Neuroanatomy and physiology

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Introduction

The goal of this chapter is to familiarize you with the basics of the nervous system, how it began, what it's all about and what it looks like when it doesn't work. A portion of the chapter will also focus on relating neurological illness to the anatomy of the nervous system.

Need-to-know facts about the nervous system: fundamentals

The nervous system can be divided into three main anatomical divisions:

- the central nervous system (CNS): consists of the brain, brainstem and spinal cord
- the peripheral nervous system (PNS): comprising the nerves that leave the brainstem and the spinal cord
- the autonomic nervous system (ANS): includes the sympathetic and parasympathetic systems.

The overall function of the nervous system is to integrate and coordinate all internal and external signals between its different parts, whether to control heart rate when stressed or propagate a grand mal seizure.

The nervous system is capable of extracting various types of sensory information in order to refine a motor or an emotional response, and effect change in the surrounding environment. Most creatures, including your pet duck, have a nervous system. Given this, part of the purpose of the CNS is species survival and reproduction.

The CNS is1,2:

- composed of a trillion neurons that communicate with each other through axons, dendrites and synapses with the help of neurotransmitters
- rapidly adaptive and can alter responses based on our environment
- covered by meninges
- hydrated by cerebrospinal fluid (CSF)
- protected from infiltration of bacteria by the blood-brain barrier
- well supplied by a highly anastomotic vascular system
- housed within static bone (skull and vertebral bodies)
- composed of grey and white matter found within the brain and spinal cord
- disrupted through structural and metabolic conditions
- controls other organs through the activation of muscles or through secretions of hormones and neurotransmitters.

The brain

The brain accounts for two per cent of total body weight, has the consistency of firm custard and contains two hemispheres, a cerebellum and the brainstem. The four lobes within the hemispheres are each separated by a longitudinal fissure (crack), are mirror images of each other, but each contains areas of specialty only found in particular locations, such as expressive speech. “Gyri” or bulges of grey matter alternate with “sulci” or “fissures” that further separate each lobe.1

The brain contains both grey matter (made up primarily of cells) and white matter (made up primarily of cell processes, or axons), is protected by the meninges and eight fused bones (adult). It “floats” in CSF and receives blood flow through arteries that enter the cranial cavity through the base of the skull, and that join into an anastomotic network called the Circle of Willis. Information to be processed in the brain is encoded by neurons using electrical and chemical signals, and is transmitted by axons (the main anatomical outputs) to other neurons. Information is transmitted back and forth between the two cerebral hemispheres through the corpus callosum, a white matter structure that only contains axons and physically joins the two hemispheres (Figure 1).

Glossary:

Agnosia: complex cerebral receptive disabilities (e.g. inability to recognize faces)
Aphasia: inability to comprehend speech (receptive) or speak fluently (expressive)
Apraxia: inability to complete complex motor tasks
Babinski reflex: toes flaring out, great toe moving upwards. Is normal in babies, abnormal in adults. Is representative of a contralateral UMN lesion
Drift: a term used to describe a motor weakness in an arm (most often tested in people with SDH, vasospasm)

Hemianopsia: loss of vision in half the visual field in each eye
Neglect: inability to recognize the left side of the body as their own
Nystagmus: incoordination of eye movement secondary to cerebellar dysfunction

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2. Introduction

Ce chapitre vous présentera les grandes lignes du système nerveux, comment il a commencé, de quoi il s’agit, et à quoi il ressemble lorsqu’il ne fonctionne pas. Une partie de ce chapitre portera également sur les liens entre les maladies neurologiques et l’anatomie du système nerveux.

Figure 1: MRI of the brain: axial cut. Grey and white matter
The brain can further be divided into three “brains”¹⁻³:

- **cerebrum**: is highly advanced and includes the cerebral cortex, white matter, thalamus, hypothalamus and basal ganglia
- **cerebellum or hindbrain**: is responsible for integrating and coordinating signals required for fine motor control of the trunk and limbs
- **brainstem**: is composed of the midbrain, pons and medulla oblongata. Areas that connect the cerebral cortex and cerebellum to each other as well as to the spinal cord, as well as circuits responsible for primitive reflexes, autonomic control (e.g. heart rate and respiration), level of consciousness and arousal (the reticular activating system [RAS]) and gives rise to the cranial nerves (CN) (Figure 2).

**The spinal cord**¹⁻³

The spinal cord is approximately 42 cm in length in the average adult and is about the width of the adult thumb. The spinal cord is surrounded by CSF and meninges and is protectively housed within a bony cavity of vertebrae. The vertebrae are held in place by vertical and longitudinal ligaments and are separated by small pulposus cushioning discs. Between the vertebrae are spinal nerves that are part of the PNS, and that become the peripheral nerves that innervate the body. These nerves contain both sensory (spinthalamic, spinocerebellar) and motor (corticospinal) pathways connecting our external body to our internal environment. A total of 31 spinal nerves exit at various levels from the spinal cord with the chief goal of connecting the CNS with the body and effecting motor and/or sensory responses to environmental cues (Figure 4).

**The peripheral nervous system (PNS)**

**Spinal cord and cranial nerves: lower motor neurons** (Figure 5)

The PNS is composed of the cranial and spinal nerves. Many fibres of those nerves arise from neurons located in the brainstem or spinal cord that send motor signals to various muscles in the body (lower motor neurons, or LMN). Other PNS fibres are sensory, and arise in neurons found in sensory ganglia that send processes to the periphery as well as into the spinal cord. LMN cell bodies are located in the anterior grey columns of the spinal cord, and send axons that extend within the peripheral nerve directly to the muscle.² Other peripheral nerves, the cranial nerves (CN), can be motor or sensory nerves (or both), and supply most of the face. The spinal nerves are topographically associated with specific myotomes (muscle groups) and

**Did you know?**

That the sea sponge lacks a nervous system and that the jellyfish and starfish lack a brain (but have a central nervous system).⁴

The fruit fly and the roundworm hold the record for being the most studied organisms of all brain researchers — the researchers even discovered our biological clock gene in the fruit fly!⁵

**The brainstem**¹⁻²

The brainstem is on average the length and width of the adult thumb and connects the spinal cord to the cortex and cerebellum. The brainstem houses and functionally manages 10 out of the 12 cranial nerves, pyramidal and extrapyramidal tracts, the RAS, the respiratory and cardiac centres and is supplied by the “posterior circulation” through the vertebral arteries that join to become the basilar artery. Given its small size and eloquent function, injuries to the brainstem are generally poorly tolerated, and this leads to high mortality and morbidity (Figure 3).
dermatomes (sensory areas). For example, the sixth cervical nerve (C6), supplies motor function to the biceps and sensory function to the radial side of the forearm and to the thumb. Examples of diseases affecting the LMN include spinal cord lesions affecting the anterior horns, poliomyelitis and amyotrophic lateral sclerosis (ALS).

