

PAIN RESPONSE

(CHAPTER 32)

QUESTION 1

Describe the four stages of pain processing.

transduction



transmission



perception



modulation

Transduction is the **creation** of an electrical pain signal in the free nerve endings of a **nociceptor**.

A noxious stimulus (heat, cold, mechanical pain) creates a **graded potential** which, if intense enough, will trigger an **action potential**, leading to...

Transmission, in which the action potential travels down the length of the nerve, entering the spinal cord and then traveling upward to the brain.

Once it arrives in the brain...

Perception occurs, in which the brain actually perceives or feels the sensation of pain.

After the signal is received and processed in the brain...

The final step, **modulation**, kicks in.

The brain sends a signal **back down** the spine, causing the release of endogenous opioids which inhibit the pain signal at synapses **in the spinal cord**.

QUESTION 2

Why are these stages useful?

Understanding the four stages of pain processing is useful because they present us with the possible avenues of pain **treatment** and **prevention**.

You can:

- Block the signal from being created (at the source)
- Intercept or block the signal during transmission
- Alter the perception of the signal in the brain

(We'll go into more depth on this with question 24.)

QUESTION 3

Describe the mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) in relief from pain.

Prostaglandins are a type of chemical produced throughout the body which play a vital role in the body's inflammatory response, producing pain, swelling, and vasodilation.

They contribute to pain **transduction** by altering the membrane potential of nociceptors.

Prostaglandins are produced by a pair of enzymes known as **cyclooxygenases** (COX-1 and COX-2,) which create them from the precursor **arachidonic acid**.

NSAIDs block the action of one or both of these COX enzymes, reducing the body's ability to produce prostaglandins.

(Most NSAIDs block both, but a few, such as celecoxib (Celebrex) block only COX-2. You'll talk about this more in pharm.)

QUESTION 4

Describe the two types of pain fibers.

Two types of nerve fibers involved in pain response:

A δ (A-delta) fibers are **thicker, myelinated** neurons, meaning **low resistance** and **super fast** transmission.

C fibers are **thinner** and **unmyelinated**, meaning the action potential travels **much more slowly**.

QUESTION 5

What types of pain do the two types of pain fiber transmit?

Myelinated **A δ fibers** enable **immediate response** to a stimulus by triggering quickly and getting the signal to the brain **as fast as possible**.

They are usually associated with a sharp, stinging or burning sensation.

Unmyelinated **C fibers**, which are much more numerous, provide a **low, ongoing response** to a persistent stimulus.

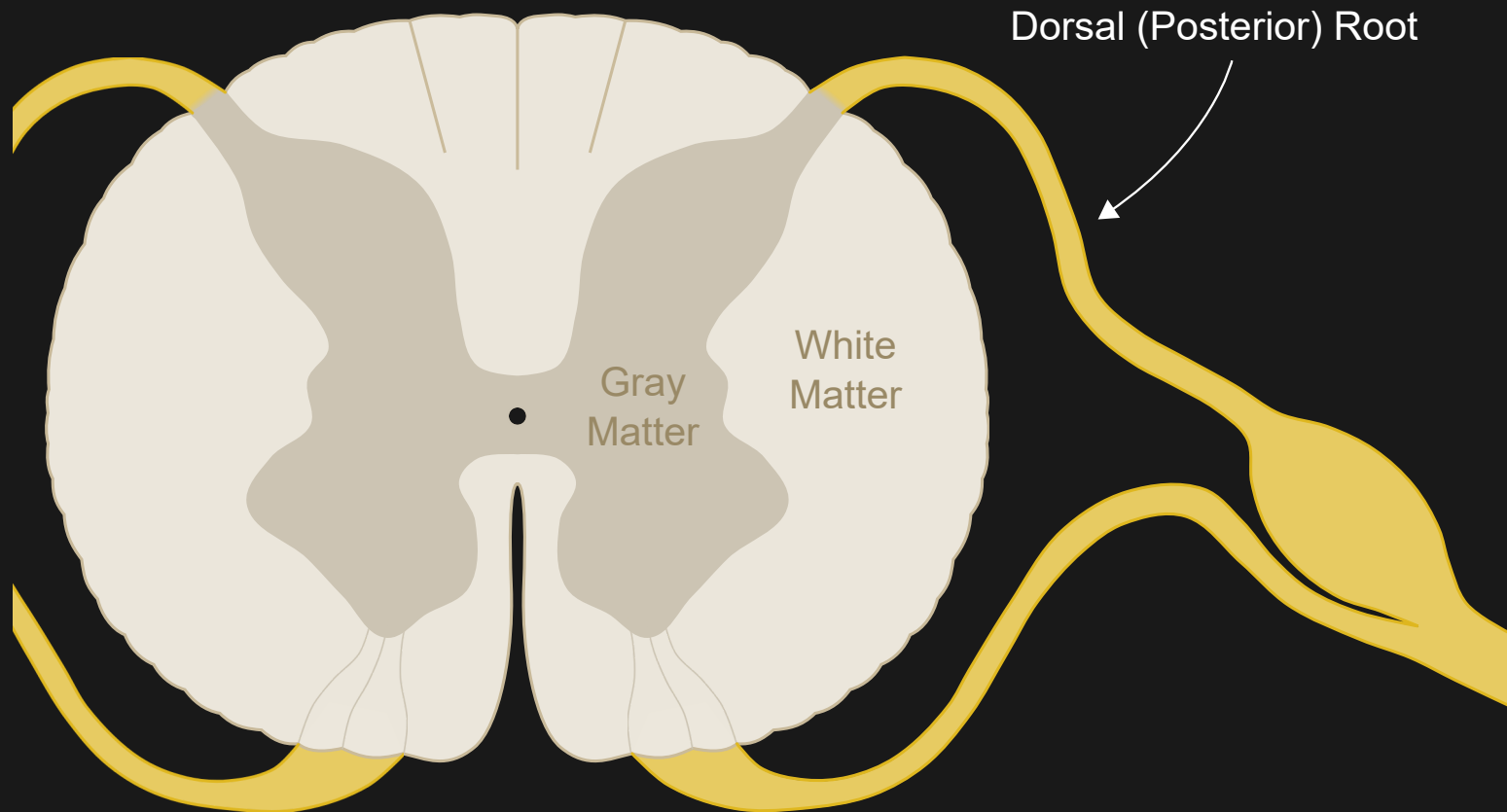
They are usually associated with a dull, ongoing soreness or aching sensation.

