

Pain, fatigue and autonomic disorders

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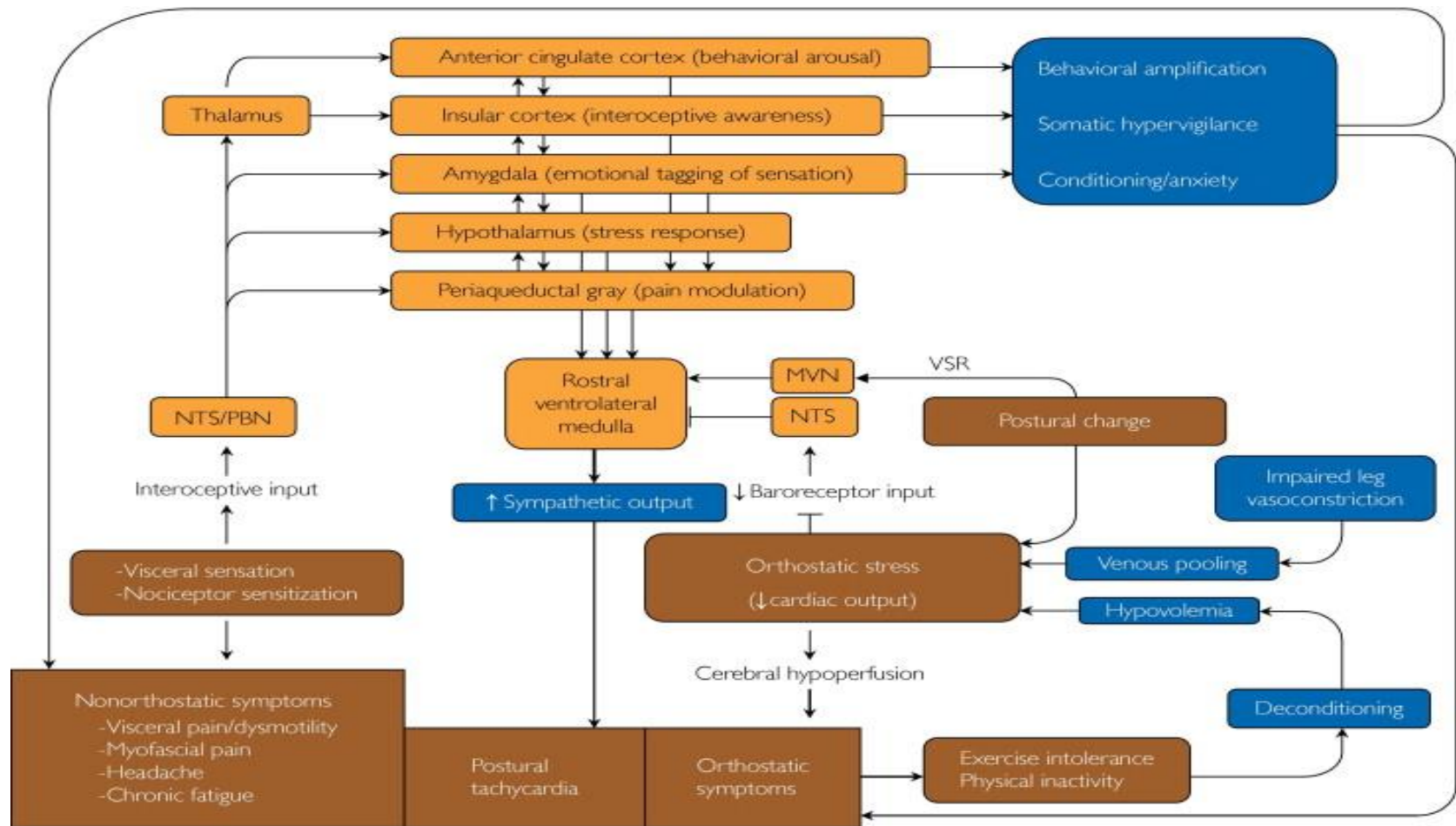


Figure Complex pathophysiology of postural tachycardia syndrome (POTS). The mechanisms of orthostatic intolerance in POTS include impaired sympathetic vasoconstriction leading to venous pooling, hypovolemia, deconditioning, and hyperadrenergic state. Excess reflex sympathoexcitation may be triggered by orthostatic stress via reduced baroreceptor input to the nucleus of the solitary tract (NTS) and activation of vestibulosympathetic reflexes (VSR). Relayed via the medial vestibular nucleus (MVN), resulting in increased activity of sympathoexcitatory neurons of the rostral ventrolateral medulla. Many comorbidities of POTS, including visceral pain and dysmotility, other chronic pain conditions, and dizziness may reflect abnormal processing of interoceptive information, relayed via the NTS and parabrachial nucleus (PBN) via the ventromedial portion of the thalamus to a central network that includes the anterior cingulate cortex, insula, amygdala, hypothalamus and periaqueductal gray region.

Eduardo E. Benarroch

Postural Tachycardia Syndrome: A Heterogeneous and Multifactorial Disorder
 Mayo Clinic Proc. 2012

Introduction

- Chronic pain, often of uncertain causes, is a challenge for all medical specialties. Its impact on patients' quality of life and its socioeconomic burden are astronomical.
- Although pain can have different etiologies, many symptoms and manifestations are common to all chronic pain syndromes.
- Chronic pain syndromes can be grossly divided into 3 subgroups:
 - Myofascial pain syndromes
 - Visceral pain syndromes
 - Neuropathic pain: maybe visceral pain should be considered a variant of it

Introduction (cont.)