**Did you know?**

Spinal polio is a highly contagious viral infection of the anterior horn cells of the spinal cord (lower motor neurons). Infection leads to destruction of the nerve cells and the inability to send impulses to their associated muscles. Within two to three days muscles will atrophy, become floppy and paralyzed. Polio can affect one or both limbs but is often asymmetrical. Of interest, the muscles closest to the body are the weakest.

The autonomic nervous system (ANS)\(^1\)\(^2\)\(^7\) (Figure 6)

The ANS is a system that regulates homeostasis and vital organ function through the ongoing manipulation of our visceral organs including smooth (involuntary), cardiac muscles and glands. The ANS is divided into the sympathetic (SNS) and parasympathetic systems (PSNS) and is functionally supplied by the somatic nervous system. Though they function in opposition to each other (fight and flight or rest and digest), these two systems are complementary. For example, the maintenance of heart rate is controlled by the PNS and the SNS in a second to second complementary system. Most of the neurons for the SNS are found in the thoracic and lumbar regions (T1–L2) of the spinal cord, whereas the parasympathetic system neurons begin in the CN III, VII, IX, X and sacral nerves S2–4. They are intricately connected with the hypothalamus.

- **sensory neurons of the ANS**: Sensory neurons of CN VII, IX, and X monitor blood levels of carbon dioxide, oxygen, blood sugar, arterial pressure, and composition of the gut and relay this information to the medulla oblongata. Information from the medulla is used to unconsciously modulate the system.
- **motor neurons of the ANS**: Motor neurons of the SNS run in two chains along the spinal cord, whereas the PSNS neurons are located very close to the target organ. Examples of PSNS neurons and location include the salivary glands and CN X.

Though the goal of the ANS is homeostasis, either system will “kick-in” when required.

Table 1: Systemic examples of our ANS responses

<table>
<thead>
<tr>
<th>System</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Diverts flow away from skin</td>
<td>No change or returns to normal</td>
</tr>
<tr>
<td></td>
<td>Makes you sweat</td>
<td></td>
</tr>
<tr>
<td>Muscles</td>
<td>Enhanced flow</td>
<td>No change or returns to normal</td>
</tr>
<tr>
<td>Lungs</td>
<td>Dilatation of bronchioles</td>
<td>Constricts bronchioles, stimulates secretions</td>
</tr>
<tr>
<td>Heart rate, contractility</td>
<td>Increased</td>
<td>Decreased heart rate with no change in contractility</td>
</tr>
<tr>
<td>Pupils</td>
<td>Dilate</td>
<td>Constrict</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Rises</td>
<td>Falls or returns to normal value</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Dilates cardiac and skeletal</td>
<td>No change</td>
</tr>
<tr>
<td>Peristalsis</td>
<td>Inhibits peristals</td>
<td>Increases peristals</td>
</tr>
<tr>
<td>Gut</td>
<td>Diverts blood flow away from gut</td>
<td>Dilates blood vessels to gut</td>
</tr>
<tr>
<td>Salivation/tearing</td>
<td>No effect</td>
<td>Stimulation</td>
</tr>
<tr>
<td>Urinary system</td>
<td>Urinary retention</td>
<td>No change</td>
</tr>
<tr>
<td>Responsible neurotransmitter</td>
<td>Norepinephrine Epinephrine ATP Acetylcholine</td>
<td></td>
</tr>
</tbody>
</table>
Cellular structures of the CNS

Back to the beginning
At approximately three weeks’ gestation, the nervous system begins as an undifferentiated ectodermal tissue known as the “neural crest” (Figure 7). During fetal growth, the neural crest folds into the neural. By 20 weeks’ gestation, grey and white matter are formed. The neuron will contain a cell body, an axon, multiple dendrites and, in the case of a motor neuron, the axon will terminate with a motor end plate. The brain at this stage would be the size of a small grape.

Migration of neurons and cells to their final destination does not end at birth, but continues for a few months after. Migration is facilitated with neuronal “growth cones”. Curved growth cones, assisted by glial cells, are studded with chemicals that “source out” their local environment. They are either attracted or repelled, and in the end will be “pulled” to their particular destination. Newer cells are formed deep in the brain and eventually find their place superficially in the cortex. The motor neurons, being the largest, differentiate first, followed by smaller sensory and glial cells. Cerebellar cells are found superficially, then migrate deep into the cerebellar lobes. “Lost” axons, or those unable to find their end destination, are removed via a process called “pruning” in which these axons die back due to the lack of guidance cues and/or trophic factors.

A note on neural tube defects
Neural tube defects are caused by the failure of the neural tube to close during development and is associated with folate deficiency. Defects are divided into anterior, midline and posterior defects, with posterior defects occurring most commonly. Most neural tube defects are accompanied by a vertebral defect. With the bony defect, there is a protrusion of the spinal cord and nerves. Some tube defects are incompatible with life, such as anencephaly in which the entire brain is missing and the bony component (skull) fails to form or is empty.

Myelomeningocele, also known as spina bifida (Figure 8), is a protrusion of the spinal cord, nerves and CSF through a posterior vertebral defect. About 80% of cases occur in the lumbar region. In spina bifida occulta, the cord and nerves are anatomically normal and the defect is not apparent to the naked eye. It can be found in 10–25% of all infants and commonly appears like an abnormal coarse hairy growth at the lumbar region or a midline dimple or port-wine stain. It causes minimal to no neurological problems and most can be correctly surgically if it causes symptoms.
Grey matter1–3 (Figures 9 & 10)  
The grey matter is 1–4 mm in depth and is found in both the brain and spinal cord. It is composed of the cell bodies of neurons and of supporting glial cells. Areas where grey matter is found include the cortex, thalamus, cerebellum, hypothalamus, basal ganglia, putamen, globus pallidus, brainstem and some deep structures, such as the red nucleus and substantia nigra.