Example: When you get an injection, your A δ fibers transmit the immediate "ouch." Your C fibers are the dull, sore sensation that lingers afterward.

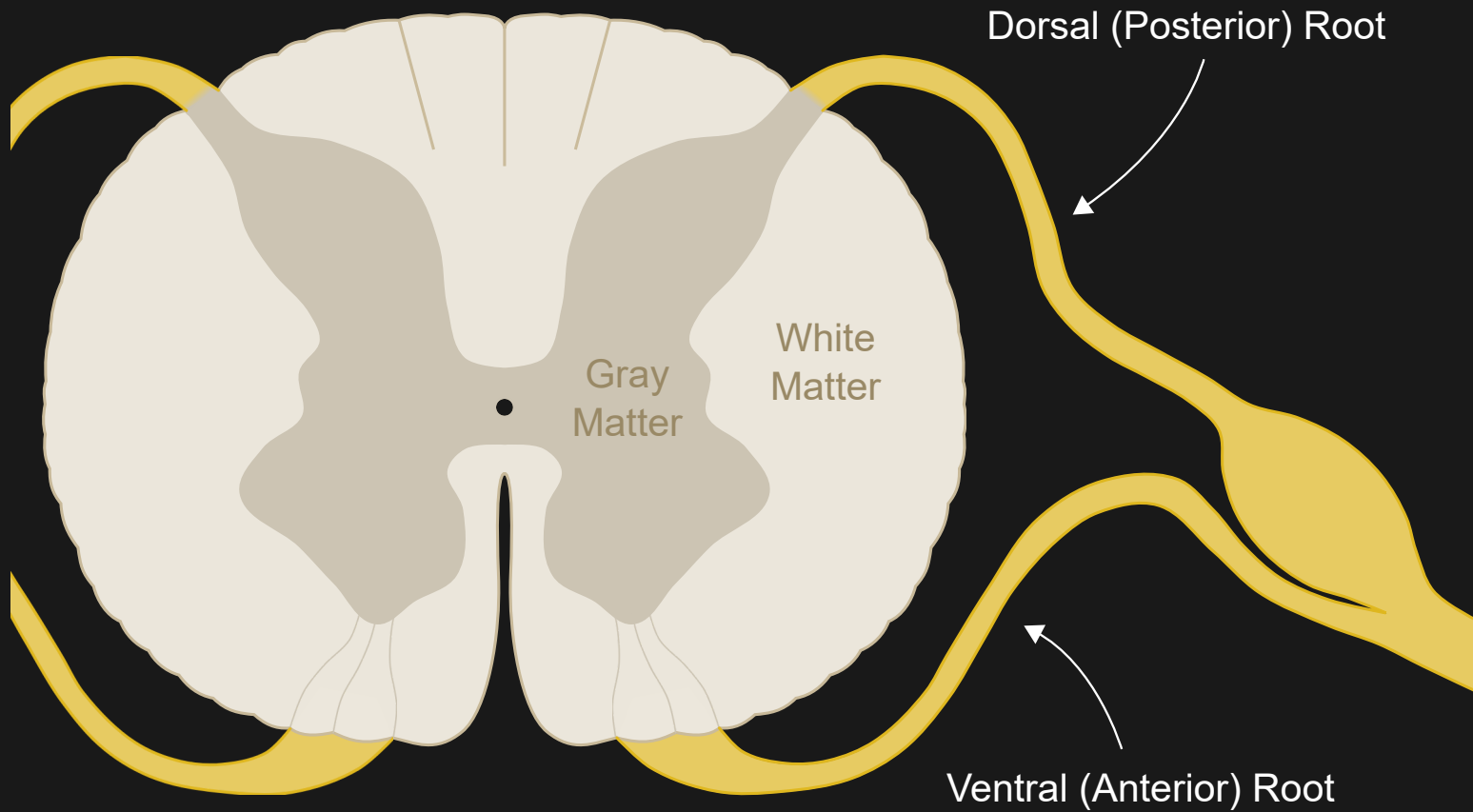
QUESTION 6

Where do the pain fibers enter the spinal cord?

