transverse sections of the brain. Also reviewed are 3 sections of the spinal cord, cranial and peripheral nerves (trigeminal and sciatic, respectively), and intestinal autonomic ganglia. The review is limited to the evaluation of hematoxylin and eosin–stained tissue sections, as light microscopic evaluation of these sections is an integral part of the first-tier toxicity screening of environmental chemicals, drugs, and other agents. Prominent neuroanatomical sites associated with major neurological disorders are noted. This guide, when used in conjunction with detailed neuroanatomic atlases, may aid in an understanding of the significance of functional neuroanatomy, thereby improving the characterization of neurotoxicity in general toxicity and safety evaluation studies.

Keywords: neuropathology; neuroanatomy; NTP; brain; spinal cord; nerve; functional neuroanatomy.

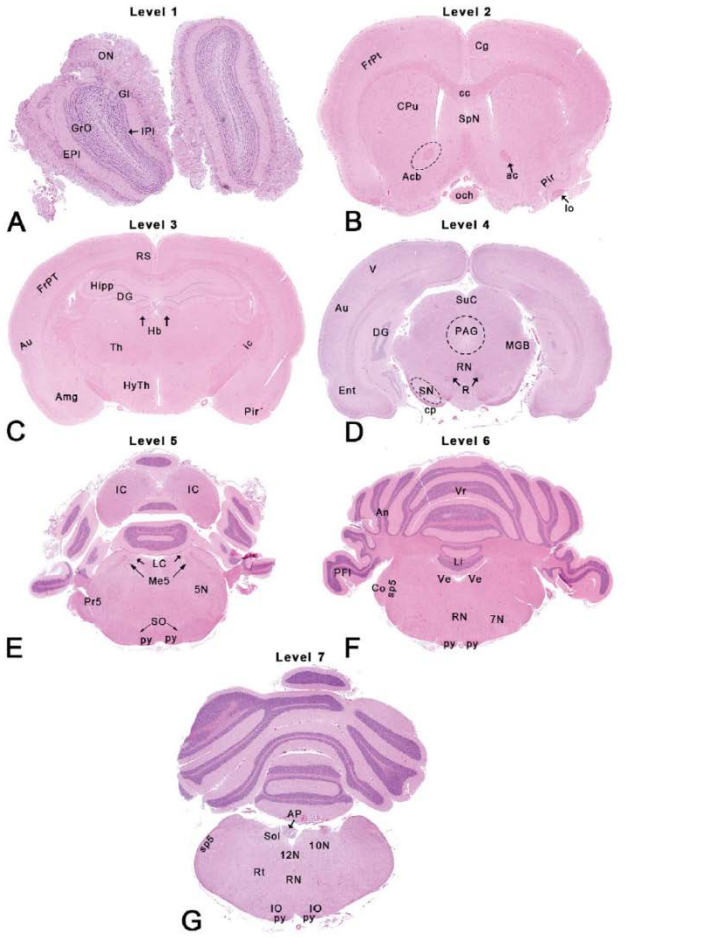


FIGURE 2.—Rat: H&E. Seven transverse sections depicting neuroanatomical subsites. Abbreviations in italics below correspond to abbreviations used in the Paxinos rat brain atlas (Paxinos and Watson 2009). Dotted outlines are close approximations and use of an atlas is recommended for accuracy.

