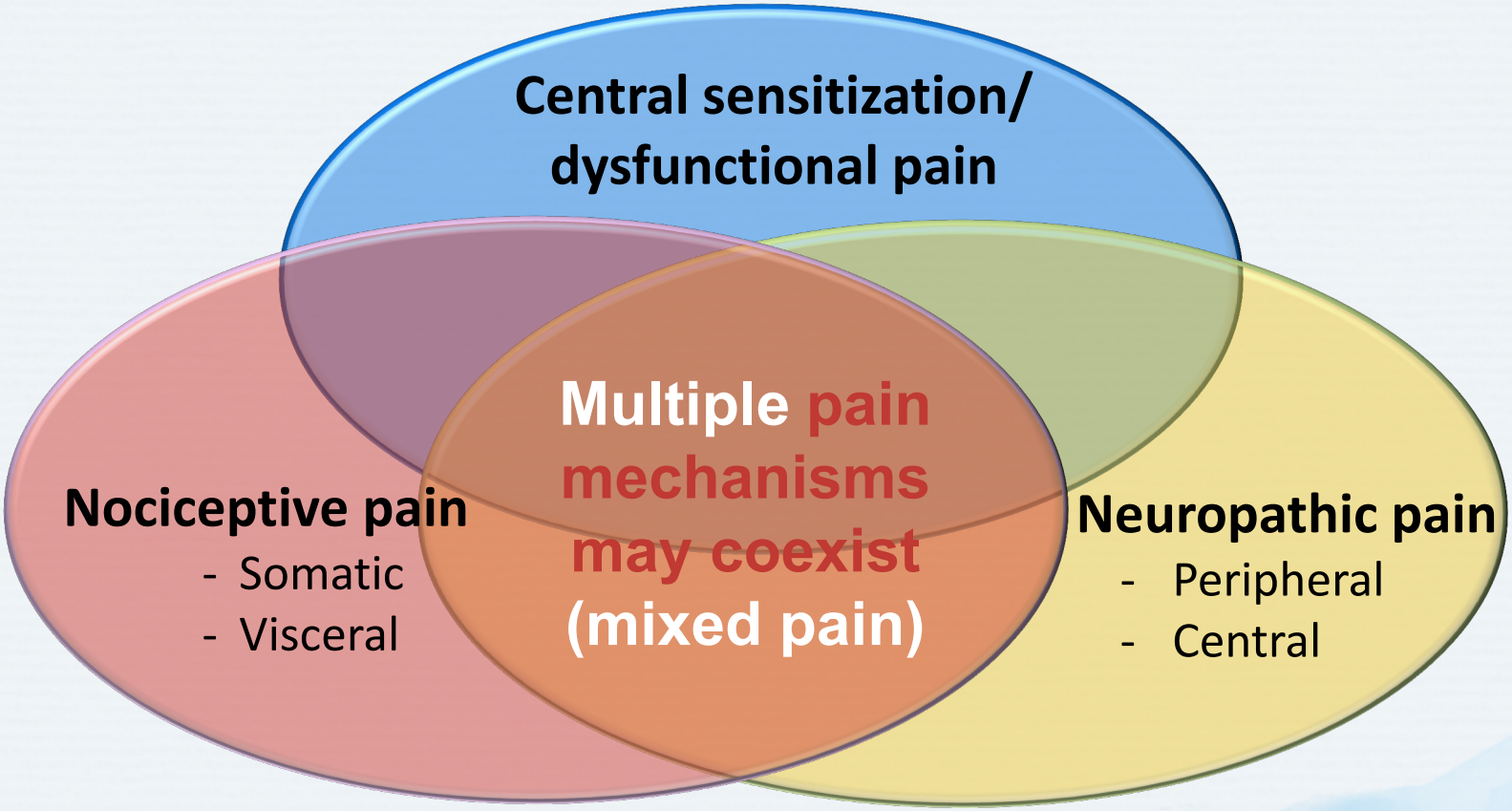
PATHOPHYSIOLOGY

Overview

Pathophysiological Classification of Pain



Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90; Jensen TS *et al. Pain* 2011; 152(10):2204-5;
Julius D *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Ross E. *Expert Opin Pharmacother* 2001; 2(1):1529-30; Webster LR. *Am J Manag Care* 2008; 14(5 Suppl 1):S116-22; Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

What is central sensitization/ dysfunctional pain?

Definition

- Amplification of neural signaling within the CNS that elicits pain hypersensitivity

Examples

- Fibromyalgia
- Tension-type headache
- Irritable bowel syndrome
- Interstitial cystitis
- Temporomandibular joint pain
- May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis

Pain Quality

- Often diffuse
- Frequently with allodynia and/or hyperalgesia
- Rarely burning, lancinating or electric shock-like

CNS = central nervous system

Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Clinical Features of Central Sensitization/Dysfunctional Pain

Pain

- Pain all over body
- Muscles stiff/achy
- Headaches
- Pain in jaw
- Pelvic pain
- Bladder/urination pain

Anxiety/depression

- Sad or depressed
- Anxiety
- Stress makes symptoms worse
- Tension in neck and shoulder
- Grind/clench teeth

Fatigue

- Do not sleep well
- Unrefreshed in morning
- Easily tired with physical activity

Other symptoms

- Difficulty concentrating
- Need help with daily activities
- Sensitive to bright lights
- Skin problems
- Diarrhea/constipation

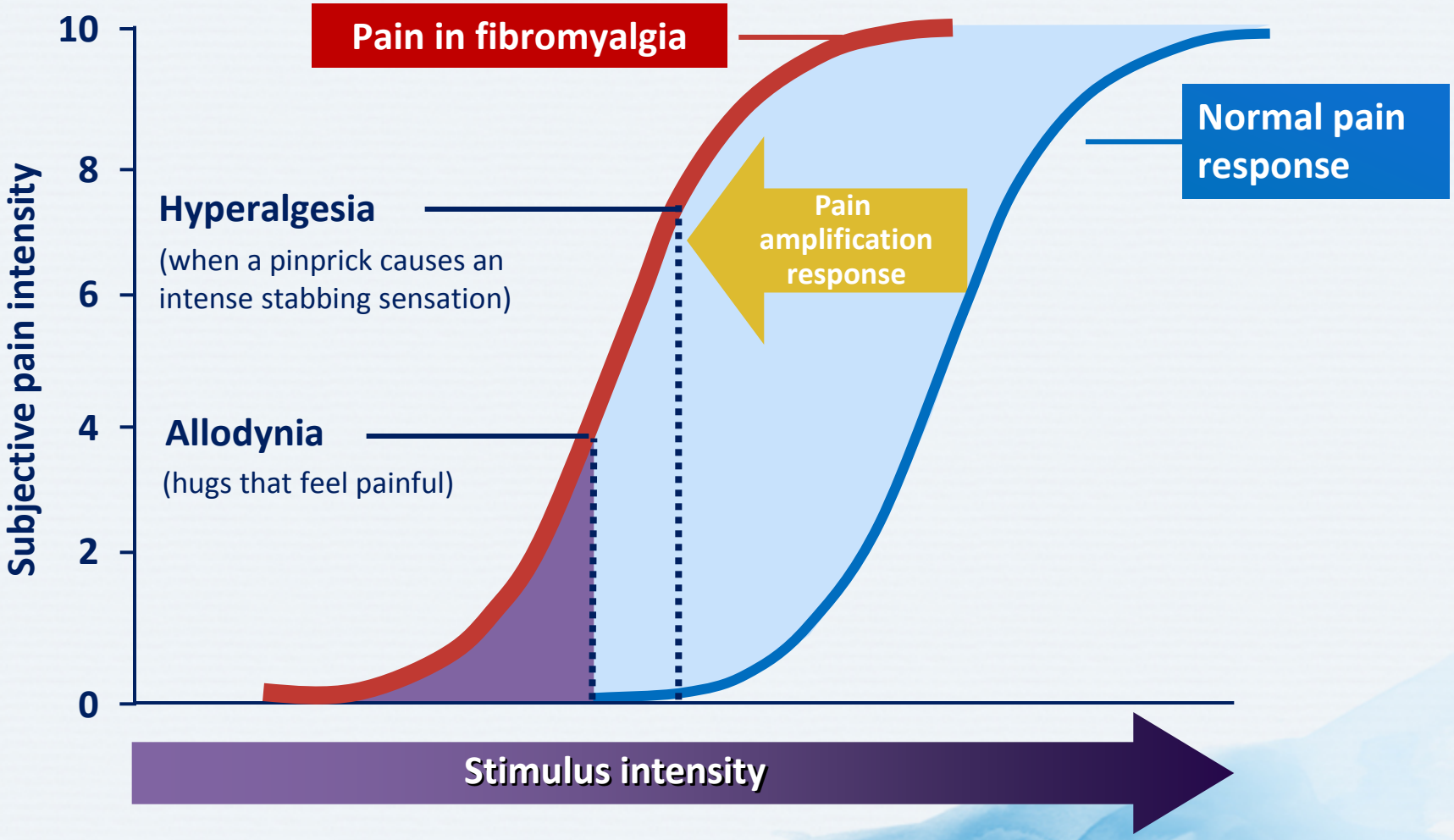
Mayer TG *et al. Pain Pract* 2012; 12(4):276-85.