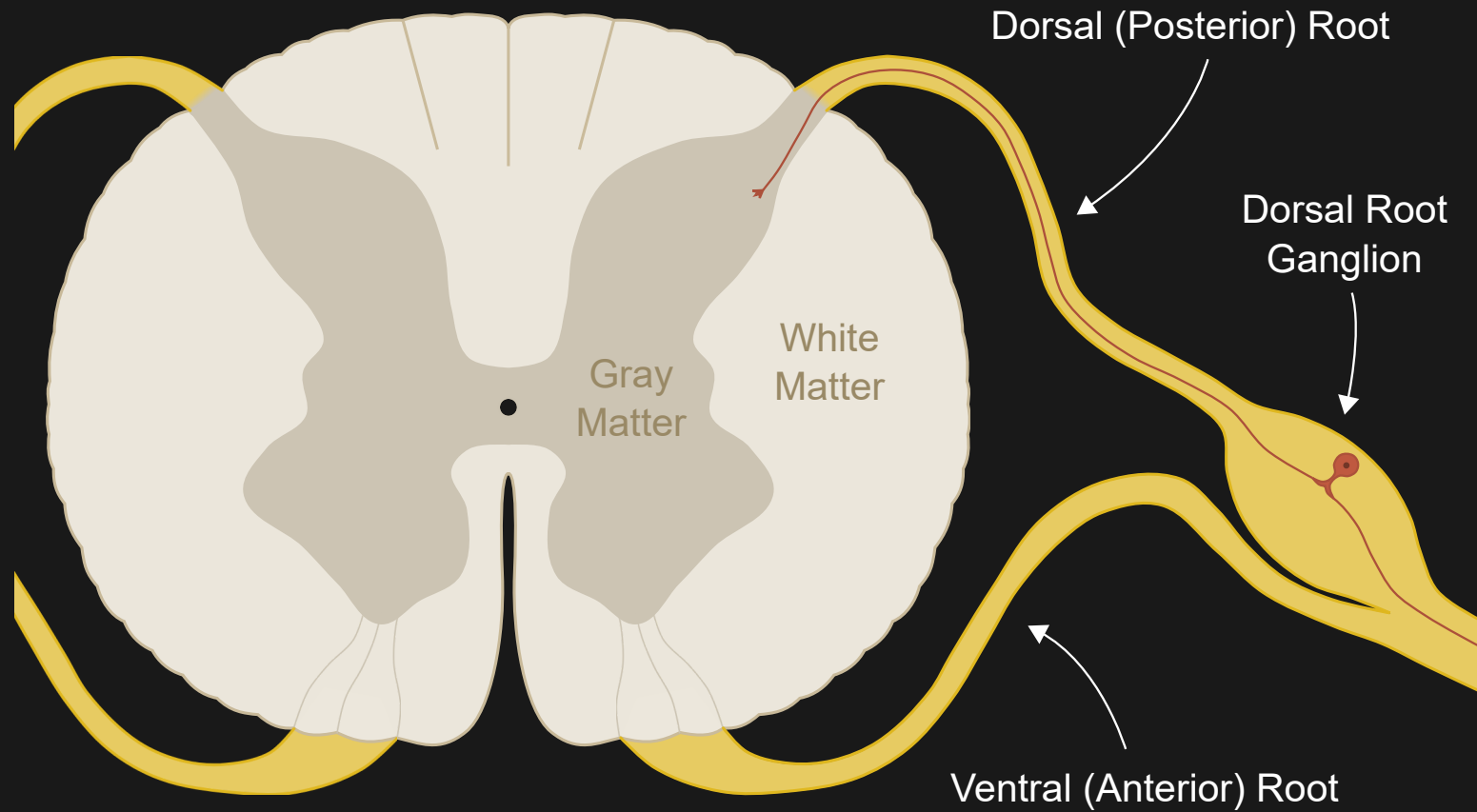
First, let's review some A&P...



Remember that sensory (afferent) nerves enter through the **dorsal root**...



and motor (efferent) nerves exit through the **ventral root**.



Nociceptors are **pseudo-unipolar neurons** in the **dorsal root ganglia**.

Pain signals originate from **free nerve endings** at the end of the nociceptor's dendrite, and travel along the dendrite towards the CNS.

They then follow the axon through the **dorsal (posterior) root** and enter the gray matter of the spinal cord.

QUESTION 7

What are the major neurotransmitters released by pain fibers?

The major **excitatory** neurotransmitter of sensory nerves (including nociceptors) is **glutamate**.

In addition, nociceptors utilize the neurotransmitter **substance P**, which is **unique** to the pain response.