- Data is not clear cut: some studies are of questionable quality and difficult interpretation
- Patients may not be homogeneous: same is true for many pain studies when no clear organic basis is present
- Chronic pain affects the person as a whole, in what is represents the pain complex experience. The pain origin/localization is various, but central integration and sensitization occur in all chronic pain cases, thus resulting in the emotional and cognitive changes that are easily recognized in any chronic pain sufferer

The Multiple Dimensions of the Pain Sensation

Pain is a **physiological alarm mechanism** that signals the presence of a stimulus that can produce actual or potential **tissue damage**

Dimensions of the pain sensation:

- **sensory-discriminative** (intensity, location)
- **cognitive-evaluative** (bodily sensation)
- **affective-emotional** (suffering)

Nociceptive Pathways

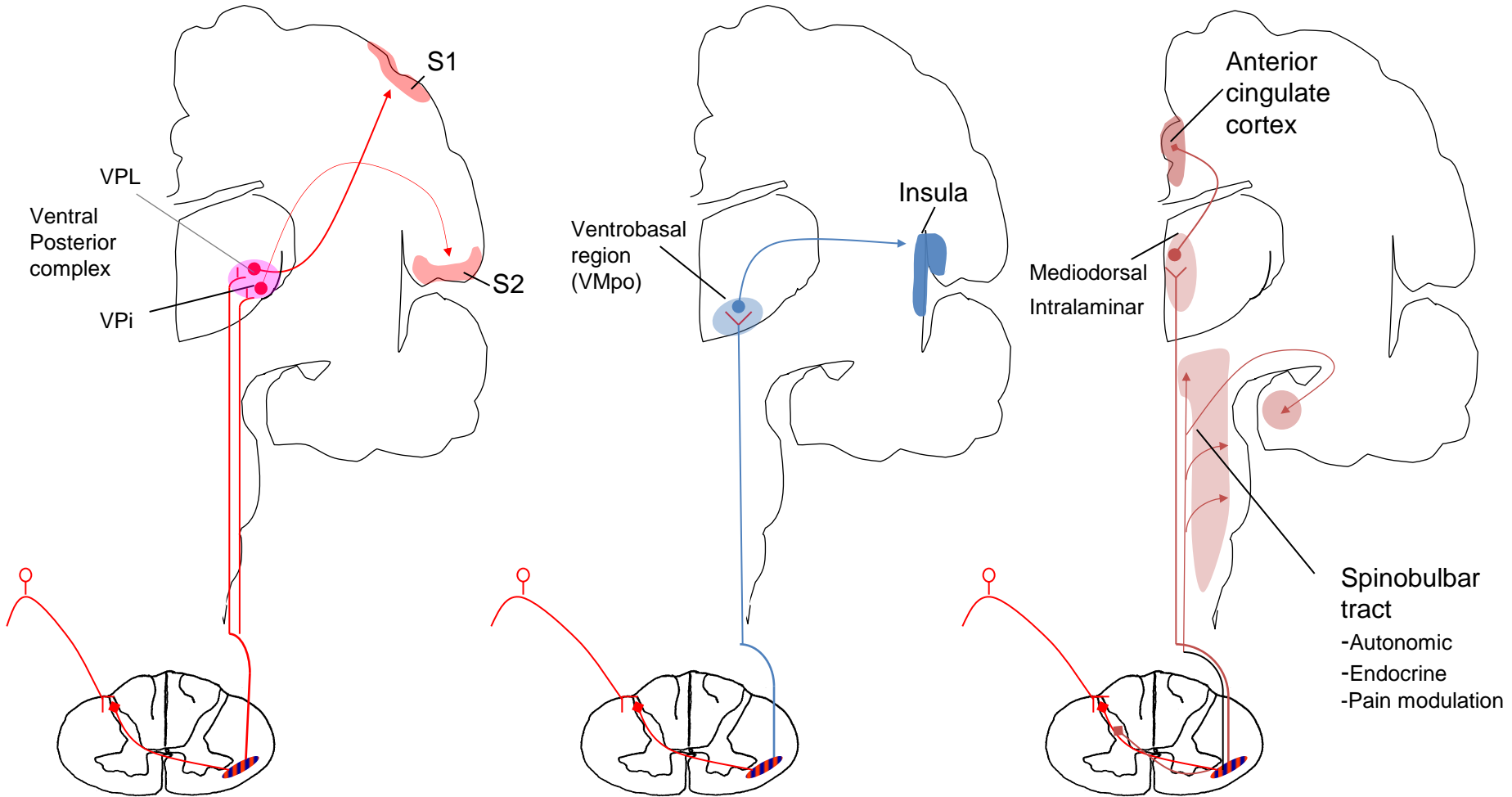
Lateral pain pathways

Medial pain pathways

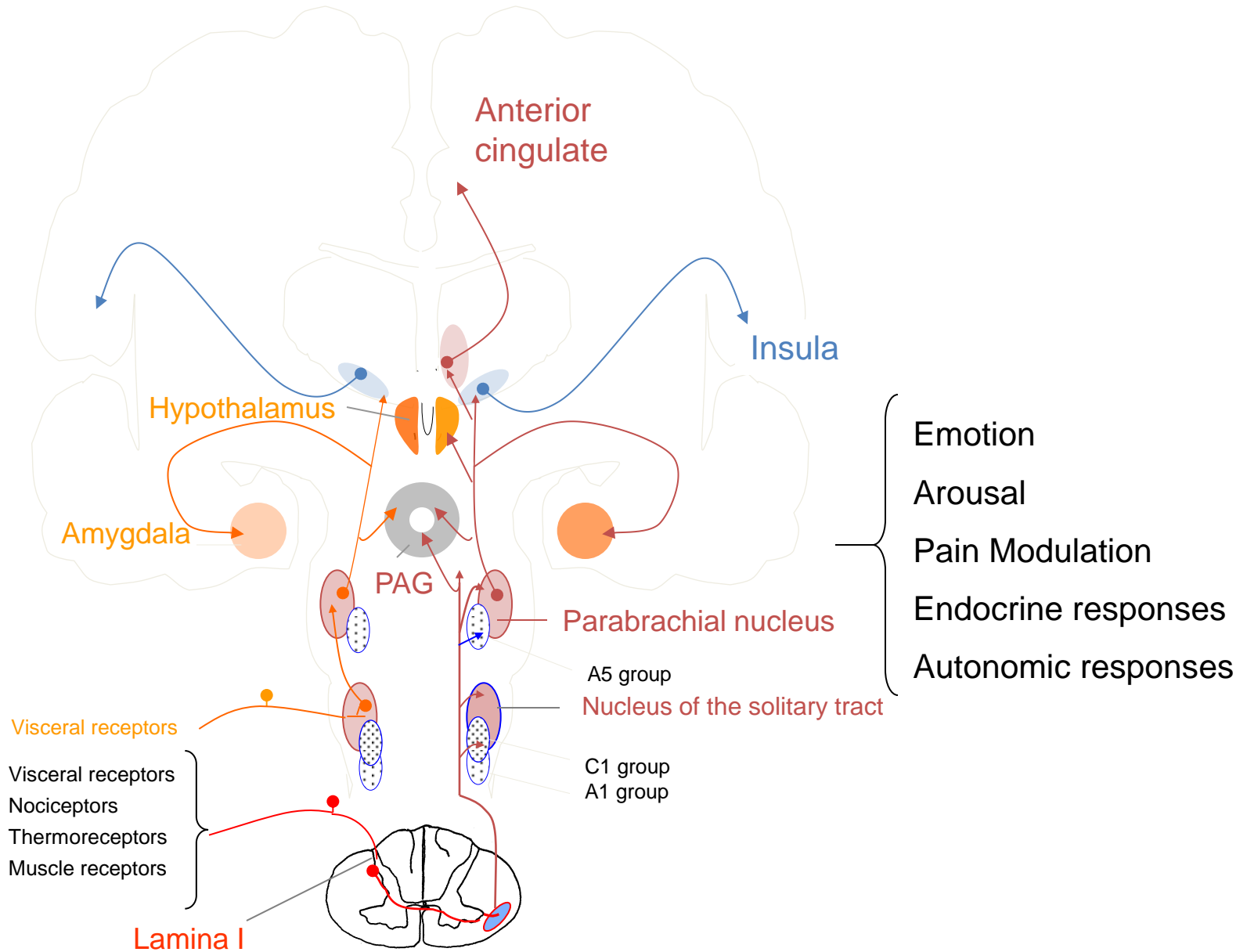
Sensory-discriminative

Evaluative (bodily sensation)