What is fibromyalgia?

Fibromyalgia is a common chronic widespread pain disorder, characterized by an amplification of pain signals, analogous to the "volume control setting" being turned up too high.

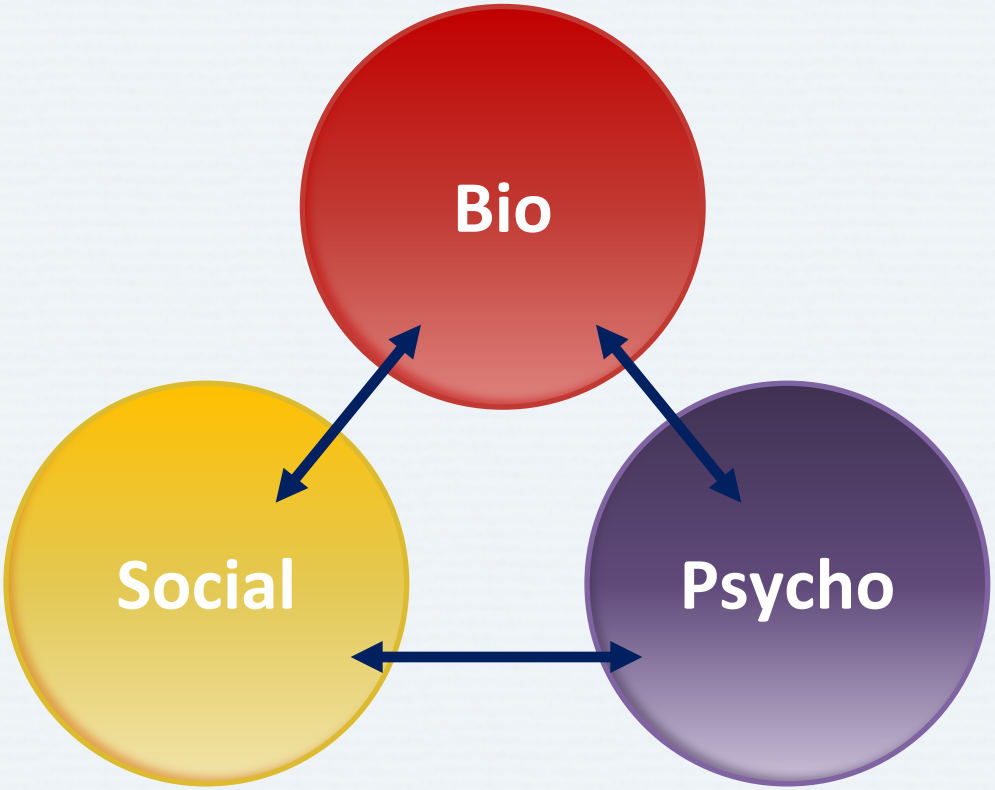
Clauw DJ *et al. Mayo Clin Proc* 2011; 86(9):907-11.

Fibromyalgia: An Amplified Pain Response



Adapted from: Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10):1979-86.

Biopsychosocial Model of Pain



Gatchel RJ *et al. Psychol Bull* 2007; 133(4):581-624.

Etiology

Etiology of Central Sensitization Syndromes

- ***Central sensitization syndromes*** are a group of medically indistinct disorders for which no organic cause can be found
  - Examples include:
    - Fibromyalgia
    - Chronic fatigue syndrome
    - Irritable bowel syndrome
    - Temporomandibular joint disorder
    - Tension headache/migraine
- These disorders share many symptoms, including pain
- Central sensitization has been proposed as root etiology for these conditions

Neblett R *et al. J Pain* 2013; 14(5):438-45.

Etiology of Fibromyalgia

- Etiology and pathogenesis still not fully understood
- Several factors appear to be involved, including:
  - CNS and autonomic nervous system dysfunction
  - Neurotransmitters
  - Hormones
  - Immune system
  - External stressors
  - Psychiatric aspects

CNS = central nervous system

Bellato E *et al. Pain Res Treat* 2012; 2012:426130.

Etiology of Fibromyalgia

- **Central sensitization** is considered to be **main mechanism** involved
  - Defined by increased response to stimulation mediated by CNS signaling
  - Due to spontaneous nerve activity, enlarged receptive fields, and augmented stimulus responses transmitted by primary afferent fibers
  - Various neurotransmitters, especially serotonin, implicated
- **"Windup"** is important
  - Increased excitability of spinal cord neurons
  - After a painful stimulus, subsequent stimuli of the same intensity are perceived as stronger
  - Occurs normally in everyone but is excessive in patients with fibromyalgia
- **Impaired descending inhibitory pain pathways**
  - Modulate spinal cord responses to painful stimuli
  - Impairment in patients with fibromyalgia exacerbates central sensitization

CNS = central nervous system

Bellato E *et al. Pain Res Treat* 2012; 2012:426130.

What causes fibromyalgia?

- Pain-prone phenotype?
- Role of genetics (family members, relatives)?
- Environmental factors?
  - Infections
  - Motor vehicle trauma
  - Psychological stress
- Inflammation?
  - Approximately 10-30% of patients with osteoarthritis or inflammatory arthritis also meet criteria for fibromyalgia
- Small fiber neuropathy? Hyperexcitable small nerve fibers?
- Abnormal central pain processing?

Clauw DJ. *JAMA* 2014; 311(15):1547-55; Oaklander AL *et al. Pain* 2013; 154(11):2310-6; Rahman *A et al. BMJ* 2014; 348:g1224; Serra J *et al. Ann Neurol* 2014;75(2):196-208; Üçeyler N *et al. Brain* 2013; 136(Pt 6):1857-67.

Pathophysiology

Why do patients suffering from central sensitization experience dysfunctional pain?

- During central sensitization, the sensation of pain is enhanced as a result of:
  - Changes in nerve fibers and the environment
  - Modifications of the functional properties and the genetic programming of primary and secondary afferent neurons

Fornasari D. *Clin Drug Investig* 2012; 32(Suppl 1):45-52.

Sensory Hypersensitivity

- Pain hypothesized to be a result of persistent neuronal dysregulation or dysfunction
- No identifiable nerve or tissue damage
- **Fibromyalgia is the prototype condition**
- May drive/contribute to the pain of irritable bowel syndrome, temporomandibular joint disorder, chronic fatigue and chronic low back pain, as well as osteoarthritis and rheumatoid arthritis

Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Pathogenesis of Fibromyalgia: Overview

- Fibromyalgia is a condition of **global dysregulation of pain processing**
- Central sensitization is one component
  - Mechanisms of central sensitization

Excitatory mechanisms

Inhibitory mechanisms

Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Henriksson KG. *J Rehabil Med* 2003; 41(41 Suppl):89-94; Larson AA *et al. Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Price DD, Staud R. *J Rheumatol* 2005; 32(Suppl 75):22-8; Rao SG. *Rheum Dis Clin North Am* 2002; 28(2):235-59; Staud R, Rodriguez ME. *Nat Clin Pract Rheumatol* 2006; 2(2):90-8; Vaerøy H *et al. Pain* 1988; 32(1):21-6; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14.