White matter1–3 (Figures 11 & 12)  
White matter makes up the bulk of the deep parts of the brain, cerebellum, superficial parts of the spinal cord and ventricles. Grey matter primarily surrounds it.

Three types of white matter tracts are found within the CNS:
- projection tracts: send action potentials from neurons in the cortex to other regions, from brain to muscles, or from sensory receptors to the brain  
- commissural tracts: carry information from left-right hemispheres  
- association tracts: carry information between the lobes on the same side.

Considered the “cables” of the system, white matter is primarily responsible for the connection and carrying of neural impulses from grey matter to grey matter. White matter fibres can be either myelinated (surrounded by insulating myelin produced by oligodendrocytes and able to effect rapid propagation of nerve impulses) or unmyelinated (effect slower propagation of nerve impulses).

Dendrites: are the structures that transmit electrical impulses toward the cell body. They are the structures that contain the receiving side of synapses (the specialized structures in which stimuli from one neuron are conveyed to another neuron using chemical neurotransmitters), are generally multiple in number and receive information from several other neurons.

Facts about neurons1,2,14  
- the CNS contains approximately one trillion neurons  
- mature neurons lack mitotic ability and cannot replicate  
- motor neurons are the largest  
- neurons vary in size and complexity: some connect short distances such as distances from one cell to another, whereas others connect areas all the way from the motor cortex to the end of the spinal cord (four feet in the adult)  
- some neurons carry information from the periphery to the CNS (Afferent neurons), whereas some carry information from the CNS to the periphery (Efferent neurons)  
- the majority of neurons in the CNS are “interneurons”. These are the neurons that relay information between major neuron groups located in the same areas  
- neurons with a common function are grouped together into areas called “ganglia”  
- neurons with a common target are grouped together into areas called “nuclei”  
- they have a cell body, an axon and a dendrite  
  - cell body: is the metabolic and genetic centre, receives information and is covered by processes from other neurons and glia  
  - axons and dendrites: most neurons have one axon (the component of the neuron that transmits information away from the cell body), and multiple dendrites, which are the processes that transmit electrical impulses toward the cell body.
Tracts: are bundles of nerve fibres (axons) whose function is to carry and transfer information. Groups of tracts are called “columns”. They can either ascend or descend in the spinal cord (e.g. the dorsal columns) or can travel horizontally (commissures) in the brain. In case of injury where a “tract” is damaged or lost, the CNS contains multiple tracts that would sometimes allow continued transfer of information to support function.

Myelin: Myelin is the lipid rich layer that surrounds axons and gives the white matter its appearance. The development of myelin is not completed until two years of age. In the PNS, myelin is produced by Schwann cells and in the CNS by oligodendrocytes. The sheaths have small breaks along the way, called the “nodes of Ranvier” (Figure 14 and Figure 15). The nodes serve to speed up the transmission of electrical impulses along the axon. Generally large neurons are myelinated (in order to speed up transmission) and small ones are not. Myelination of the CNS begins at approximately three weeks’ gestation and continues after birth. Myelin regeneration

Myelin in the PNS has an ability to regenerate as seen in patients diagnosed with Guillain-Barré Syndrome (GBS). As the cells “heal”, the GBS patients will slowly recover neurological function. In the CNS, breakage in myelin is found, for example in MS, the myelin is sometimes the source of a myelin “scar” that makes axonal regeneration impossible.

Transmission of information through the CNS

Neurons transmit information using electrical and chemical signals. The electrical signals are transmitted along dendrites, cell bodies and axons due to the flow of charged ions across the cell membrane. This flow is possible because the ions are maintained at different concentrations on the inside of the

Interesting fact

If we made the cell body the size of a human, the axon of a motor neuron would be a few centimetres in width and greater than 1 km in length.

Critical thinking

“Myelin” tumours develop where white matter is found. In the case of the PNS, “acoustic schwannoma” is a myelin tumour of the acoustic, or eighth cranial nerve, while “oligodendrogioma” are myelin tumours of the CNS or brain. Diagnostically, therefore, myelin tumours are found on the cranial nerves or deep within the white matter. This fact is important to help identify the possible tumour variety.

Multiple sclerosis (MS) is a disease of myelin destruction. As myelin is found in both hemispheres, MS can be difficult to diagnose, as there can be more than one neurological presentation.

axon or dendrite. The PNS is slightly different. Shortly after an injury to the axon, the damaged end will begin to enlarge. These enlargements are known as “growth cones”. Growth cones begin to send out “feelers” (Figure 16). If the feelers can move past the point of scar or injury and reconnect, then there can be regrowth of the axon and a potential for restoration of function.

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Interesting fact

Motor axons will more frequently reconnect with motor neurons and sensory to sensory. Axons will choose the original muscle to innervate. Incorrect innervation is called “anomalous re-innervation”. This is noted with unwarranted motor responses after an injury. For example, with the phenomenon called “jaw winking” the muscle axon intended for the jaw also goes to the eye. Every time you chew, you blink.
cell as compared to the outside. The separation of electrical charges across the cell membrane results in a difference in voltage (membrane potential) on the inside vs. the outside of the cell. When the neuron is in a resting state, the “resting potential” is about -70 millivolts (mV) and there is no movement of sodium (Na⁺) or potassium (K⁺) ions across the cell membrane. There is more K⁺ generally inside the cell, and more Na⁺ inside the cell.

The flow of K⁺ and Na⁺ across the cell membrane is achieved through ion channels—proteins that comprise pores in the cell membrane that are either open or closed. The ion channels open or close, depending on the voltage across the cell membrane.