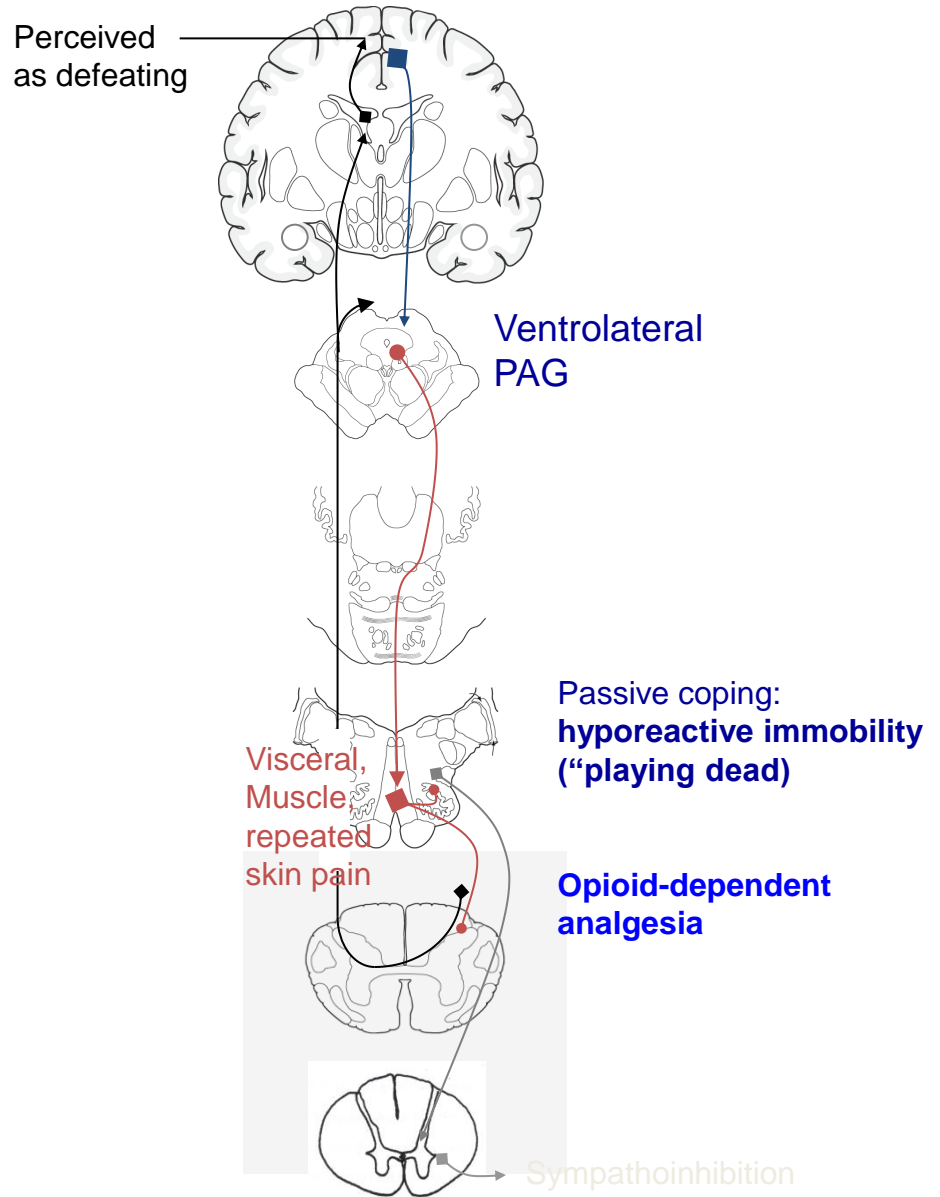
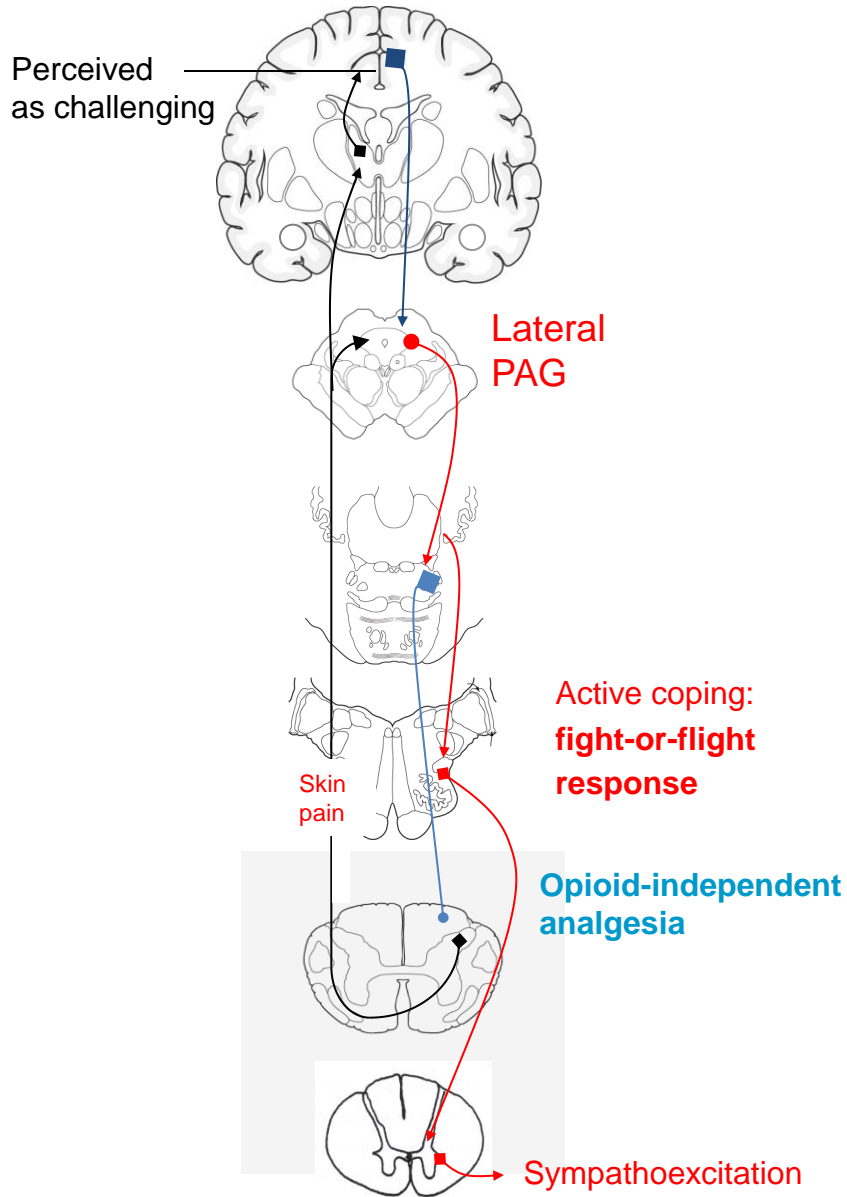
Affective-emotional



Spinobulbar pathways



Functional specialization of the PAG:



Neuropathic Pain Syndromes (Visceral Pain is a form of it)

- Chronic conditions, associated with lesions involving the **peripheral or central** components of the **nociceptive pathways**
- Pathophysiologically **heterogeneous**
- Manifestation of **plasticity** of the nociceptive system
- Depend on interactions among neurons, glia, and **inflammatory** cells

Central Sensitization: in the dorsal horn and at supraspinal level

- Increased excitability of WDR spinothalamic neurons
- Activation of postsynaptic NMDA and NK-1 receptors
- Upregulation of Nav 1.3 channels
- Intracellular phosphorylation cascades (PKC, MAPK)
- Impaired inhibition of lamina I neurons
- Descending excitatory pain modulation
- Microglial activation and neuron-glia interactions
- New synapses formation and limbic augmentation