Overview of Pathophysiological Observations in Fibromyalgia

- **Peripheral**
  - Peripheral sensitization
  - Temporal summation (wind-up) (short-term)
- **Spine and brain**
  - Central sensitization (long-term)
  - Change in gray matter volume
- **Descending inhibition**
- **Other factors**
  - Hypothalamic-pituitary-adrenal axis dysregulation
  - Sleep disturbance
  - Cognitive effects

Despite extensive research, the exact cause of pain in fibromyalgia is not clearly understood.

Crofford LJ, Clauw DJ. *Arthritis Rheum* 2002; 46(5):1136-8; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl 41):89-94; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14; Staud R, Rodriguez ME. *Nat Clin Pract Rheumatol* 2006; 2(2):90-8; Vaerøy *et al. Pain* 1988; 32(1):21-26;

Autosensitization

- Repeated stimulation of vanilloid receptors in nociceptors by heat, capsaicin or acidic pH cause
  - Rapid increase in receptor sensitivity
  - Increase in substantial but readily reversible “autosensitization”

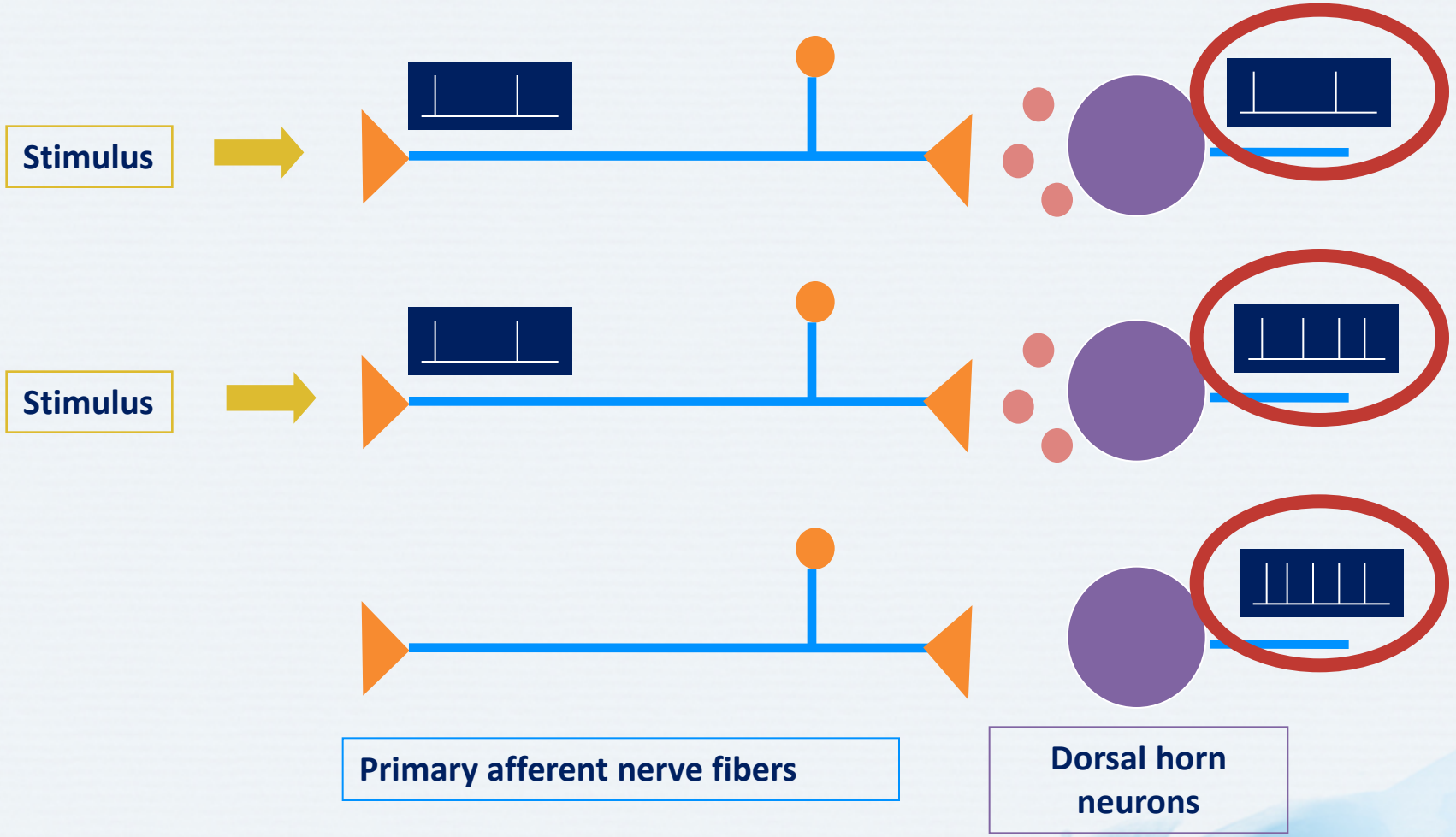
Caterina MJ *et al. Nature* 1997; 389(6653):816-24; Guenther S *et al. Eur J Neurosci* 1999; 11(9):3143-50; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Wind-Up

- Dorsal horn: intense or sustained noxious stimuli cause:
  - Release of neuromodulators (e.g., substance P) and glutamate
  - Long-lasting slow excitatory postsynaptic potentials and cumulative depolarization
  - Cascade of events further potentiate depolarization
  - Net result: “wind-up” of action potential discharge