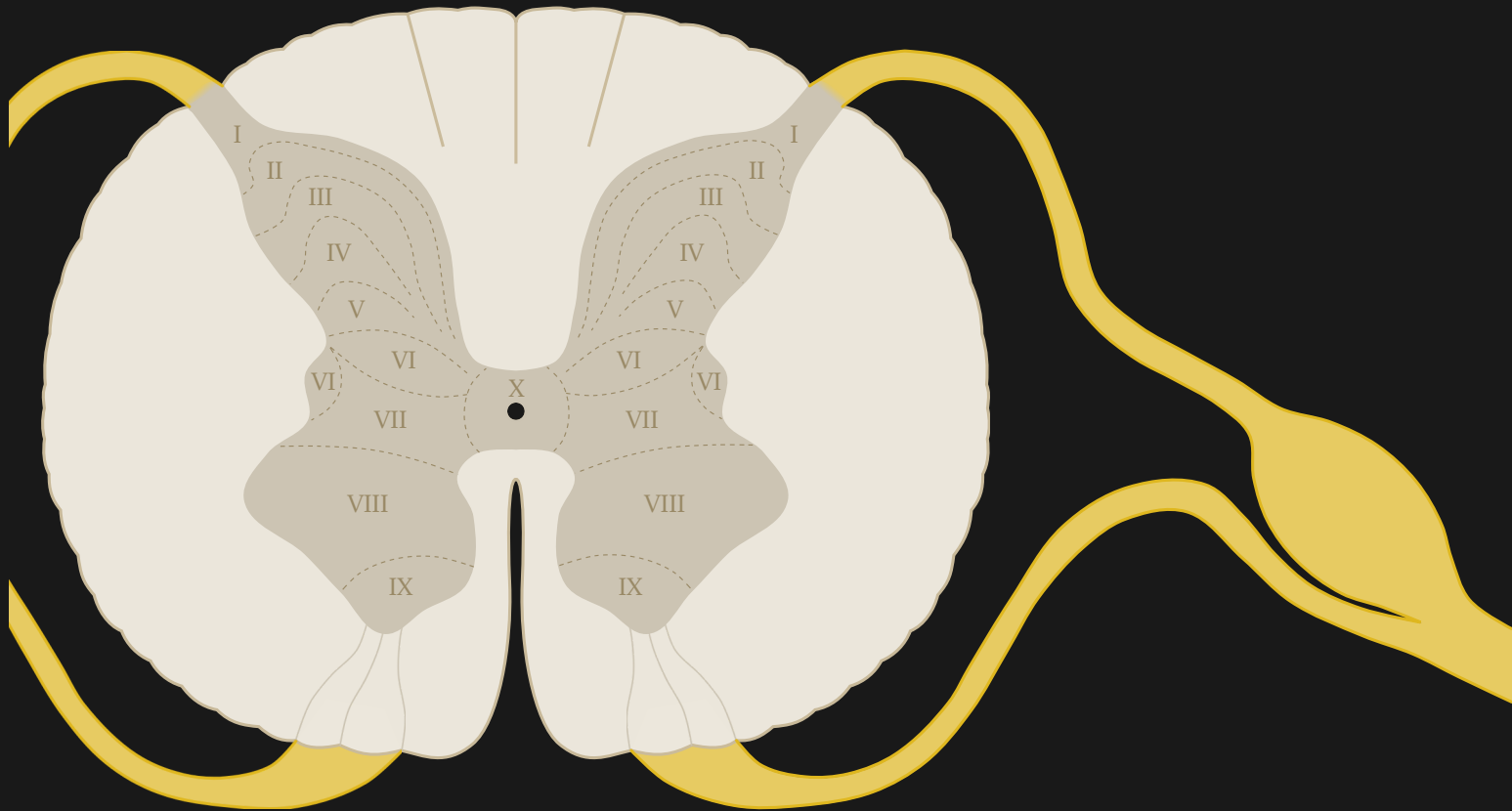
One thing to know about glutamate:

Repeated, long-term exposure of C fibers to glutamate can cause them to become **more sensitive**, leading to chronic pain **even after the stimulus is removed**.

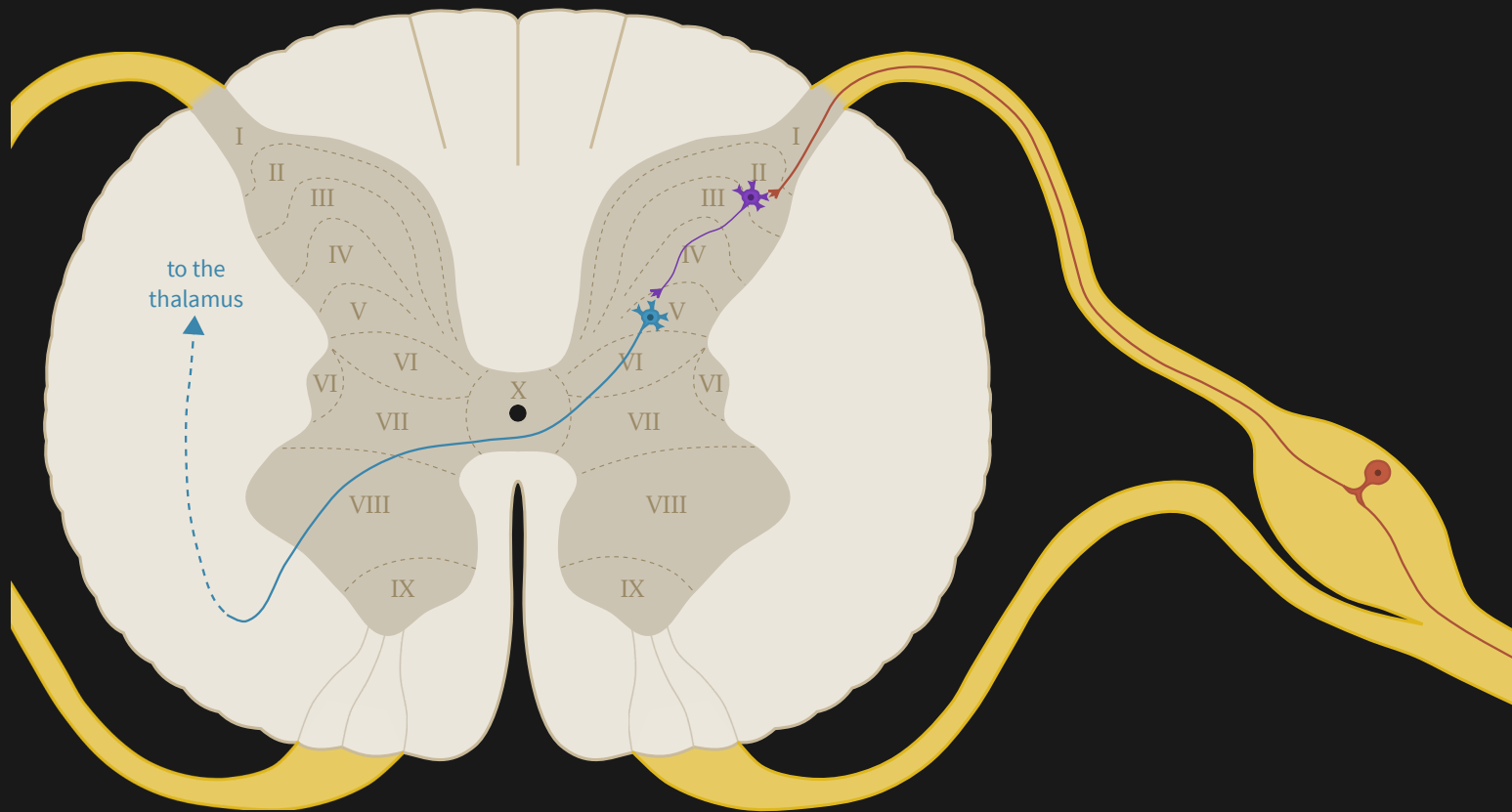
This condition is referred to as **central sensitization** or the "**wind-up phenomenon**."