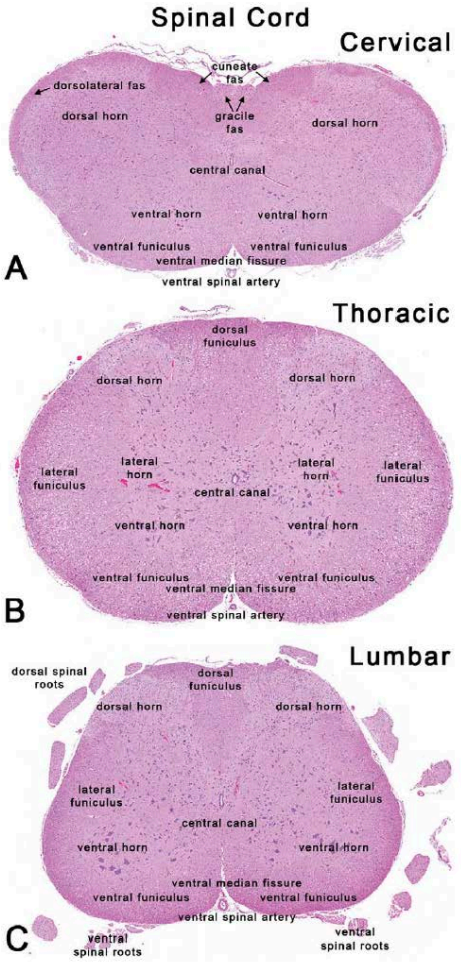


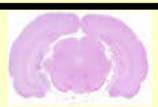
FIGURE 10.—Rat: H&E. Transverse sections of the spinal cord through the first cervical, mid-thoracic, and mid-lumbar levels. cun fas = cuneate fasciculus; dorsolateral fas = dorsolateral fasciculus; gr fas = gracile fasciculus.

TABLE 2.—Summary of the functional significance corresponding to the various neuroanatomic subsites.

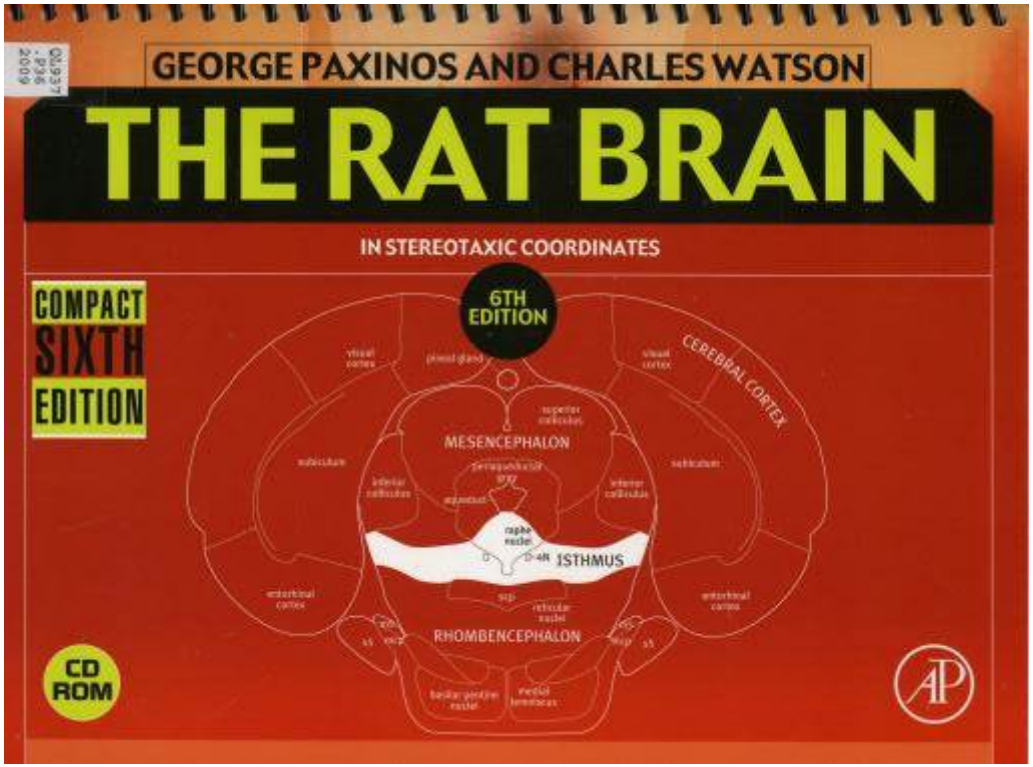
Level	Subsite	Function and significance
NTP-7 level 1	Olfactory bulb	Olfaction; site for neurogenesis; olfactory neuroblastomas with procarbazine hydrochloride, and N,N′N′-triethylenethiophosphoramide
NTP-7 level 2	Frontoparietal cortex	Motor (frontal cortex) and somatosensory (parietal cortex) functions
	Cingulate cortex	Spatial learning and delayed response tasks; susceptible to damage by MK-801
	Piriform cortex	Olfaction; susceptible to neuronal excitotoxicity
	Striatum (caudate–putamen)	Regulate movement via the extrapyramidal and striatonigral circuits; may be affected in Parkinson's disease; affected in Huntington's diseases
	Septal nuclei	Reward and reinforcement
	Nucleus accumbens	Addiction and fear conditioning
	White matter tracts (corpus callosum and anterior commissure)	Connect the right and left cerebral hemispheres; psychiatric disorders including bipolar syndrome, migraine, and depression in humans
NTP-7 level 3	Hippocampus	Epilepsy, learning and memory processing; affected in Alzheimer's disease; trimethyltin and benzyl acetate affects the granule cell layer in the dentate gyrus
	Thalamus	Somesthesis; relay of touch and proprioceptive information from the spinal cord to the somatosensory cortex
	Hypothalamus	Vital homeostatic mechanisms and in hormonal and behavioral circadian rhythms
	Habenular nucleus	Pain processing, reproductive behavior, nutrition, sleep–wake cycles, stress responses, and learning activities
	Amygdaloid nuclei	Role in memory of emotional reactions, fear, anxiety, and depression
NTP-7 level 4	Superior colliculus	Directing visual attention and controlling eye movements; role in attention deficit hyperactivity disorder