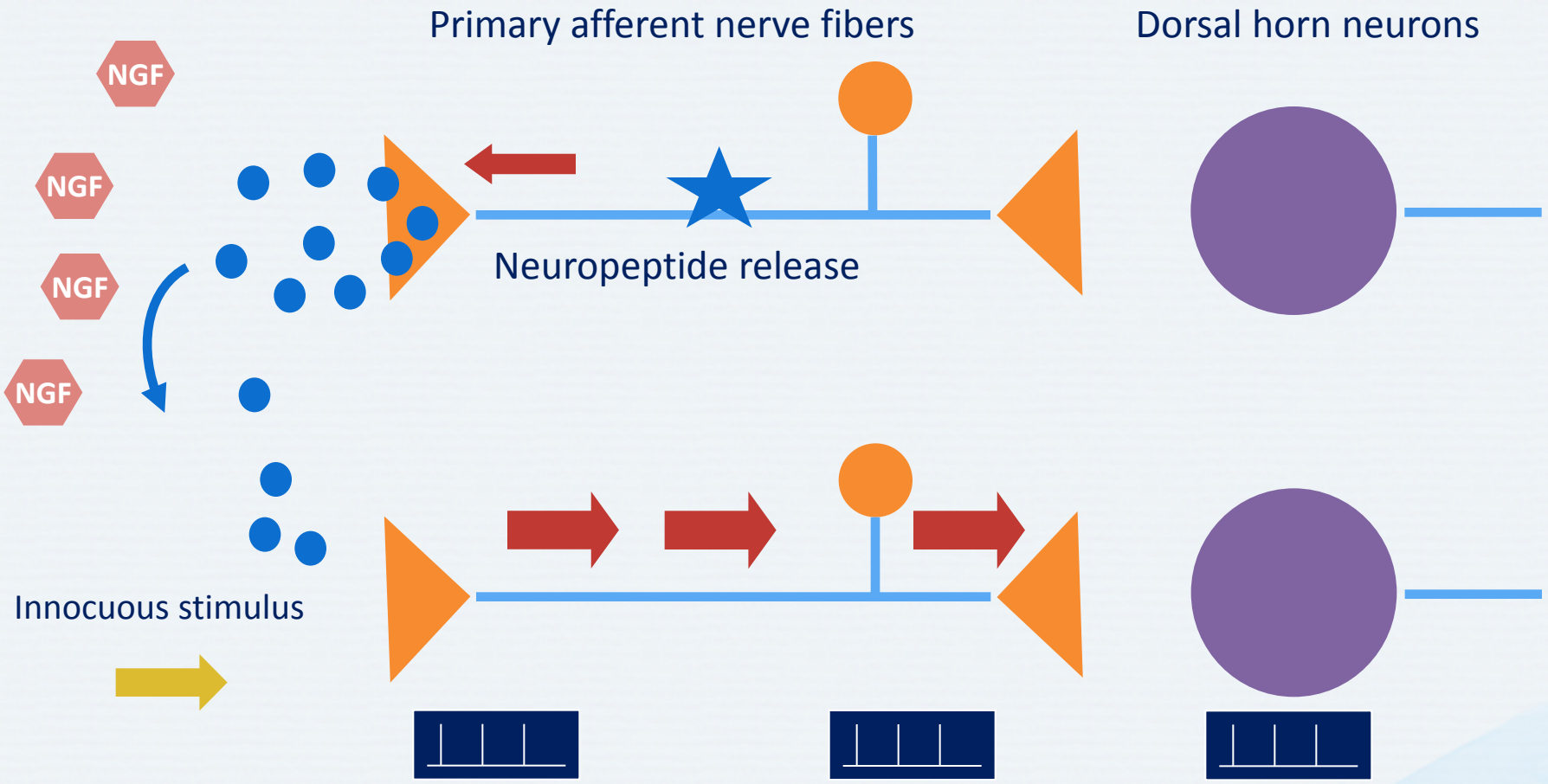
Caterina MJ *et al. Nature* 1997; 389(6653):816-24; Guenther S *et al. Eur J Neurosci* 1999; 11(9):3143-50; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Wind-Up



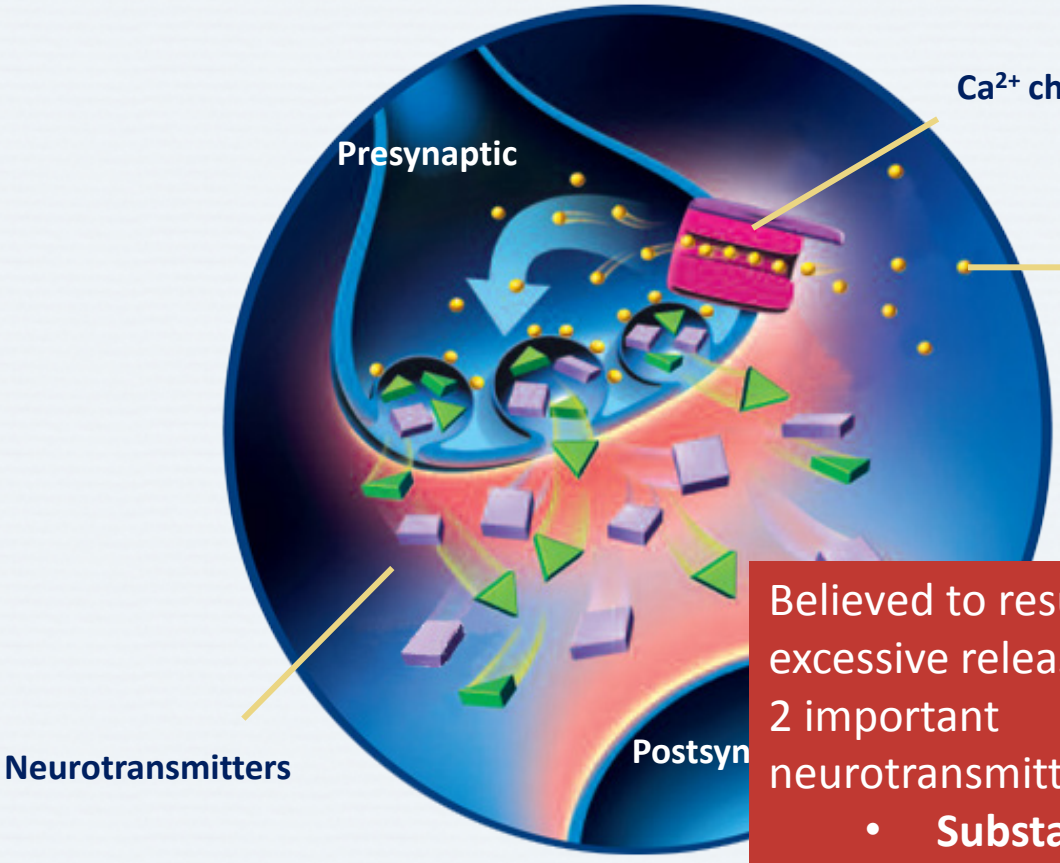
Doubell TP *et al.* In: Wall PD, Melzack R (eds). *Textbook of Pain*. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Mannion RJ, Woolf CJ. *Clin J Pain* 2000; 16(3 Suppl):S144-56; Siddall PJ, Cousins MJ. *Spine (Phila Pa 1976)* 1997; 22(1):98-104; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

Peripheral Sensitization



Ørstavik K *et al*. *Brain* 2003; 126(Pt 3):567-78; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