QUESTION 8

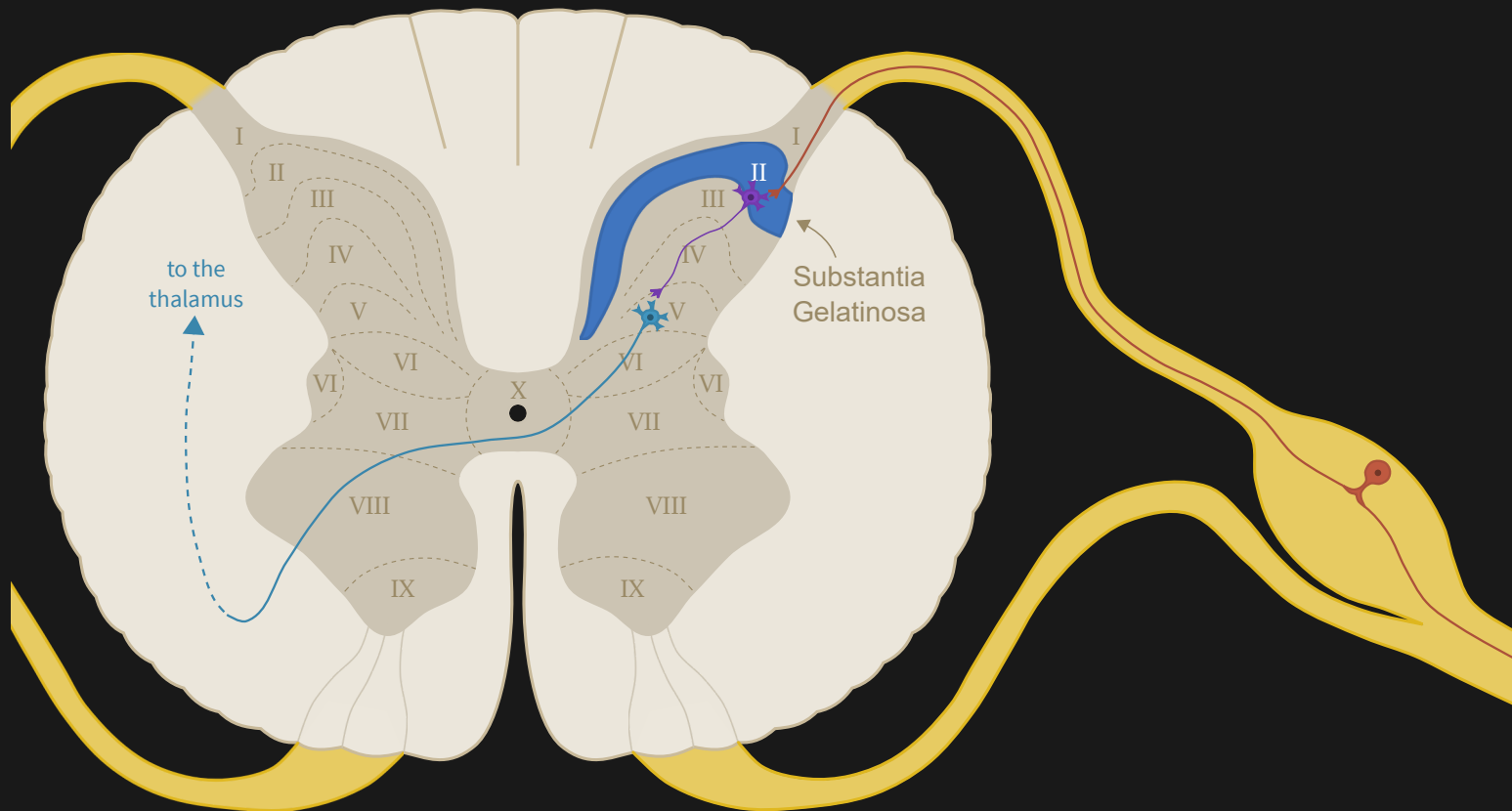
Which area of the spinal cord can enhance or inhibit pain?