	Medial geniculate body	Likely role in influencing the direction and maintenance of attention in response to auditory stimuli
	Red nucleus	Motor activity; may serve as a premotor center
	Raphe nuclei	Major serotonergic center with divergent fibers to the rostral brain and caudal brain stem
	Substantia nigra	Predominantly dopaminergic; affected in Parkinson's and Huntington's diseases
NTP-7 level 5	Inferior colliculus	Major role in the auditory pathway; highly susceptible site based on high blood volume, rate of blood flow and glucose metabolism
	Superior olivary nucleus	Processing of binaural cues for sound localization
	Locus coeruleus	Synthesis of norepinephrine; role in responses to stress and panic; may play a role in Alzheimer's disease
	Trigeminal complex of CN V	Masticatory reflexes and control of jaw movements (motor trigeminal nucleus); sensory input from muscles of mastication and mandibular teeth (mesencephalic nucleus); sensory input from maxillary, mandibular, and ophthalmic nerve innervation areas of the skin (principal sensory nucleus of CN V)
	Pyramids	Motor tracts carrying information regarding voluntary motor activity
NTP-7 level 6	Cerebellum	Motor coordination and muscle tone; cognitive functions; hyperactivity disorders
	Vestibular nuclei	Maintenance of balance and equilibrium
	Cochlear nuclei	First relay station along the central auditory pathway
	Facial nucleus	Motor neurons controlling superficial muscles of the head and neck
	Spinal trigeminal tract	Carries afferents from the ophthalmic, maxillary, and mandibular regions
NTP-7 level 7	Area postrema	A target site for lesions from substances that cannot cross the blood–brain barrier; may play a role in triggering emesis
	Vagal Nucleus/Dorsal Motor Nucleus of Vagus	Source of general visceral efferent fibers in the vagus nerve
	Hypoglossal nucleus	Motor neurons that innervate the lingual muscles
	Reticular formation	Maintenance of alert mental status; coordinating apparatus for sensory-motor functions
	Inferior olivary nucleus	Efferent fibers are associated with cerebellar motor functions