Central Sensitization

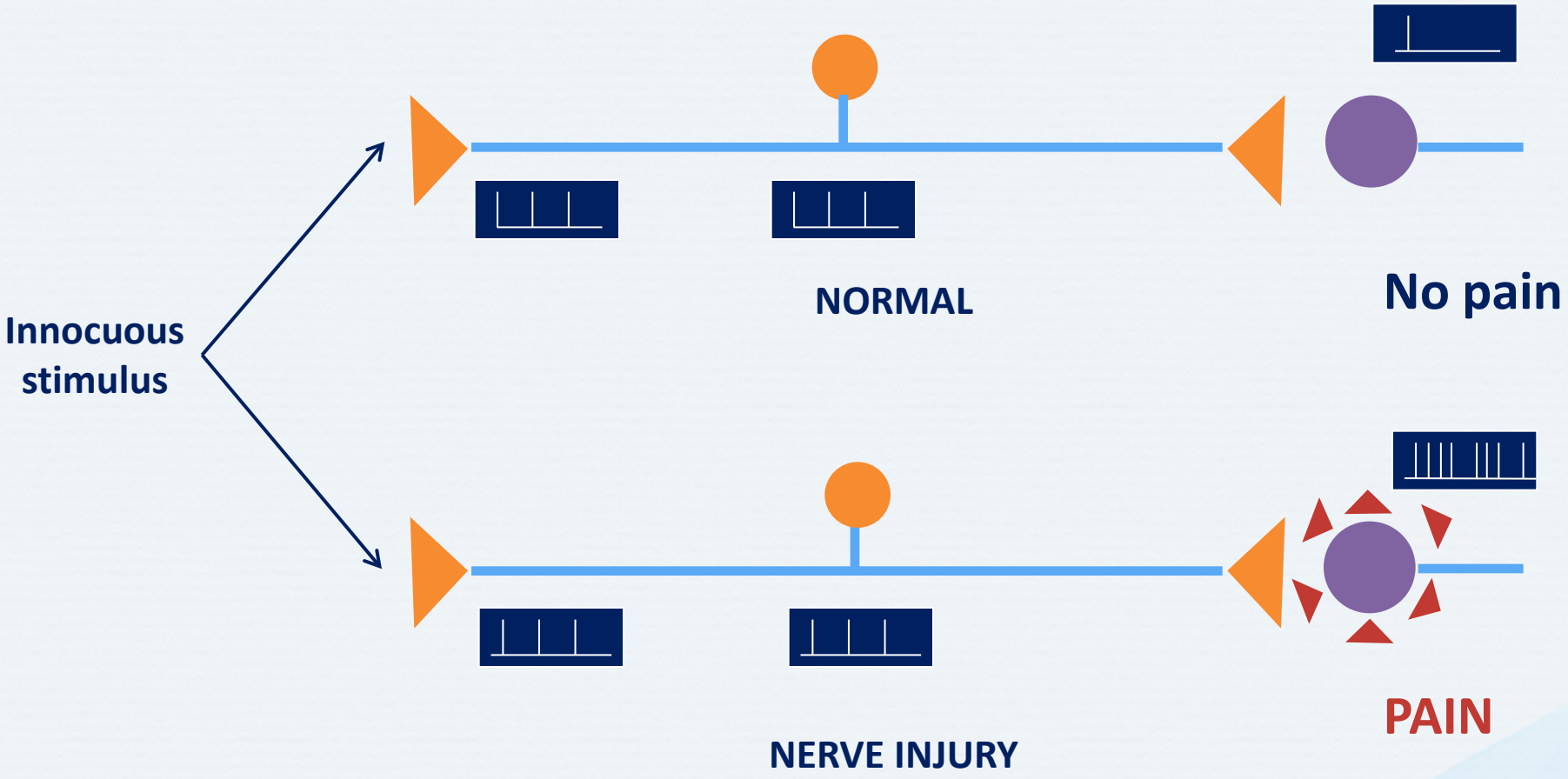


Believed to result from excessive release of 2 important neurotransmitters:

- **Substance P**
- **Glutamate**

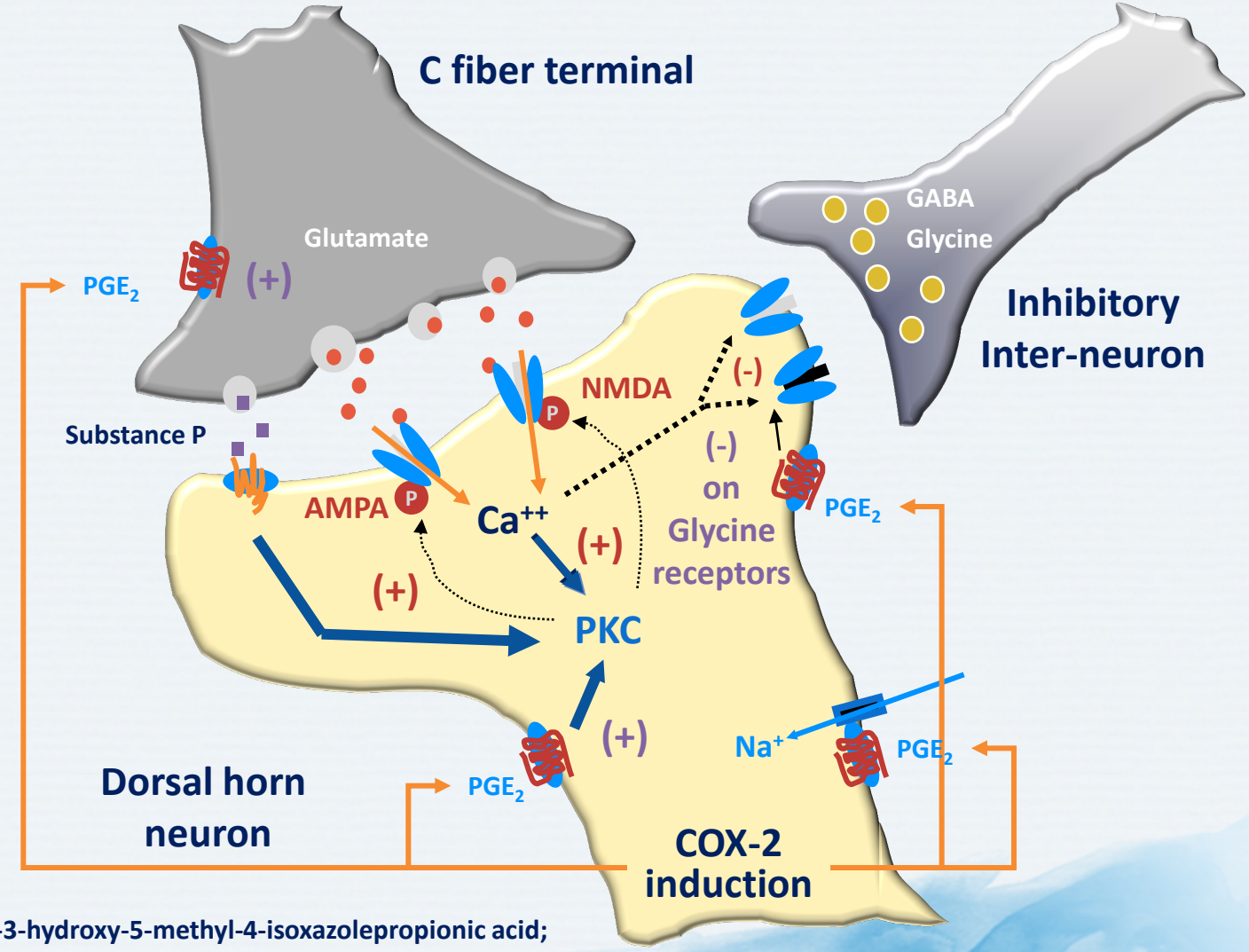
Costigan M *et al. Annu Rev Neurosci* 2009; 32:1-32; Costigan M *et al.* In: Siegel GJ *et al* (eds). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. 7th ed. Elsevier Academic Press; Burlington, MA: 2006; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14.