The gray matter of the spinal cord is divided into 10 areas called **laminae**.



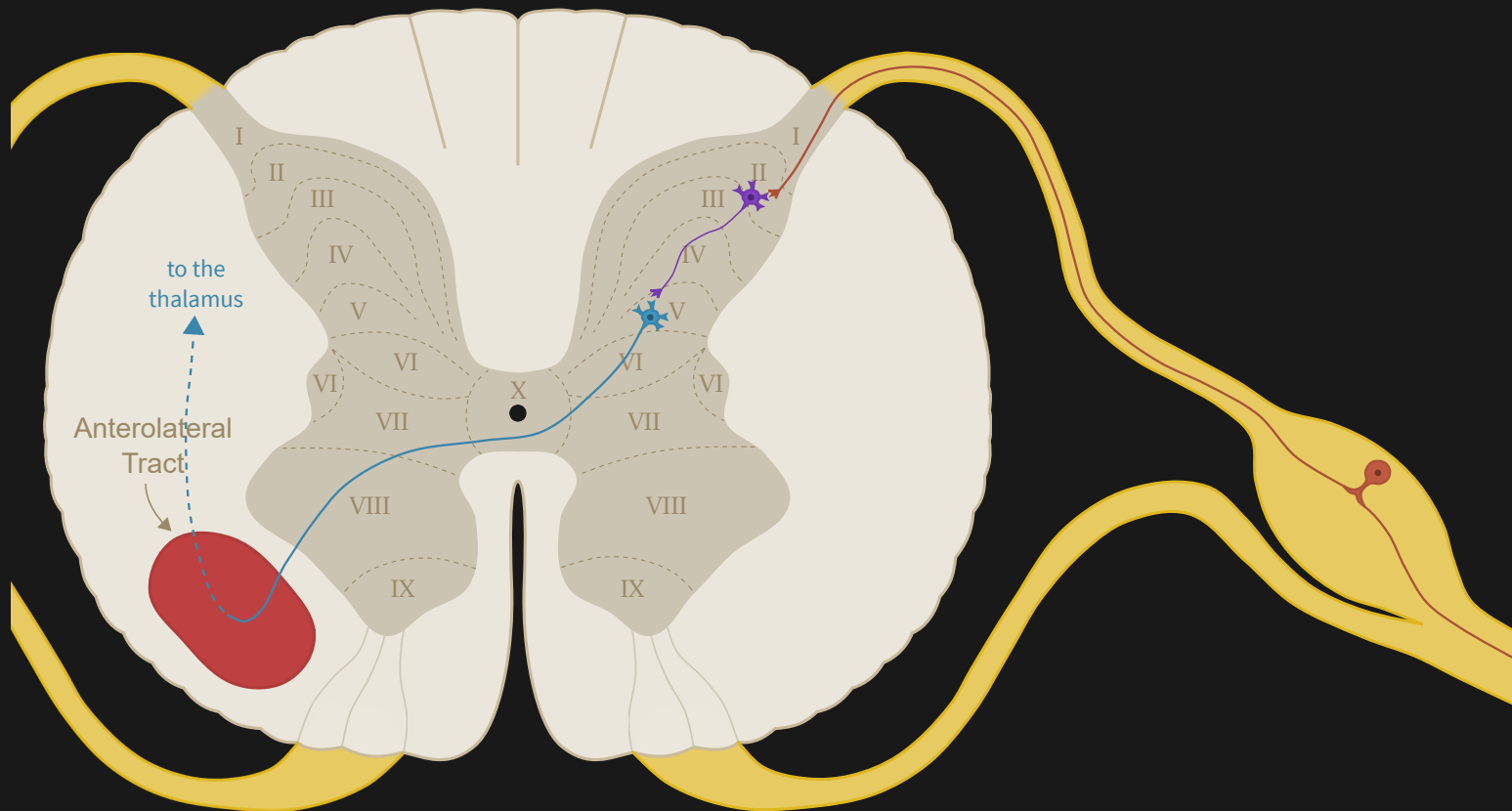
Nociceptors synapse with second-order neurons and interneurons in laminae I, II, and V.



Pain modulation primarily occurs in lamina II, the **substantia gelatinosa**.

QUESTION 9

Describe the difference between the neospinothalamic and paleospinothalamic tracts.