Summary

1. Pain is a **complex sensation** that includes discriminative, evaluative, and emotional components
2. Nociceptors are an **heterogeneous population** with unique expression of ion channels and receptors
3. Nociceptive transmission in the dorsal horn is affected by the pattern of nociceptor activity, local influences and descending modulation
4. Each component of the pain sensation is conveyed via **parallel and partially overlapping** pathways
5. **Different cortical areas** dynamically participate in specific processing of pain
6. There is a **central network** that elicits a **bimodal modulation** on pain sensation
7. **Attention** and **emotion** strongly affect central modulation of pain

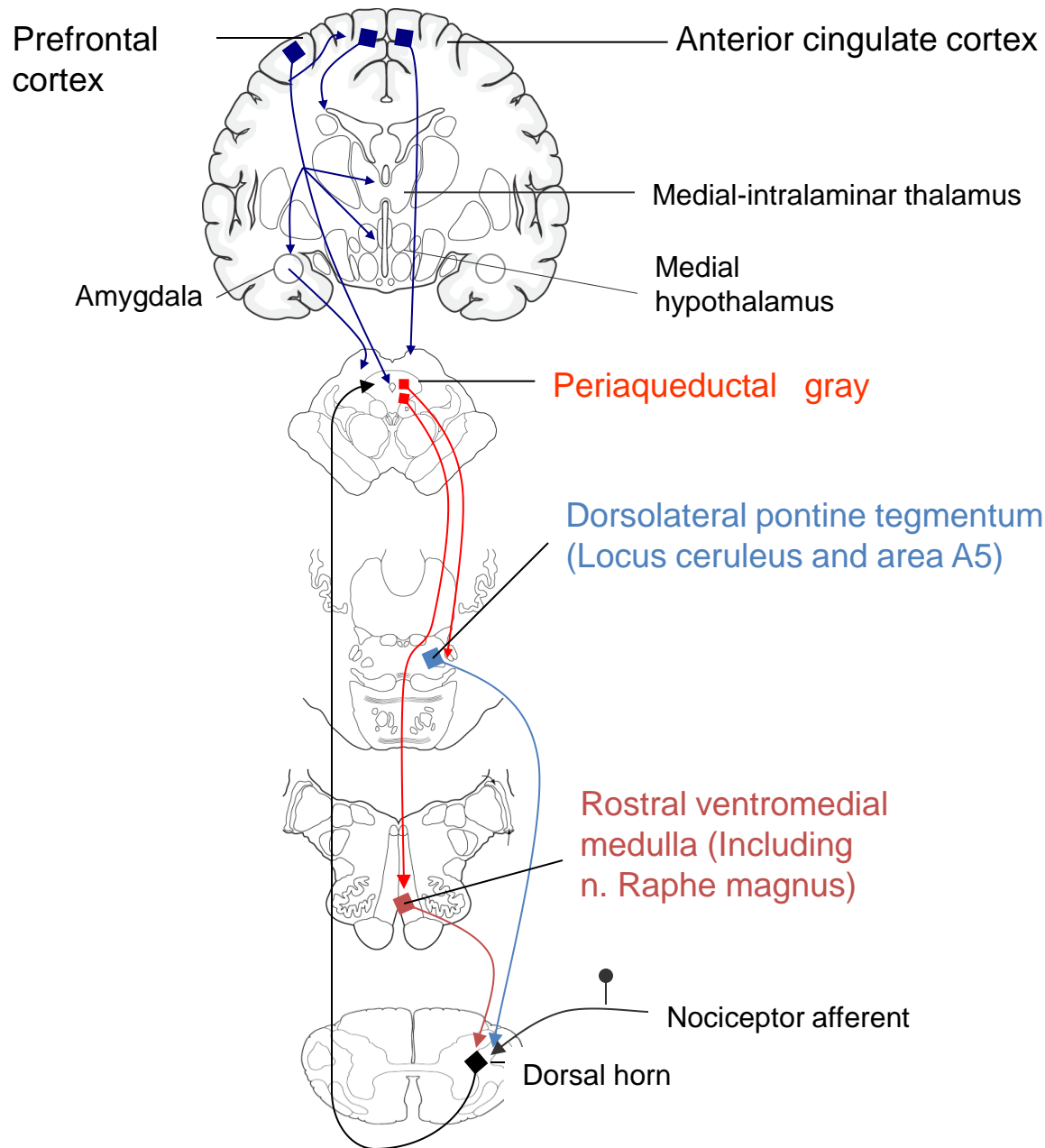
Summary (cont)

8. Visceral pain is a chronic, complex and heterogeneous syndrome that reflects the **plasticity** of the peripheral and central nociceptive pathways
9. Plasticity in the nociceptive system manifests with changes of expression and activity of **ion channels and neurotransmitter receptors**
10. Plasticity leads to peripheral and central **sensitization** of the nociceptive system
11. Plasticity may be triggered by continuous peripheral **nociceptor activity** and is maintained by effects of products of **inflammation**