Let’s say your CNS needs to transmit information along the axon. The sequence is easy to understand and takes milliseconds to occur:
1. Firstly, the oncoming electrical impulses pinch the Na⁺ channels on the cell membrane.
2. “Pinching” causes the Na⁺ channels to open, allowing the extracellular Na⁺ to flood in.
3. This shift causes the K⁺ channels to open and forces the intracellular K⁺ out.
4. At the same time, Na⁺ continues to enter the cell.
5. The open Na⁺ channels cause a very fast depolarization of the membrane potential generating a “spike” in the membrane potential.
6. At this point K⁺ flows outward, to cause repolarization of the membrane potential and the action “spike”, or action potential is over.
7. Once the action potential reaches the axonal end, the impulse triggers a series of chemical events that cause the release of neurotransmitters from the presynaptic terminal. Neurotransmitters cross from the presynaptic terminal to the postsynaptic terminal found on a dendrite, and trigger the opening of more ion channels that cause the propagation of the electrical signal.

These steps cause the action potential to propagate along an axon, because one area of an axon that depolarizes causes changes in membrane potential in adjacent portions of the action. These changes in membrane potential cause the ion channels in these adjacent segments to repeat the same sequence as above, thus resulting in propagation of the action potential.

**Myelinated axons: saltatory conduction**

On the myelinated axon, the process is slightly different in that the impulse does not travel along the axon, but jumps from node of Ranvier to node of Ranvier, increasing the speed of transmission. The speed is dependent upon the thickness of myelin and the distance between the nodes.

**Critical thinking**

Diagnostically, astrocytoma can be found in the thalamus, high cortical regions or sitting on the blood-brain barrier (BBB). Since astrocytes are found only in grey matter or BBB, “astrocytomas” are tumours of grey matter.

**Did you know?**

That glial cells replicate and are therefore able to form primary brain tumours?

**Interesting fact**

Action potentials last < 1/1000 of a second and travel 1–100 m/second (white and grey matter). Electrical signals in myelinated axons move faster than in unmyelinated ones. Some neurons emit action potentials between 10–100/second and some are very quiet.

**Seizures**

It is believed that seizures are the result of neuronal “synchronicity”, in that multiple neurons depolarize at the same time, resulting in a seizure.
Let’s have a “synaptic” moment\textsuperscript{1,2}

For communication between neurons to occur, information carried by the action potential needs to be able to jump across from one neuron to another. Synapses are the structures across which information jumps. Synapses can be found between the terminal portion of an axon (presynaptic terminal) and the receiving dendrite (postsynaptic terminal). Sometimes, synapses are found between the axon and nerve body or axonal terminal and another axon (axon-axonic transmission). Some large cell bodies can have multiple dendrites and hundreds of thousands of postsynaptic terminals. Propagation of signals from the presynaptic junction to the postsynaptic junction is accomplished with the use of neurotransmitters.

What else do we know about synapses?
- some are excitatory (produce a signal that causes excitation of the cell—more electrical activity)
- some are inhibitory (produce a signal that inhibits the cell from producing electrical activity)
- some are large, some are small, some are flat and some are round.

Did you know?
The average infant has 2,500 synapses per neuron, which increases by 600\% by the age of two. By the time the brain reaches adulthood, we have about 7,500 synapses per neuron. Old, damaged or dead synapses are removed via synaptic pruning.\textsuperscript{21}

Did you know?
That a cubic millimetre of cerebral cortex contains one billion synapses.\textsuperscript{22}

I’m so excited: Common neurotransmitters of the nervous system (Figure 17)
Neurotransmitters (NT) are chemicals whose function is to transfer information from one neuron to another. Neurons consistently release the same single or the same combination of neurotransmitters. Made mainly from modified amino acids, these abundant transmitters have various functions and can be paramount in some disease processes.\textsuperscript{1,2}

NTs are packaged in tiny vesicles (synaptic vesicles) at the pre-synaptic terminal waiting to be called upon. Once an action potential reaches the end of an axon, the electrical signal produced by the action potential causes ion channels permeable to calcium to open within the presynaptic terminal. This causes an influx of calcium ions into the presynaptic area, and the rise in intracellular calcium is the trigger that elicits the release of neurotransmitters. The NT diffuses across the synapse (in the synaptic cleft) and binds to post-synaptic receptors on the receiving side of the synapse (Figure 18). Different neurotransmitters bind specifically to different kinds of post-synaptic receptors. Free-floating NTs that are not bound or degraded are taken back up into the pre-synaptic terminals for re-use, or are mopped up by glial cells.

“Excitatory” neurotransmitters bind to postsynaptic receptors whose activation increases the probability that the target cell will generate an action potential and thus propagate information to the next neuron.\textsuperscript{3,23} “Inhibitory” neurotransmitters bind to receptors whose activation reduces the probability of generating an action potential.

Did you know?
Amphetamines and cocaine bind to the transporters that are used to uptake dopamine in the synapse. Excessive synaptic dopamine affects our pleasure centres, thereby making us enjoy the drug experience.

Did you know?
That the nearby chemoreceptor centre can detect toxins in the blood and CSF and is essential for inducing vomiting. It also contains the “conditional taste aversion centre” which ensures that once an animal tastes a poison it will never eat that object again.\textsuperscript{25}
Structures of the brain and skull

The adult brain is housed within a skull and is surrounded by the meninges. At any given time, there is a fine balance between the skull contents, including brain, CSF and blood. The pressure within the skull is measured as intracranial pressure (ICP). Pressure is relatively static with the average ICP of 0–15 mmHg, but can fluctuate wildly during normal activities such as sneezing or lifting weights. In general terms, if any one component contained in the skull changes in volume, other parts of the system must shift. For example, in the case of hydrocephalus, there is an excessive accumulation of the CSF component, causing either a displacement of the brain, or a rise in ICP. Changes in ICP in compensation to shifts in the volume of various intracranial components are described by the “Monro-Kellie” doctrine. This “doctrine” describes the relationship between changes in intracranial volume and pressure. Over time, and if the pressure continues to increase, decompensation will occur (see below).

Cranial bones (Figures 19 & 20)

The function of the skull is for protection of the brain and contents. Newborns have a total of six separate cranial bones, separated by tough elastic fibrous tissues called “sutures”, “soft spots” or “fontanelles”. The purpose of the sutures is to allow the head to change its shape to facilitate the baby’s delivery, for brain growth and development and for protection from minor injury. Infants have six sutures, including two major fontanelles: occipital (posterior) and frontal (anterior) (Figure 21). The fontanelles can be fused at birth or within two to three months (posterior) or by 18 months of age (anterior). Fusion leads to the arrest of bony growth and the skull becomes rigid.