Note: CN = cranial nerve; NTP = National Toxicology Program.

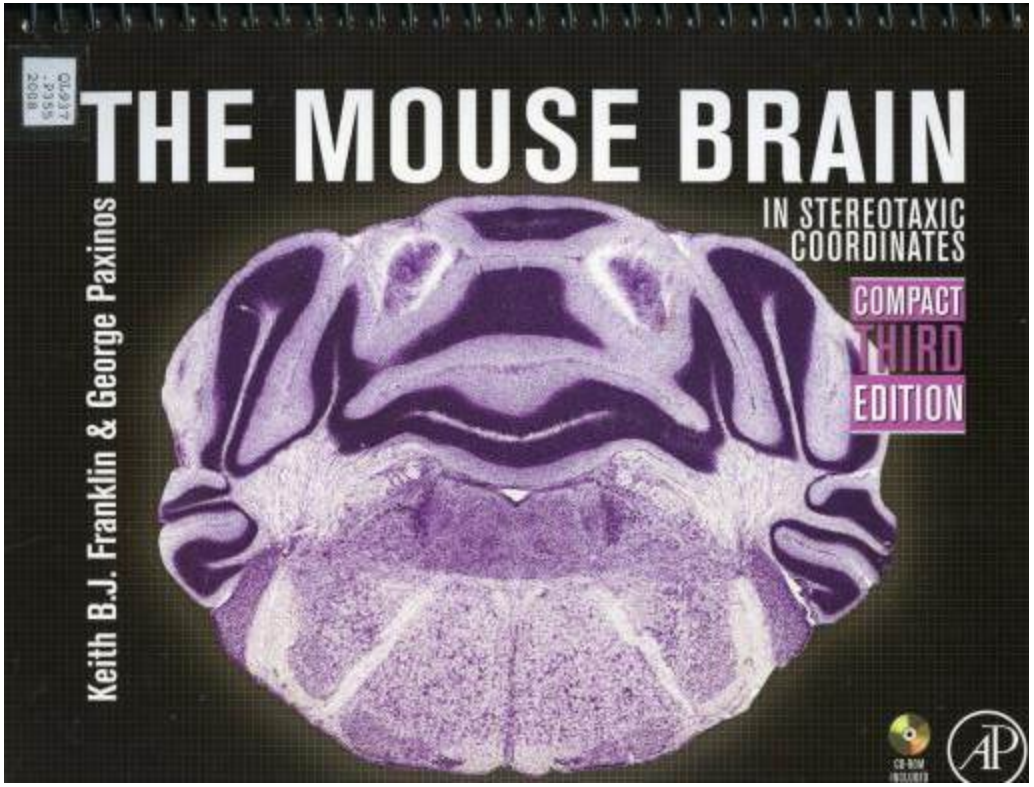
Neuroanatomic subsites

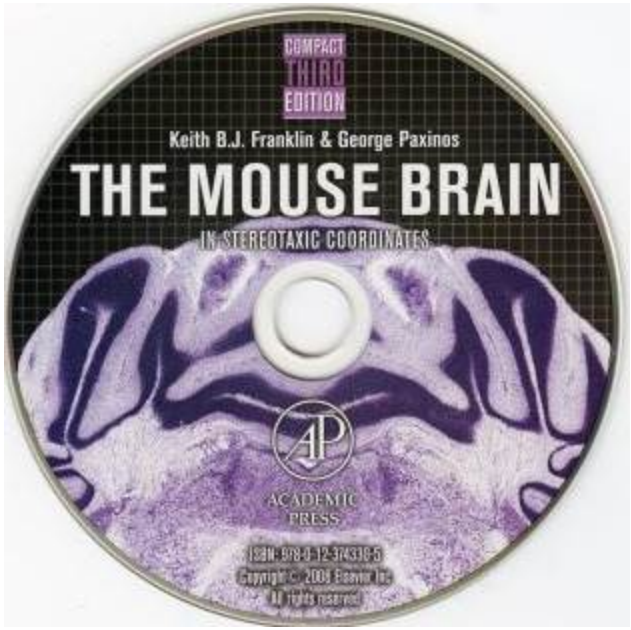
NEUROANATOMIC SUBSITES		
	**NTP-7 Level 1**	olfactory bulb (olfactory nerve layer, glomerular layer, external and internal plexiform layers, mitral cell layer, and granule cell layer)
	**NTP-7 Level 2**	fronto-parietal cortex, cingulate cortex, corpus callosum, caudate-putamen, (internal capsule, globus pallidus), septal nuclei, anterior commissure, accumbens nucleus, piriform cortex, optic chiasm or nerve, lateral olfactory tract
	**NTP-7 Level 3**	fronto-parietal cortex, retrosplenial cortex, auditory (temporal) cortex, amygdaloid nuclei, hippocampus (CA regions - 1,2,3, dentate gyrus), habenular nucleus, thalamus, hypothalamus, internal capsule, (globus pallidus)
	**NTP-7 Level 4**	visual (occipital) cortex, auditory (temporal) cortex, entorhinal cortex, superior colliculus, periaqueductal gray, medial geniculate body, red nucleus, raphe nuclei, cerebral peduncle, substantia nigra
	**NTP-7 Level 5**	inferior colliculus, locus coeruleus, mesencephalic trigeminal nucleus, principal sensory nucleus of CN V, motor trigeminal nucleus, superior olivary nucleus, pyramidal tracts
	**NTP-7 Level 6**	cerebellar lobules (vermis, ansiform, paraflocculus, lingula), facial (CN VII) nucleus, spinal trigeminal tract, vestibular nucleus, cochlear nucleus, raphe nuclei, pyramidal tracts
	**NTP-7 Level 7**	area postrema, solitary tract nucleus, vagal (CV X) nucleus, hypoglossal (CN XII) nucleus, reticular formation, raphe nuclei, inferior olivary nucleus, pyramidal tracts, spinal trigeminal tract