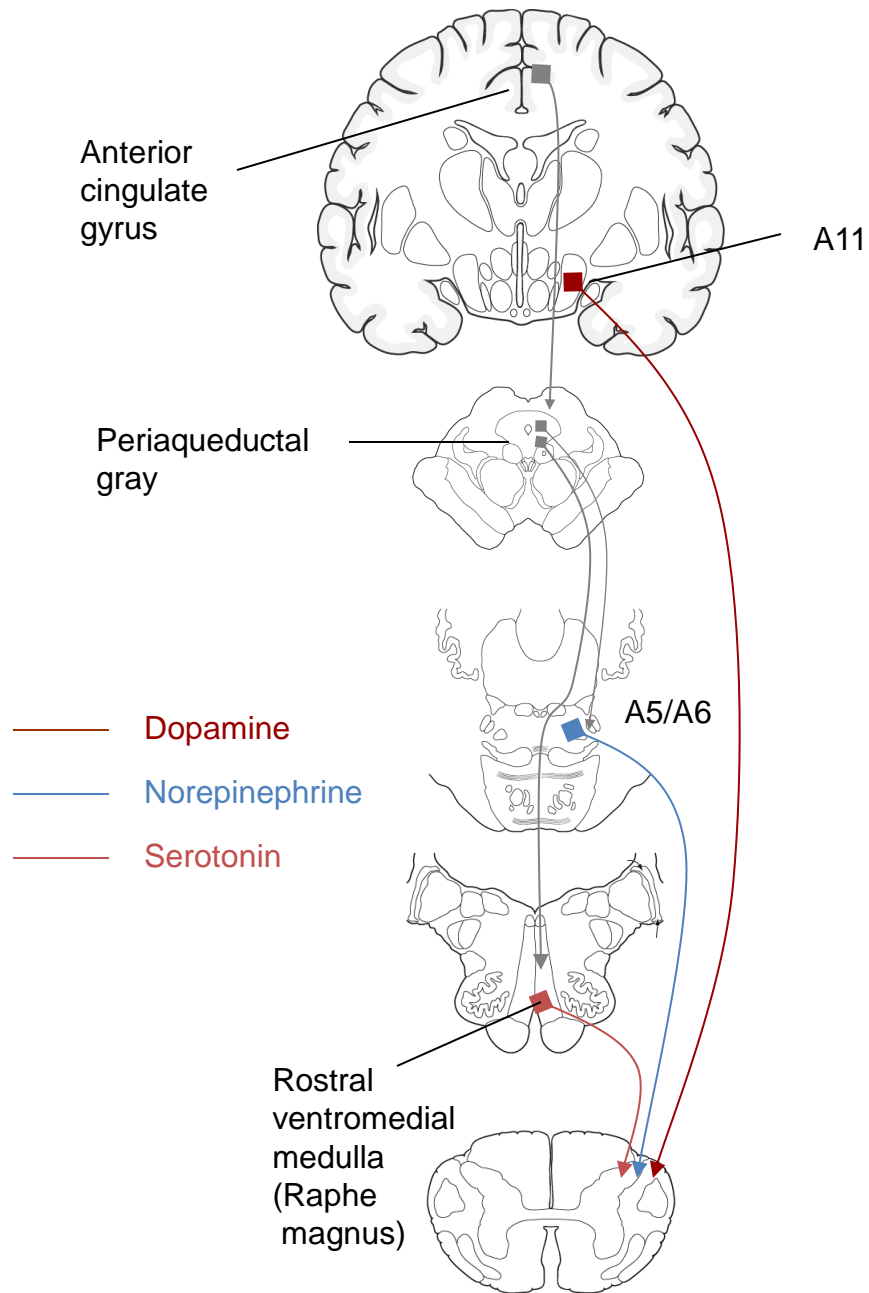
Summary (cont)

12. The severity of pain may be strongly influenced by attentional and emotional processing
13. Cortical areas involved in attention and emotion affect pain sensation via the central pain modulatory network
14. Management of pain requires both pharmacological and behavioral approaches
15. Surgical procedures, including deep brain stimulation affecting central pain-modulatory networks, may be helpful in highly selected cases of pain