Central Sensitization after Nerve Injury



Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

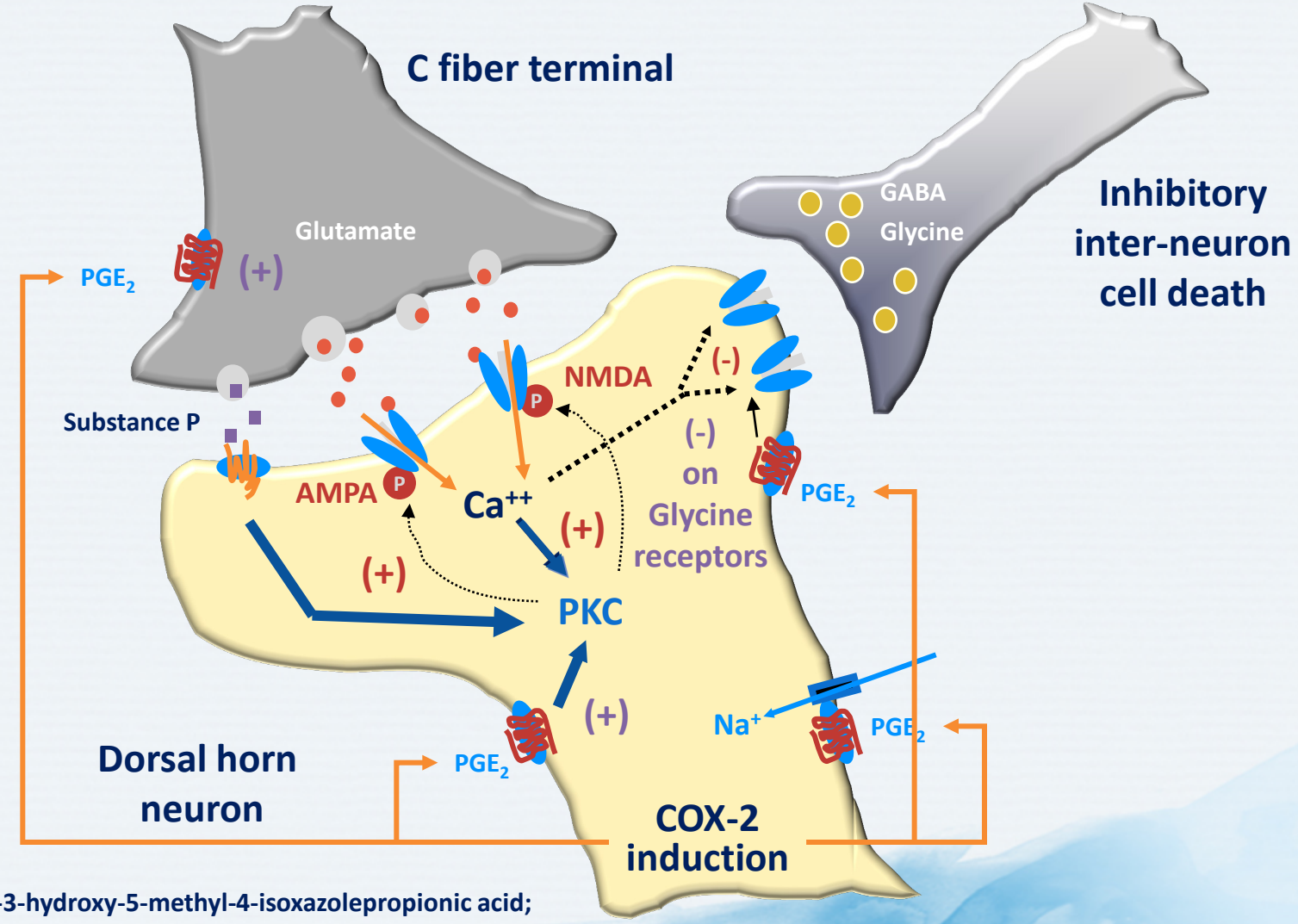
Central Sensitization



AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Central Sensitization



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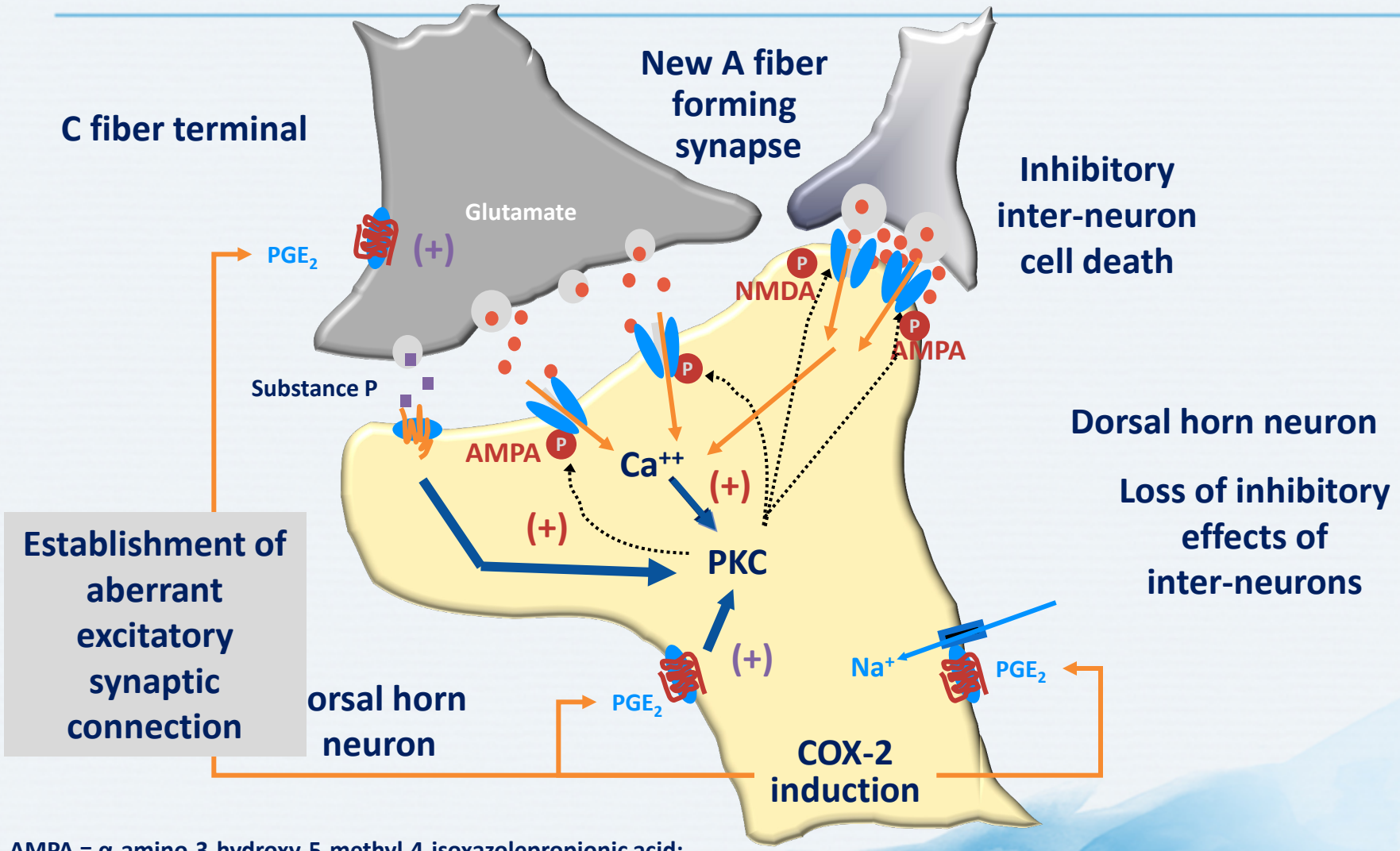
Central Sensitization