Table 3: Neurotransmitters

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Action</th>
<th>Functional location</th>
<th>Common neurological illnesses that may be related to neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Excitatory, Inhibitory</td>
<td>Forebrain, CN, thalamus, hippocampus (HC), hypothalamus</td>
<td>Alzheimer’s disease, Myasthenia gravis, Huntington’s chorea (movement disorder)</td>
</tr>
<tr>
<td>Glutamate (most common)</td>
<td>Excitatory</td>
<td>Spinal cord, brainstem, HC, cortex</td>
<td>Cell death post injury</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Inhibitory</td>
<td>Hypothalamus, midbrain, basal ganglia</td>
<td>Parkinson’s, schizophrenia</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Excitatory</td>
<td>SNS, wide spread</td>
<td>Panic attacks, sleep/wake cycle disturbance</td>
</tr>
<tr>
<td>GABA (2) (γ-amino butyric)</td>
<td>Inhibitory</td>
<td>Hindbrain, cortex, HC, limbic</td>
<td>Behavioural changes, memory loss, emotional and movement disorders</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Inhibitory</td>
<td>PNS in gut, widespread</td>
<td>Regulates appetite, affects memory and learning, temperature, mood, cardiovascular and endocrine function</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Excitatory</td>
<td>Adrenal cortex</td>
<td></td>
</tr>
</tbody>
</table>

Interesting fact

In the child, bulging or sunken fontanelles can be a sign of increased ICP or of dehydration respectively.
Disorders of infant and childhood sutures: Craniosynostosis is the premature closure of one or all of the six sutures. This rare disorder, more common in males, can result in microencephaly (small head) or an abnormally shaped head. As the skull is forced to grow irregularly in a different direction, children will begin to show changes in facial appearance.\(^2\)

The adult skull includes 22 fused bones (except the mandible). The adult skull includes eight bones of the skull and 14 bones of the face. The intracranial compartment is subdivided into anterior, middle and posterior cranial fossa. Most of the bones are peppered with holes to allow nerves and arteries to pass through.\(^2\)

Of note, the temporal bone encases six bones that make up the inner ear. The occipital bone contains a large central opening to accommodate the brainstem and spinal cord known as the “foramen magnum”. The average adult skull is 6.5–7.1 mm in width and 171–176 mm in length, and has an average weight of 2.5 pounds empty and 11–14 pounds with all of its contents.\(^2\)

Interesting fact

*Getting punched in the nose and sense of smell.* The cribiform plate is a boney area found at the front of the skull. It is the area through which the olfactory nerves, which terminate in the olfactory bulbs, extrude processes that travel through the cribriform plate and into the nasal cavity. These processes contain the receptors that make olfaction possible. Fracture of the cribiform plate can disrupt these processes and lead to disruption of sense of smell, complete lack of smell, or smelling stuff that isn’t there, including smelling offensive odours (that could be bad...).

Meninges\(^1,3,24\) (Figure 22)
The outer coverings of the brain are called the meninges and include three layers:

- the *dura mater*, “tough mother”, leather-like outer layer, which is fused to the skull in various places, restricts brain movement and is continuous with the spinal canal. The dura matter separates the hemispheres from each other and also separates the cerebellum from the cerebrum. The dura mater contains the dural sinuses which form part of the venous drainage of the brain, and that also contain structures responsible for passive reabsorption of CSF produced by the brain. The dura is innervated by cranial nerve V (trigeminal nerve) and by the first cervical nerve.

- the *arachnoid* is “spidery mother” and is a layer that forms a space over the brain and spinal cord in which is found the CSF and the blood vessels. It is usually watertight. The arachnoid space also contains arachnoid villi or granulations that extend up into the dura and the venous sinuses where the CSF is reabsorbed into the blood stream.

- the *pia mater* is the “soft mother” and is comprised of a thin layer of cells. It is adherent to the surface of the brain.

A word on meningitis

Meningitis is the name given to inflammation of the meninges and comes with a classic set of symptoms: nuchal rigidity, headache, photophobia with or without fever. Remember that there are many causes of meningitis including bacteria, virus, surgery, and chemical.
Cerebrospinal fluid:
- is produced in the choroid plexus, a highly vascular delicate structure located in the walls of the lateral ventricles and the roof of the third and fourth ventricles. The choroid plexus is covered with ependymal cells
- CSF circulation is aided by pulsations in the choroid plexus and ependymal cells
- bathes the brain and spinal cord allowing the brain to float, and cushions the CNS central from injury
- plays a role in homeostasis regulation as it removes toxins and metabolites
- is fundamental in the maintenance of the Monro-Kellie doctrine (see current chapter)
- approximately 140 cc of CSF is found within the ventricles and subarachnoid spaces at any time
- total production is approximately 500 cc/day or 20 cc/hour and turns over 3.7 times daily
- production in children is only slightly less than in adults.

CSF components include:
- colour: clear and colourless
- glucose: two-thirds of the serum glucose level or 3.3–4.4 mmol/L
- protein: 15–45 mg/dl
- WBC: < 4/mm
- RBC: zero

Interesting fact
The fourth ventricle is about the size of a pea and holds approximately 5 cc of CSF. Having 10 cc of blood in the fourth ventricle, through a subarachnoid hemorrhage, can cause acute and sudden hydrocephalus.
Assessment of CSF: Infection or hemorrhage

A lumbar puncture (LP) can obtain CSF for culture and sensitivity and assess for blood products. As the spinal cord ends at L1–2, LPs are done at the level of L3–4 or below, as there is limited possibility of injury to the cord.

All the values in Table 4 are listed across all age groups.

**Intracranial pressure**

The pressure is building: A word on intracranial pressure (ICP) and the Monro-Kellie doctrine

ICP is described as the pressure within the incompressible skull and includes the dynamic balance of CSF, brain and blood vessel volumes. The constancy of cerebral hemodynamics, including blood flow, brain volume, CPP and CSF are required to maintain ICP at 5–15 mmHg. This is also referred to as the Monro-Kellie doctrine.