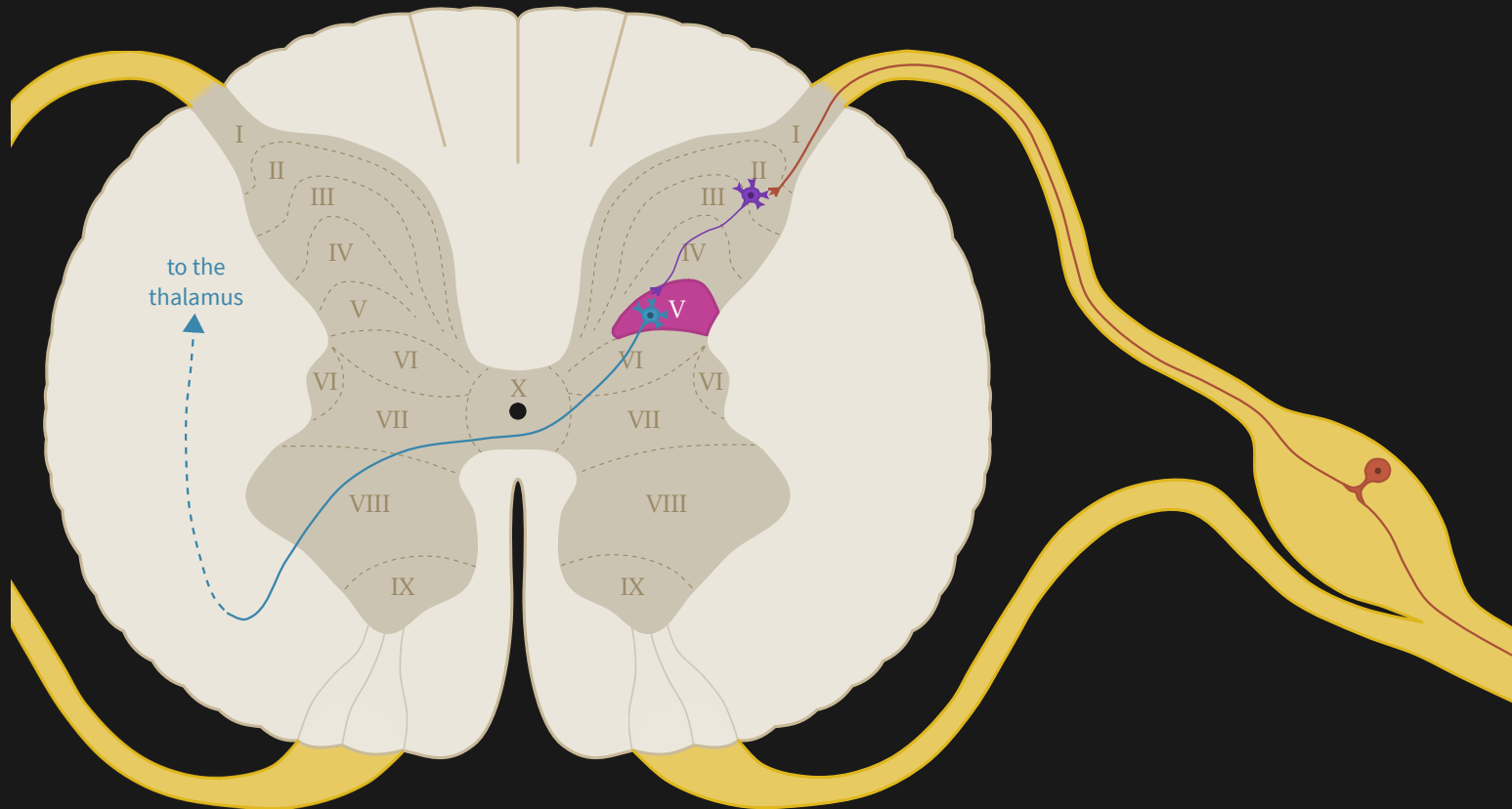
Both **spinothalamic tracts** are found in the **anterolateral white column**.

The **neospinothalamic** division carries signals from **A δ** (fast) fibers towards the cerebral cortex, synapsing again in the thalamus.

The **paleospinothalamic** division carries signals from **C** (slow) fibers to various destinations in the midbrain.

QUESTION 10

Which lamina of the spinal cord dorsal horn gray matter is involved in referred pain?



Referred pain originates in lamina V. Why does referred pain occur?

Neurons synapsing in lamina V have "**wide dynamic range**," meaning they transmit a wide range of visceral and somatic sensory signals.

This can lead to neurons getting cross-wired and visceral pain being interpreted as somatic pain.

QUESTION 11

Which part of the brain is involved in the localization of pain?

The sensation, quality, and location of pain are interpreted in the **primary sensory cortex** of the cerebrum. Remember that this is the final destination of the **neospinothalamic tract**.

In contrast, the **midbrain** controls only the conscious **awareness** of pain, not interpretation.

QUESTION 12

How are dermatomal maps helpful in the determining the source of pain?

Dermatomal maps provide a layout of which areas of the body are innervated by neurons from each level of the spinal column.

This is useful for determining the source of **neuropathic** pain.

If you determine where it **feels** like the pain is coming from, you can determine which nerves are involved.

QUESTION 13

Distinguish between pain tolerance and pain expression.

pain tolerance - how much pain you can **internally**
handle

(How much pain does it take before it becomes unbearable and you seek relief?)

pain expression - how do you externally display or communicate your pain to others?

Both of these vary widely from person to person, and pain expression also has a strong **cultural aspect**.

QUESTION 14

Describe presynaptic inhibition of pain.

Presynaptic inhibition occurs when a **first-order neuron** is prevented from transmitting its signals to a second-order neuron or interneuron.

This cuts off or dampens (**modulates**) the pain signal, preventing it from reaching the brain. Thus, the pain is **less severe** or **not experienced** at all.