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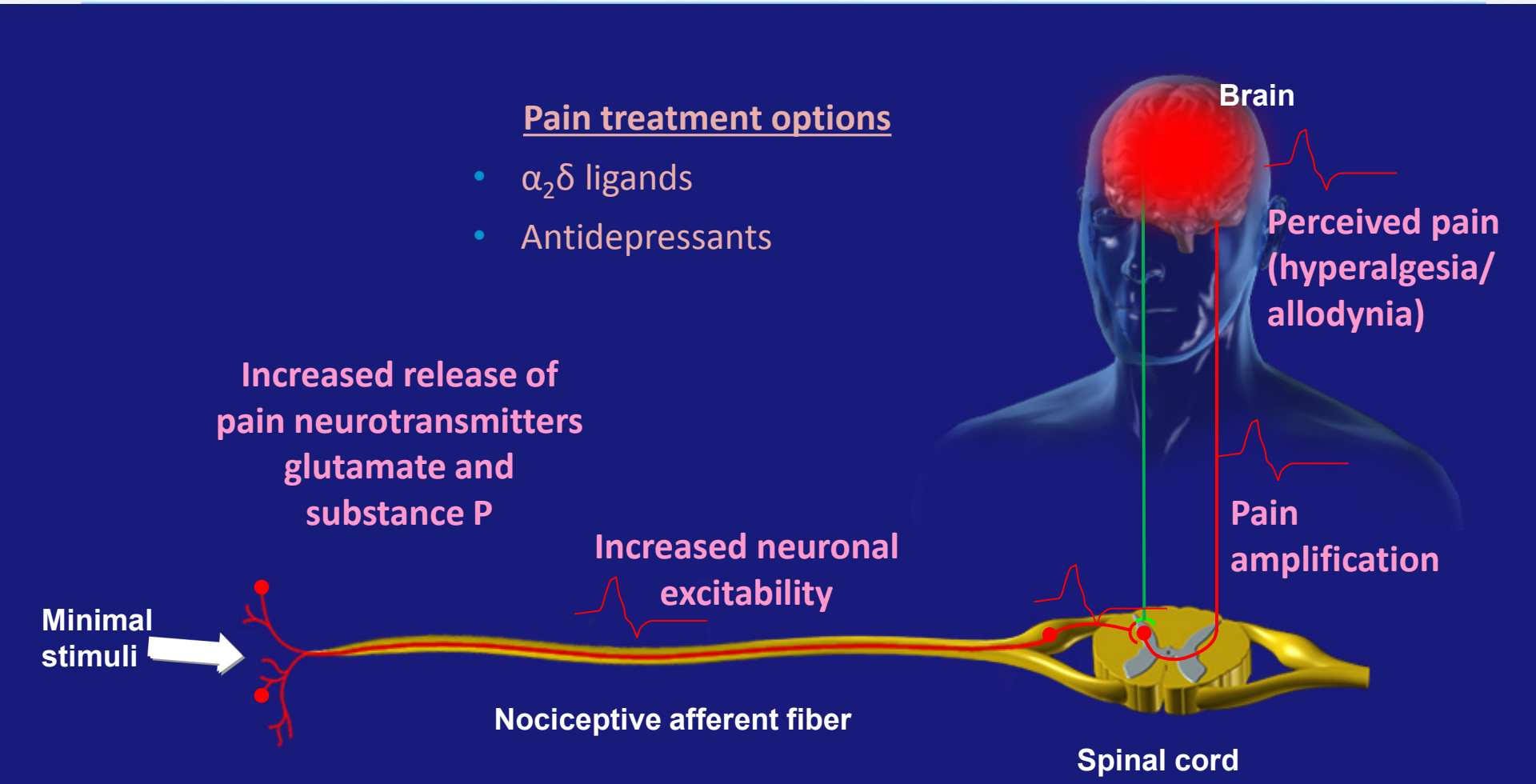
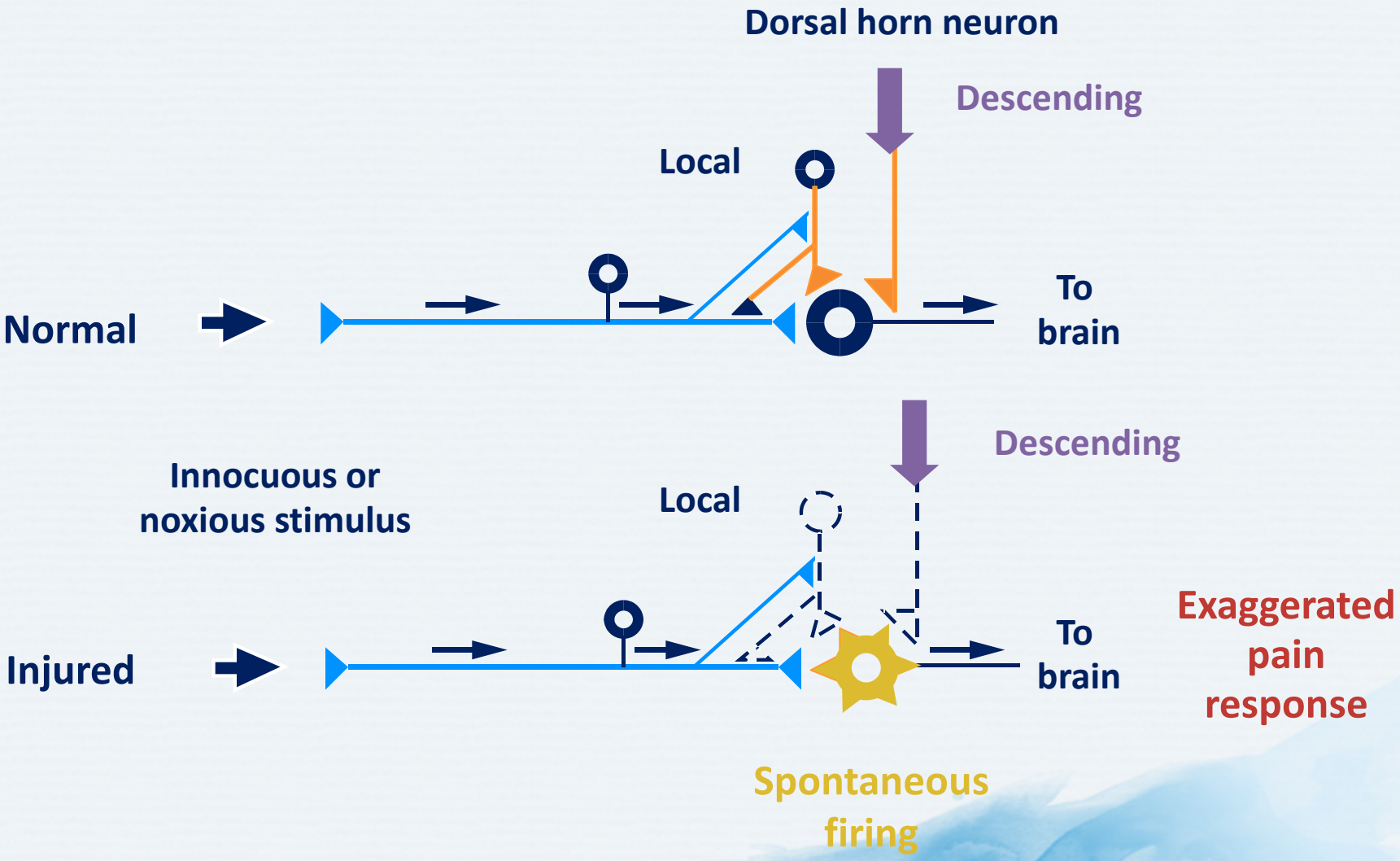
Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Central Sensitization Produces Abnormal Pain Signaling



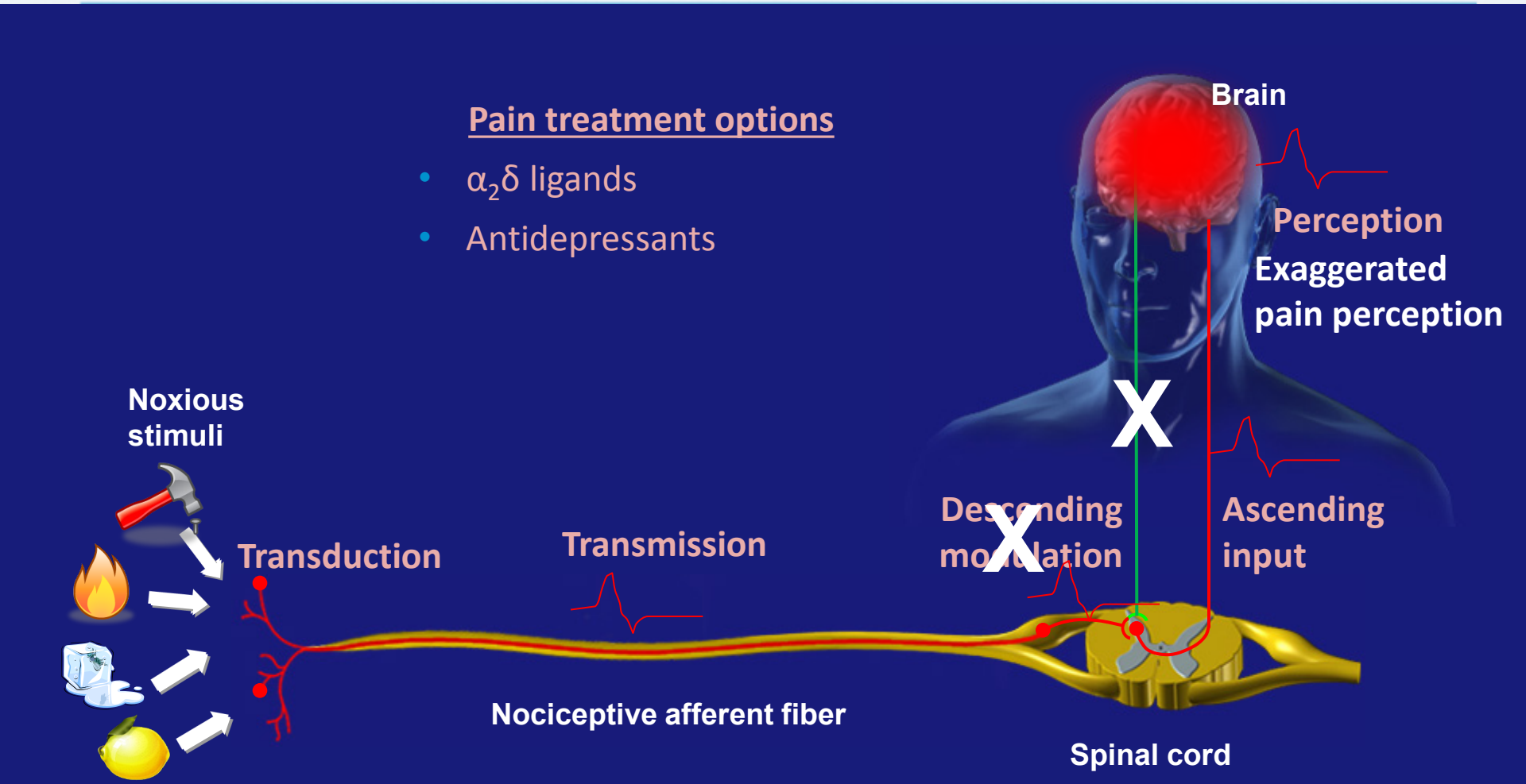
Adapted from: Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10)1979-86; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl):89-94; Larson AA *et al. Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Rao SG. *Rheum Dis Clin North Am* 2002; 28(2):235-59; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14; Staud R, Rodriguez ME. *Nat Clin Pract Rheumatol* 2006; 2(2):90-8; Vaerøy H *et al. Pain* 1988; 32(1):21-6; Woolf CJ *et al. Ann Intern Med* 2004; 140(6):441-51.