**Factors involved in the maintenance of the Monro-Kellie doctrine**

- compensation: an increase in one component (brain, CSF, blood) requires a decrease in another
- about 20% of “brain volume” is fluid that sits around the cells
- CSF is the most readily displaced and can be displaced into the spinal cord
- ICP can become elevated due to non-pathological causes (sneezing, coughing) or to pathological causes (tumour, stroke, abscess, hemorrhage)

**Table 4: CSF results**

<table>
<thead>
<tr>
<th>Colour</th>
<th>Protein</th>
<th>Glucose</th>
<th>WBC</th>
<th>RBC</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CSF</td>
<td>clear and colourless</td>
<td>15–45 mg/dl</td>
<td>two-thirds of serum glucose, or 3.3–4.4 mmol/L</td>
<td>&lt; 4 cells</td>
<td>negative by third/fourth tube</td>
</tr>
<tr>
<td>CSF with subarachnoid hemorrhage</td>
<td>bloody at third/fourth tube</td>
<td>slight increase</td>
<td>no change</td>
<td>no change</td>
<td>very high</td>
</tr>
<tr>
<td>CSF with bacterial meningitis</td>
<td>cloudy or purulent may be thick</td>
<td>very high</td>
<td>very low (consumed by leukocytes)</td>
<td>increased</td>
<td>slight increase or normal</td>
</tr>
<tr>
<td>CSF with malignancy</td>
<td>clear yellow, may be thick</td>
<td>slight increase or normal</td>
<td>normal</td>
<td>very high</td>
<td>slight increase or normal</td>
</tr>
<tr>
<td>CSF with MS/autoimmune disease</td>
<td>clear yellow</td>
<td>slight increase or normal</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
</tr>
</tbody>
</table>

Figure 25: Hydrocephalus. CT of the head. Note the size of the enlarged ventricles. This person would be diagnosed with hydrocephalus

- ICP can be “managed” until it reaches 25 mmHg, then compensation begins
- pressure will eventually look for areas of least resistance (such as the brainstem). Movement towards the brainstem is called “herniation” (see coma section)
- once ICP becomes > 40–50 mmHg, loss of consciousness occurs and there is a decrease in cerebral perfusion
- sustained ICP > 50 mmHg leads to infarction and death.
Symptoms of elevated ICP

Symptoms of elevated ICP can be listed according to location of the elevation within the CNS. Symptoms of increased pressure around the level of the brainstem are different from those in the cerebrum. Brainstem findings often indicate a grave prognosis (Table 5).

### Table 5: Symptoms of raised ICP

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Anatomical location</th>
<th>Significance to the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Cortical: pressure on the meninges</td>
<td>Can be viewed as an early warning sign. Need to rule out other causes of headache.</td>
</tr>
<tr>
<td>Pupillary changes (dilated and not reactive)</td>
<td>Midbrain level and is secondary to shifting of the uncus of the temporal lobe until it compresses the third cranial nerve, which causes the pupillary dilatation</td>
<td><em>Is a potentially grave, yet early sign. The cause of the increased pressure is ipsilateral to the dilated pupil. Suggests that the pressure is reaching a level that causes the brain to shift onto the brainstem. Requires urgent surgical attention.</em></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Roof of fourth ventricle or pressure on the hypothalamus</td>
<td>Suggest brainstem or hypothalamic involvement.</td>
</tr>
<tr>
<td>Nausea</td>
<td>Hypothalamic area</td>
<td>Need to rule out other causes of nausea.</td>
</tr>
<tr>
<td>Altered level of consciousness</td>
<td>Thalamus and upper brainstem (involvement of the reticular activating system (RAS))</td>
<td>Suggests that ICP change is affecting both hemispheres or is causing significant pressure on the brainstem. Most likely the ICP is greater than 25 mmHg. Need to rule out other sources of altered LOC: metabolic, medications, fever (see coma section below).</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Optic chiasm and optic nerves</td>
<td>Suggests that pressure is long-standing, causing edema in the optic nerve all the way to the retina (optic disk). Patient needs a diagnosis (start with brain imaging).</td>
</tr>
<tr>
<td>Cheyne-stoke respiration</td>
<td>Any level throughout the neuroaxis</td>
<td>Patient may suffer airway compromise. Need to assess airway and oxygen saturation.</td>
</tr>
<tr>
<td>New onset hemiplegia</td>
<td>Any level throughout the neuroaxis, but is typically due to a unilateral lesion</td>
<td>Requires urgent medical or surgical care.</td>
</tr>
<tr>
<td>Pinpoint pupils</td>
<td>Pons</td>
<td>Is a late sign (if not due to medication) suggesting brainstem involvement and potential fatal herniation. Check medication history.</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Medulla</td>
<td>Is a late sign suggesting brainstem involvement and potential fatal herniation.</td>
</tr>
<tr>
<td>Cushing Triad</td>
<td>Medulla: hypertension, wide pulse pressure, bradycardia, irregular breathing</td>
<td>Is a late sign suggesting lower brainstem involvement and potential fatal herniation.</td>
</tr>
<tr>
<td>Enlarged fontanelles when sitting up</td>
<td>Seen in young children pre-fusion of sutures</td>
<td>Is a compensatory mechanism for high ICP.</td>
</tr>
</tbody>
</table>
| Sunset eyes (inability to look upwards) | Brainstem: dorsal midbrain and pons  
Seems most frequently in children and suggests pressure on cranial nerves III, IV, VI. The eyes appear to look downward | Indicates either increased ICP (e.g. from hydrocephalus), or a mass lesion compressing the brainstem — both need urgent diagnosis and medical/surgical attention. |
| Bradycardia                      | Seen in patients with high ICP                                                       | Abnormal finding suggesting brainstem involvement.                                      |

Critical thinking

The nurse at the bedside is the first person to assess for changes in ICP with accompanying neurological changes. It is critical to be aware of any rapid or progressive neurological change.
ICP decompensation is categorized into four stages (Table 6)²⁹,³³,³⁴
- decompensation will occur once all of the compensatory mechanisms available to the CSN to prevent a rise in ICP fail. Such mechanisms may include a decrease in the intracranial volume of CSF when there is an increase in the volume of another compartment, such as tissue from a brain tumour
- death (if untreated and rising) will typically occur from end-stage raised ICP that causes compression of the brainstem (herniation).