QUESTION 15

Which neurotransmitters are involved in presynaptic inhibition (modulation) of pain?

Modulation is primary achieved through the action of **endogenous opioids** such as **β -endorphin** and **enkephalins**.

In addition, the neurotransmitter γ -aminobutyric acid (GABA) also plays a role.

QUESTION 16

Describe the gate control theory of pain relief.

Thick **A β fibers** linked to **touch** receptors can **take priority** over A δ /C pain signals when stimulated.

Gate control theory states that pain can be reduced by providing an additional, non-noxious stimulus to trigger A β fibers and cut off pain transmission.

QUESTION 17

What types of stimulus can activate the "gate" as described in gate control theory?

Stimulation of **non-nociceptive** sensory neurons in the **same area** of the body can occlude the transmission of pain signals: this can be as simple as **rubbing** or **massaging** the affected area.

In addition, **transcutaneous electrical nerve stimulation** (TENS) therapy stimulates nerve fibers with electricity to reduce pain.

QUESTION 18

What are the names of the endogenous opioids?

First, what *are* endogenous and exogenous opioids?

endogenous opioids – opioids produced **internally** by the body

exogenous opioids – **external** opioids introduced to the body, e.g. as drug therapy

Endogenous opioids fall into two categories:
endorphins and **enkephalins**.

(Note that the word "endorphin" comes from "endogenous morphine")

There are actually five endogenous opioids in total: α -, β -, and γ -endorphins, and leu- and met-enkephalin, but in general just know the two overall classes.

QUESTION 19

What are some examples of exogenous opioids?

Exogenous opioids are opioid **medications** that we give in order to **artificially** stimulate opioid receptors in the CNS and induce pain modulation.

You're probably familiar with many of these already from pharmacology: **morphine, codeine, hydrocodone, methadone**, etc.

QUESTION 20

Which of the opioid receptors provide analgesia?

There are four types of opioid receptors in the CNS:

- μ (mu) ← ☆
- κ (kappa) ← ☆
- σ (sigma)
- δ (delta)

μ (mu) and **κ (kappa)** are the two involved in pain modulation.

QUESTION 21

Pain is classified according to three criteria. What are they?

duration – is it **acute** or **chronic**?

source – neuropathic, ischemic, somatic, visceral, etc.

location – where is the pain being experienced?

QUESTION 22

What is fibromyalgia? Describe it.

A chronic disease characterized by **widespread musculoskeletal pain** and **extreme tenderness** at specific areas of the body.

Allodynia, which we'll talk about in a second, is a typical symptom of fibromyalgia.

QUESTION 23

How does cancer cause pain?

There are many mechanisms, any of which can be considered "cancer-related" pain. They can include:

- Infiltration of organs by cancerous growth
- Pressure on nerves from a tumor (neuropathic)
- Pain secondary to cancer treatment (iatrogenic)

QUESTION 24

How is neuropathic pain different from tissue injury pain?

Most (somatic/visceral) pain signals **damage to tissues.**

In **neuropathic pain**, the **nerve itself** is the source of the pain, rather than responding to an external stimulus.

Neuropathic pain often has a shooting/burning quality and radiates along the path of the nerve.

Examples include:

sciatica – neuropathy due to impingement of sciatic nerve

trigeminal neuralgia – facial neuropathy due to demyelination of trigeminal nerve

diabetic neuropathy – neuropathy due to poor circulation to peripheral nerves

QUESTION 25

Define allodynia and hyperalgesia.

állos (other)

odúnē (pain)

ALLODYNIA

"a **painful** response to a typically **non-painful** stimulus"

hupér (over)

algéō (to feel pain)

HYPERALGESIA

"an **exaggerated** or **prolonged** response to a painful stimulus"

Remember one common source of allodynia:
fibromyalgia.

QUESTION 26

Describe diabetic neuropathy. How are the senses changed?

Chronically elevated blood glucose causes damage to peripheral blood vessels, resulting in **ischemia** of peripheral nerves (usually in legs and feet.)

This can result in both motor changes such as weakness, and sensory changes (numbness, tingling, and pain.)

QUESTION 27

Describe referred pain, post-herpetic neuralgia, and ischemic pain.

referred pain – "cross-wiring" between visceral and somatic pain neurons results in visceral pain being interpreted as somatic

(Remember the role of lamina V in this process.)

post-herpetic neuralgia – a common sequela of **shingles** in which chronic pain persists long after the initial infection has cleared

ischemic pain – acute pain due to insufficient blood flow (and thus insufficient oxygen) to tissues

(An associated term is **claudication**, ischemic pain—often in the legs—which goes away with rest.)

QUESTION 28

What are some differences in pain therapy in the young and the elderly?

Pain in the very young can be harder to diagnose and treatment is sometimes lacking.

Insufficient treatment can lead to long-term changes in the CNS.

Elderly patients can also experience pain that goes inadequately treated.

QUESTION 29

Describe the three points of pain management. Give examples.

1. blocking transduction or transmission

- NSAIDs
- local infiltration/nerve block

2. blocking/modulating pain at the spinal cord

- Transcutaneous Electrical Nerve Stimulation (TENS)
- Epidural anesthesia

3. altering perception of pain in the brain

- Opioid analgesics (also modulate)
- Non-pharmacologic techniques (breathing, relaxation techniques, etc.)