Loss of Inhibitory Controls



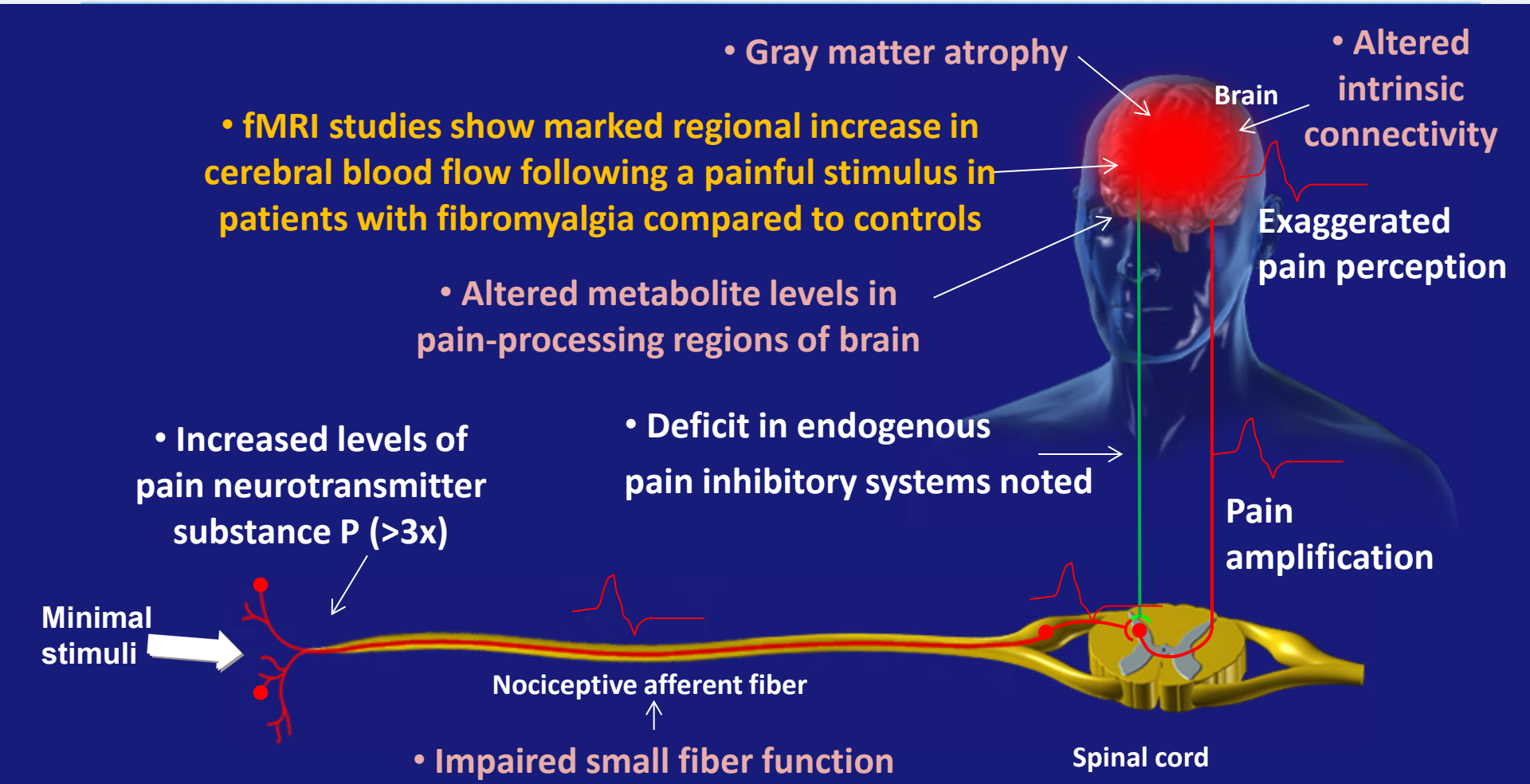
Attal N, Bouhassira D. *Acta Neurol Scand* 1999; 173:12-24; Doubell TP *et al.* In: Wall PD, Melzack R (eds). *Textbook of Pain*. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

Loss of Inhibitory Control: Disinhibition



Attal N, Bouhassira D. *Acta Neurol Scand* 1999; 173:12-24; Doubell TP *et al.* In: Wall PD, Melzack R (eds). *Textbook of Pain*. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

Pathophysiological Changes in Fibromyalgia



fMRI = functional magnetic resonance imaging

Feraco P *et al. AJNR Am J Neuroradiol* 2011; 32(9):1585-90; Gracely RH *et al. Arthritis Rheum* 2002; 46(5):1333-43; Julien N *et al. Pain* 2005; 114(1-2):295-302; Napadow V *et al. Arthritis Rheum* 2010; 62(8):2545-55; Robinson ME *et al. J Pain* 2011; 12(4):436-43; Russell IJ *et al. Arthritis Rheum* 1994; 37(11):1593-1601; Üçeyler N *et al. Brain* 2013; 136(Pt 6):1857-6; Vaerøy H et al. *Pain* 1988; 32(1):21-6.

Potential Small Fiber Pathology in Patients with Fibromyalgia

- Compared to healthy controls and controls suffering from depression (but free of pain), patients with fibromyalgia had:
  - Increased cold and warm detection thresholds in quantitative sensory testing
  - Reduced amplitudes of pain-related evoked potentials upon stimulation of face, hands and feet
  - Reduction in dermal unmyelinated nerve fibre bundles obtained through skin biopsies at the lower leg and upper thigh

Üçeyler N *et al. Brain* 2013; 136(Pt 6):1857-6.

Summary

Pathophysiology of Fibromyalgia: Summary

- Central sensitization/dysfunctional pain is hypothesized to be a result of persistent neuronal dysregulation or dysfunction
  - Fibromyalgia, a chronic, persistent and debilitating widespread pain disorder, is the most common syndrome associated with this type of pain
- Etiology and pathogenesis are still not fully understood
- Several factors appear to be involved
  - Central sensitization is considered to be main mechanism involved
  - “Wind-up” is important
  - Impaired descending inhibitory pain pathways also play a role