Consciousness and coma
Consciousness can be described as having the awareness of one's environment, being mentally perceptive and awake, providing responses to our environmental cues and being cognizant of our beliefs, ideals and thoughts. Conversely, coma has been defined as the state of altered or impaired consciousness in which both the motor and psychological responses to stimulation are completely lost, as in deep coma, to that of reduced or rudimentary responses seen in moderately deep coma.³² Two key components, arousal and awareness (content), are required for both our conscious state and our level of coma.

Critical thinking
Cerebral edema can be either vasogenic (meaning that the increased water content of the tissues is in the extracellular compartment) or cytotoxic (meaning that the increased water content is intracellular). Though both raise ICP, treatment is not the same. Vasogenic edema is often seen in brain tumours and is treated with dexamethasone. Cytotoxic edema is treated with osmotic agents such as mannitol (a dehydrating agent for the brain).

Critical thinking

Point of interest
On a normal CT scan or MRI, we often can easily see the brain “gyri”. But as ICP rises, the gyri begin to push upwards towards the inner table of the skull. As the gyri press up onto the skull, they will begin to flatten and become indistinguishable. This is known as “effacement”.

Critical thinking
Sometimes surgery or other causes of brain swelling (such as with infarction, tumour or abscess) cause a patient to be more prone to ICP problems. Pathology in the “posterior cranial fossa” or the area behind or including the brainstem (cerebellum) can be particularly problematic, because a relatively small increase in ICP can directly cause brainstem compression and a sudden respiratory arrest. Post fossa swelling can compress the fourth ventricle, which leads to hydrocephalus.

Often, early symptoms of raised ICP can be missed and associated with other common problems. For example, post-operative nausea, headache and vomiting are a common presentation post surgery.

- Headache: can be related to the surgical site, caffeine or nicotine withdrawal, blood sugar, etc.
- Nausea: could be related to the analgesics used to treat the headache, constipation, general anaesthetic, and ileus
- Vomiting: could be related to the analgesics, constipation, ileus, etc.

But, they are also symptoms of increasing ICP. So, be cognizant of the patient who has post fossa surgery...

Table 6: ICP

<table>
<thead>
<tr>
<th>Stage</th>
<th>ICP</th>
<th>Venous response</th>
<th>CSF flow</th>
<th>Tissue response</th>
<th>Arterial response</th>
<th>Exam findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• compensated</td>
<td>• decreased flow compression of veins</td>
<td>• increased reabsorption</td>
<td>• no impact</td>
<td>• no change</td>
<td>• confusion, drowsiness, slight pupil and resp. changes</td>
</tr>
</tbody>
</table>
| 2     | • intracranial hypertension  
• partial compensation | • cont. compression | • maximum reabsorption reached | • hypoxia  
• hypercapnia | • general vasoconstriction to increase BP to push through ICP  
• cerebral vasodilation | • decreasing LOC, Cheyne-stokes respiration, sluggish pupils, bradycardia, wide pulse pressure |
| 3     | • dramatic rise in ICP, decompensation  
• loss of auto-regulation, maximum constriction | • beginning of hydrocephalus | • severe hypoxia  
• acidosis | • maximum vasodilation | • coma, pupillary changes, minimal response to pain |
| 4     | • decompensation | • obstructive hydrocephalus | • herniation ischemia | • disruption of arterial blood flow | • coma, dilated fixed pupils, ataxic breathing, posturing |
The term “coma” is a lay term that is used to describe an altered level of consciousness. However, “coma” means different things to different people, because patients can have different levels of consciousness. Consequently, medical practitioners do not use the word “coma”. Rather, they use a validated scale in order to communicate the patients’ level of consciousness. This scale is called the Glasgow Coma Scale (GCS).

Other commonly used terms are “arousal” and “awareness”. Understanding the differences between the two helps in understanding the transition from a normal level of consciousness to altered consciousness. Awareness is primarily higher function (requiring acknowledgment of sometimes complex external cues), whereas arousal is a process that requires the functioning of primitive CNS structures like the brainstem and thalamus. As a person moves into a state of coma, levels of awareness are affected first.

**Awareness:** includes responses to motor stimuli, verbal responses to questions and the ability to open the eyes spontaneously or when spoken to. Of these, the motor response is the most sensitive index of the degree to which a patient’s level of consciousness is altered.

- must involve the cerebral hemispheres, which are responsible for the processing of multiple higher order functions
- must be self-promoting (on-going connections with thalamus)
- includes:
  - frontal lobe: judgment, motor responses, reasoning, memory and expressive language
  - temporal and parietal lobe: language, memory, sensation
  - occipital lobe: interpretation of visual field, visual memory.

**Arousal:** is maintained or initiated in through the reticular activating system (RAS) (Figure 27).

The RAS

- consists of a series of interconnected circuits housed within the brainstem, hypothalamus and thalamus
- is called the “ignition system” and is divided into ascending and descending tracts:
  - ascending tracts: connect the brainstem, hypothalamus and thalamus with the cortex
  - descending tracts: connects the thalamus, hypothalamus and brainstem to the cerebellum and reticulospinal tract, modulating sensory input, autonomic activity, spinal cord reflexes and postural muscles.

**Case presentation**

A 52-year-old female collapsed at work and was intubated at the scene. She arrived in ER with a Glasgow Coma Score (GCS, see below) of 3/15. The CT scan below shows that she has, among other things, an acute subdural hematoma on the left side. She also has generalized brain edema, suggestive of a hypoxic episode. Most importantly, her ventricles are small, and the midline structures are dramatically shifted to the right by the subdural hematoma and the swollen left brain. Note the lack of any clear sulci and gyro in scan 1. Her scans are suggestive of brain herniation. She succumbed to her injury the next morning.

**Alterations in consciousness**

Early changes to our level of conscious can be related to problems within the CNS or those found outside of the CNS. They can be fluctuating, progressive or sudden. When patients suffer a change in consciousness, it can either be due to metabolic causes (e.g. medications, ketosis) or due to structural causes. In the case of the latter, a change in consciousness always raises concern about compression or irritation of the strategic areas of the CNS (brainstem, thalamus).