Rat Brain Atlas



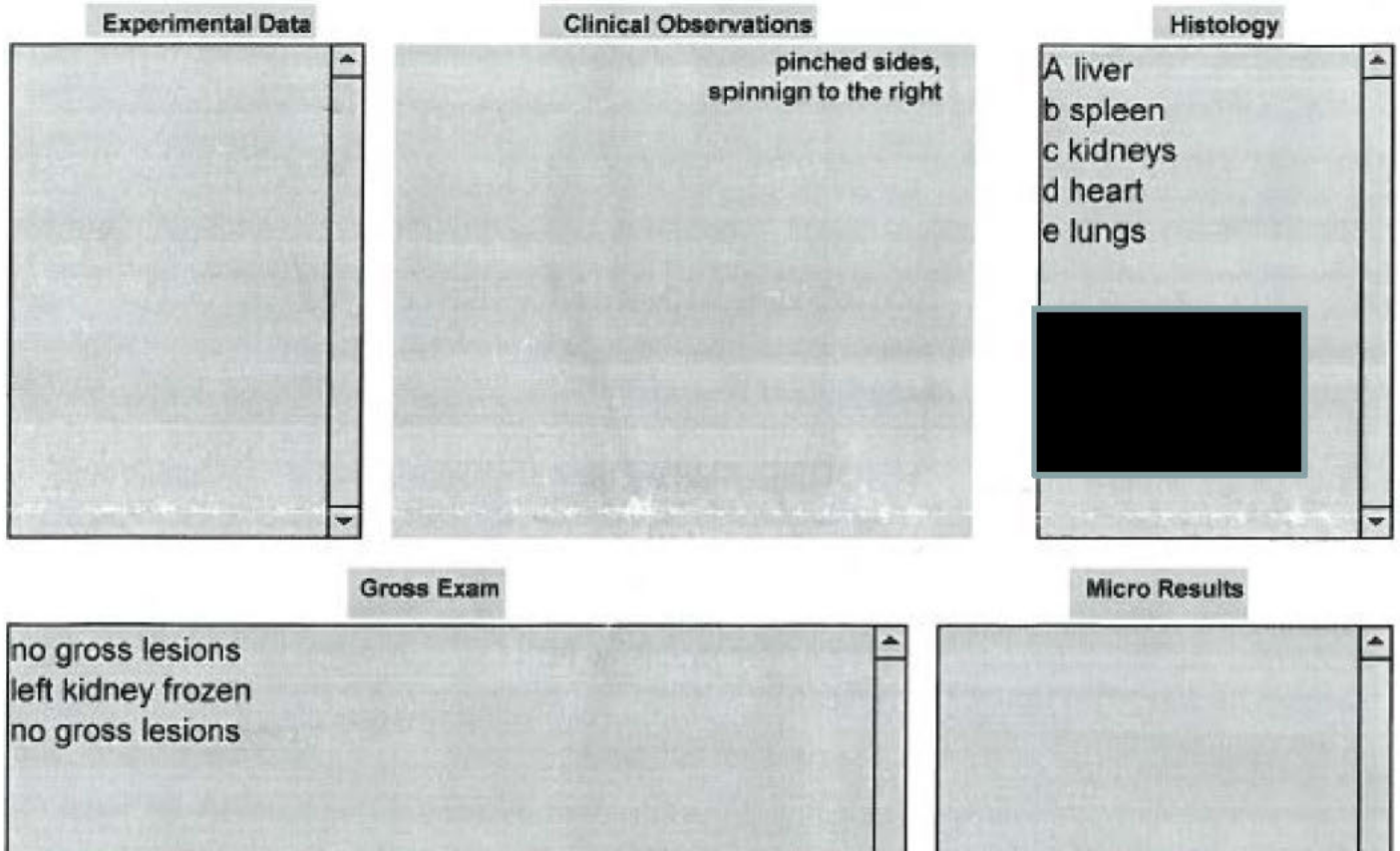
Mouse Brain Atlas





Case Presentation

- 1 month old male mouse
- Sick
- Euthanized - pentobarbitol



Microscopic Finding

The following organs were examined and considered to be within normal limits: liver, spleen, kidney (only ine kidney was present), heart, lungs.

Diagnoses/Comments

There were no histologic lesions in the tissues examined. The cause of the clinical signs was not identified, but may have been due to a lesion in the brain or inner ear. If possible, it is recommended that brain be examined for gross lesions (if not already done) and several sections be submitted for histopathologic evaluation, especially the brain stem at the locations of the vestibular nuclei.

Case Presentation

- 1 month old male mouse
- Sick
- Euthanized - pentobarbitol