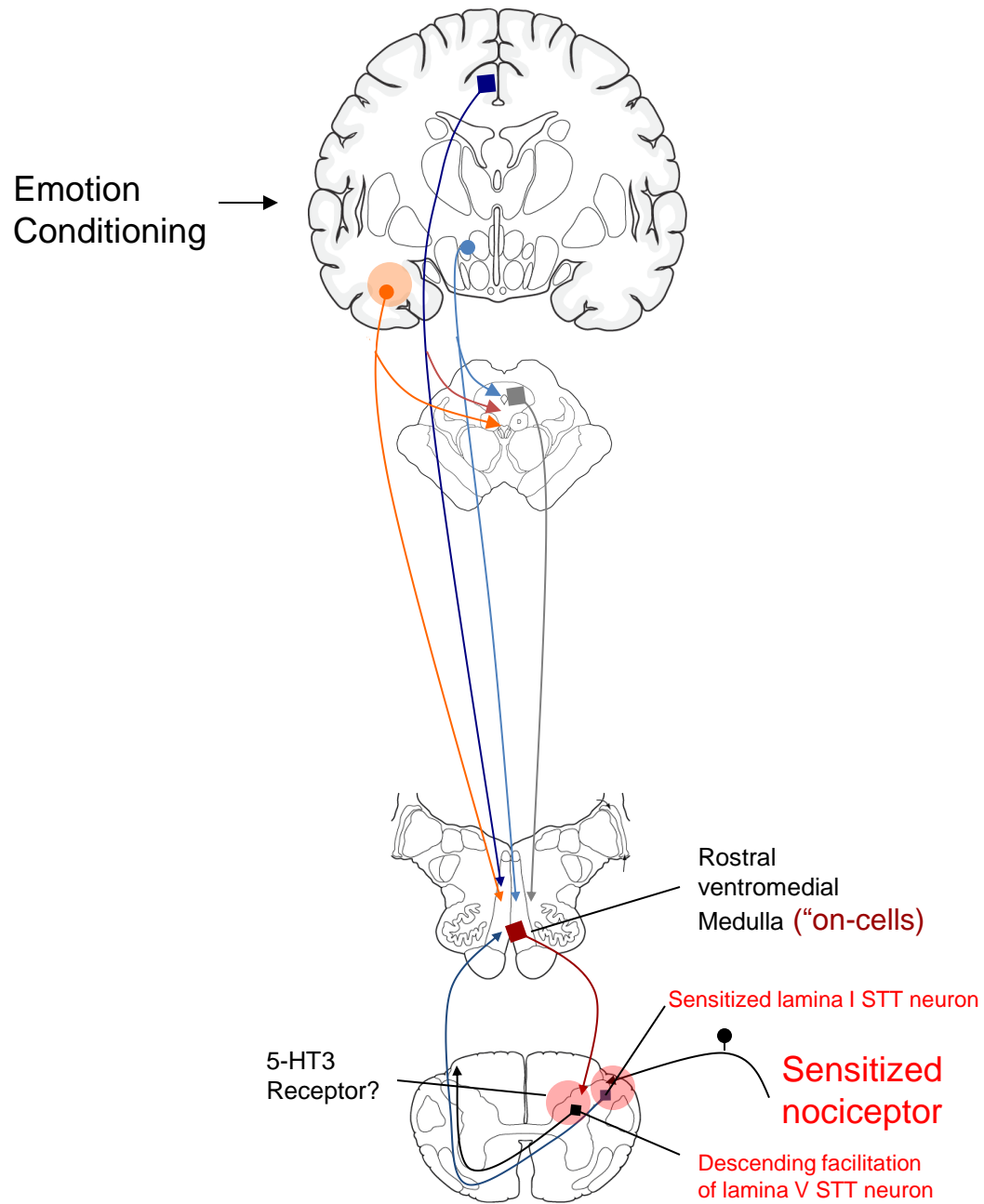
Pain Modulation Network



Descending Monoaminergic Pain Modulatory Pathways



Descending Facilitation of Pain



2010 ACR Fibromyalgia

Diagnostic Criteria:

- Widespread Pain Index
- Symptom Severity
 - Fatigue
 - Waking unrefreshed
 - Cognitive symptoms
- Additional symptoms
- Symptoms present at a similar level for at least three months

FCFC Symptom Measurement

1) Please indicate the areas in which you have had pain **in the past 7 days**.

Put a **Check** to indicate a painful region.

<input type="checkbox"/> Left Shoulder	<input type="checkbox"/> Left Upper Leg Thigh	<input type="checkbox"/> Lower Back <input type="checkbox"/> Upper Back <input type="checkbox"/> Neck
<input type="checkbox"/> Right Shoulder	<input type="checkbox"/> Right Upper Leg Thigh	
<input type="checkbox"/> Left Hip	<input type="checkbox"/> Left Lower Leg/Foot	<input type="checkbox"/> No pain in any of these areas
<input type="checkbox"/> Right Hip	<input type="checkbox"/> Right Lower Leg/Foot	
<input type="checkbox"/> Left Upper Arm	<input type="checkbox"/> Left Jaw	
<input type="checkbox"/> Right Upper Arm	<input type="checkbox"/> Right Jaw	
<input type="checkbox"/> Left Lower Arm/Hand	<input type="checkbox"/> Chest	
<input type="checkbox"/> Right Lower Arm/Hand	<input type="checkbox"/> Abdomen	

2) Which of these symptoms have you **frequently** experienced in the **past 6 months**?

- | | |
|---|--|
| <input type="checkbox"/> Headache | <input type="checkbox"/> Heart burn |
| <input type="checkbox"/> TMJ symptoms | <input type="checkbox"/> Nausea |
| <input type="checkbox"/> Muscle weakness | <input type="checkbox"/> Loss of appetite |
| <input type="checkbox"/> Numbness/tingling of extremities | <input type="checkbox"/> Bowel cramps |
| <input type="checkbox"/> Blurred vision | <input type="checkbox"/> Frequent loose stools |
| <input type="checkbox"/> Dry eyes | <input type="checkbox"/> Constipation |
| <input type="checkbox"/> Hair loss | <input type="checkbox"/> Cold intolerance |
| <input type="checkbox"/> Hearing difficulties | <input type="checkbox"/> Heat intolerance |
| <input type="checkbox"/> Ringing in the ears | <input type="checkbox"/> Multiple sensitivities (lights, sounds, smells, foods, medicines) |
| <input type="checkbox"/> Lightheadedness | <input type="checkbox"/> Rash |
| <input type="checkbox"/> Sense of imbalance | <input type="checkbox"/> Sun sensitivity |
| <input type="checkbox"/> Palpitations | <input type="checkbox"/> Hives |
| <input type="checkbox"/> Chest discomfort | <input type="checkbox"/> Easy Bruising |
| <input type="checkbox"/> Shortness of breath | <input type="checkbox"/> Decreased sex drive |
| <input type="checkbox"/> Wheezing | <input type="checkbox"/> Nervousness |
| <input type="checkbox"/> Increased sweating | <input type="checkbox"/> Difficulty falling asleep and staying asleep |
| <input type="checkbox"/> Bladder cramps | <input type="checkbox"/> Depressed mood |
| <input type="checkbox"/> Frequent urination | |
| <input type="checkbox"/> Pain or cramps in lower abdomen | |
| <input type="checkbox"/> Dry mouth | |
| <input type="checkbox"/> Oral ulcers | |
| <input type="checkbox"/> Loss of/change in taste | |