**Just think…**

The RAS keeps you awake while driving late at night. Information from the brainstem is sent forward to the thalamus, which activates the cortex. As the system begins to “peter-out” and you get tired, you may notice that you open the window, turn on the radio or engage a passenger in conversation. The purpose of this is to provide go-on stimulation of the ascending tracts and cortical stimulation. The system is, therefore, “self-promoting.”

Alterations in consciousness can be:

- fluctuating: is generally not strictly related to the CNS only but can include CNS and non-CNS causes, for example, delirium and anesthesia, or UTI and dementia
• progressive: observed primarily with primary CNS pathology and encroaching rise in ICP: changes in volumes of brain, CSF or blood. This is also witnessed in patients with CNS disease and an overwhelming systemic illness such as sepsis.
• non-pathological: sleep. During sleep the descending tracts of the RAS can turn “off”, giving us a perception of rest. Through stimulation, such as touch or voice, the ascending RAS is re-engaged and turned back “on”.

Causes for changes in the level of consciousness can be classified into three areas:
• CNS: requires bi-hemispheric changes to contents or volume related to blood, CSF or brain. This can often be measured or reflected in a rise in ICP
• non-CNS: metabolic, systemic issues (organ failure), toxins, acid-based disturbance, and anoxia
• CNS and non-CNS: includes a known diagnosis of a CNS disease (brain tumour resection) and a non-CNS insult, such as sepsis (Table 7).

Table 7: Common causes of changes in level of consciousness

<table>
<thead>
<tr>
<th>Structural</th>
<th>Metabolic</th>
<th>Mechanical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shifting of contents</td>
<td>Fluid and electrolyte imbalance</td>
<td>Hemorrhage (blood)</td>
</tr>
<tr>
<td></td>
<td>Toxins</td>
<td>Edema (brain)</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>Hydrocephalus (CSF)</td>
</tr>
</tbody>
</table>

Components required for structural causes of altered level of consciousness:
• failure of the Monro–Kellie doctrine
• progressive neurological decompensation irrespective of systemic medical condition
• pressure, destruction or irritation of consciousness key areas (brainstem or thalamus).

Alterations in LOC and progression of coma

In the adult, the volume of the intracranial cavity is fixed. When ICP begins to build, the intracranial contents will be pushed into areas where it is not normally found. This is also known as “herniation”:

1. When there is a unilateral increase in intracranial contents, such as with a unilateral brain hemorrhage, the intracranial contents will shift sideways (e.g. scan 1). The cause of the rise in pressure remains ipsilateral, though the increase in ICP is distributed throughout the intracranial compartment. Patients may exhibit symptoms of headache (see symptoms of ICP above) or exhibit focal neurological deficits such as weakness contralateral to the affected hemisphere.
2. Once the ICP increases further, the intracranial contents will shift further sideways, resulting in a shift of the midline structures of the brain (thalamus and brainstem). You will see changes in consciousness as this progresses, or changes in levels of arousal (content) and progression of focal neurological deficits. When the pressure is high, the uncus of the temporal lobes may begin to herniate through the tentorial incisura (the opening in the dura mater that contains the midbrain). This is often referred to as “midline shift” or transtentorial herniation (across the “tent”), or “uncal herniation”.
3. Once ICP is very high, the intracranial contents will shift downwards, under the thalamus to the midbrain. You will see obvious changes in LOC, the patient may not respond to pain (if compression involves the brainstem), may exhibit pupillary changes (third cranial nerve compression), and hemiplegia.
4. In its terminal stages, raised ICP causes herniation of the brainstem and cerebellum downwards into the foramen magnum. This is called “coning”, and is manifest as profoundly impaired consciousness, cardiac and respiratory instability, and a loss of cranial nerve reflexes (pupillary, corneal and gag). Death is imminent if left untreated.

Brain death

Brain death is defined as a complete and irreversible neurological failure and is most often associated with a severe brain injury. The determination of brain death can vary across age groups.

Key components are listed below:
• the diagnosis of brain death is based on a number of criteria:
  • established irreversible neurological pathology
  • radiological evidence of a devastating neurological injury consistent with brain death
  • must be cleared of all possible systemic variables, such as:
    • severe hypothermia, temperature < 34°C
    • drug intoxication
    • unresuscitated shock
    • severe metabolic disorders
    • drug induced coma (can be used for severe head injury or status epilepticus)
  • complete absence of:
    • bilateral motor responses (spinal reflexes withstanding) with any stimulation
    • respiratory effort (unable to sustain spontaneous respirations without ventilation)
    • lack of cranial nerve reflexes:
      • pupillary response: CN III, pupils need to be mid-position to large and unresponsive
      • oculocephalic reflex: lack of “doll’s eyes” and failure of caloric test
      • corneal reflex: CN V
      • facial nerve: CN VII, no facial grimacing to any stimulus
      • gag: CN IX–X, no response to posterior pharynx stimulation of cough response during suctioning.
• failure of the apnea test. Our levels of arterial carbon dioxide serve as a signal responsible for our respiratory drive; the retention of CO₂ and subsequent high pCO₂ levels cause tachypnea as we try to “blow off” our CO₂.

Apnea test:
• patients must have normal pCO₂ and be euvoletic
• receive 100% oxygen for approximately 10 minutes prior to turning off the ventilator.

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• baseline ABGs are obtained
• patient is removed from the ventilator while providing oxygen
• signs of respiratory movement, vital signs and oxygen saturation are monitored closely
• ABGs are repeated at five minutes and at 10 minutes. CO₂ must rise above 60 mmHg and 20 mmHg above the previous gas.

The test is stopped if there is:
• spontaneous respiration
• significant cardiac ectopy
• hypotension
• desaturation.

Other confirmatory tests that can be used for further evaluation (but are not essential for a brain death declaration):

• EEG
• cerebral angiography
• transcranial Doppler
• nuclear blood flow studies.

Physical findings that can be misinterpreted as brainstem function and would require adjunctive findings (listed above):
• sweating, tachycardia
• normal blood pressure
• presence of spinal reflexes: spinal cord, Babinski
• facial movement
• lack of DI
• false respiration: arching of the back, shoulder elevation, intercostal movement without changes in tidal volume.