Centers for Disease Control and Prevention (CDC) Diagnostic Criteria for Chronic Fatigue Syndrome (CFS):

- Unexplained, persistent fatigue present for 6 months or more that is not due to ongoing exertion; is not substantially relieved by rest, is of new onset (not lifelong) and results in a significant reduction in previous levels of activity.
- Additionally, four or more of the following eight symptoms must be present:

CDC Diagnostic Criteria (continued):

- Postexertional malaise (extreme, prolonged exhaustion and sickness following physical or mental activity)
- Impaired memory or concentration
- Unrefreshing sleep
- Muscle pain
- Multijoint pain without swelling or redness
- Headaches of a new type or severity
- Sore throat that's frequent or recurring
- Tender cervical or axillary lymph nodes

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

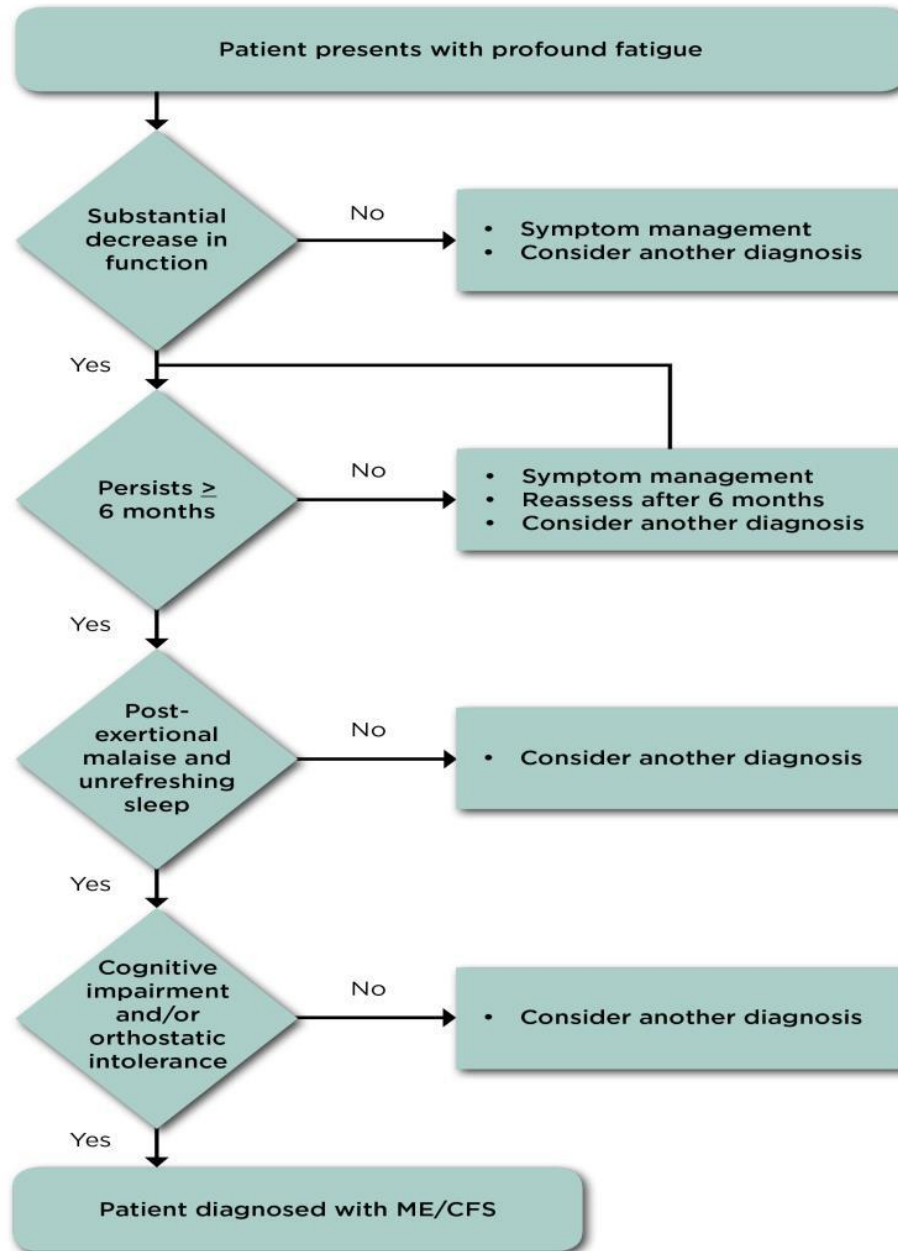
- ME/CFS affects 836,000 to 2.5 million Americans.
- An estimated 84 to 91 percent of people with ME/CFS have not yet been diagnosed, meaning the true prevalence of ME/CFS is unknown.
- ME/CFS affects women more often than men. Most patients currently diagnosed with ME/CFS are Caucasian, but some studies suggest that ME/CFS is more common in minority groups.
- The average age of onset is 33, although ME/CFS has been reported in patients younger than age 10 and older than age 70.
- ME/CFS patients experience loss of productivity and high medical costs that contribute to a total economic burden of \$17 to \$24 billion annually.

ME/CFS

- There are five main symptoms of ME/CFS:
 - reduction or impairment in ability to carry out normal daily activities, accompanied by profound fatigue;
 - Post-exertional malaise (worsening of symptoms after physical, cognitive, or emotional effort);
 - Unrefreshing sleep;
 - Cognitive impairment *; and
 - Orthostatic intolerance *

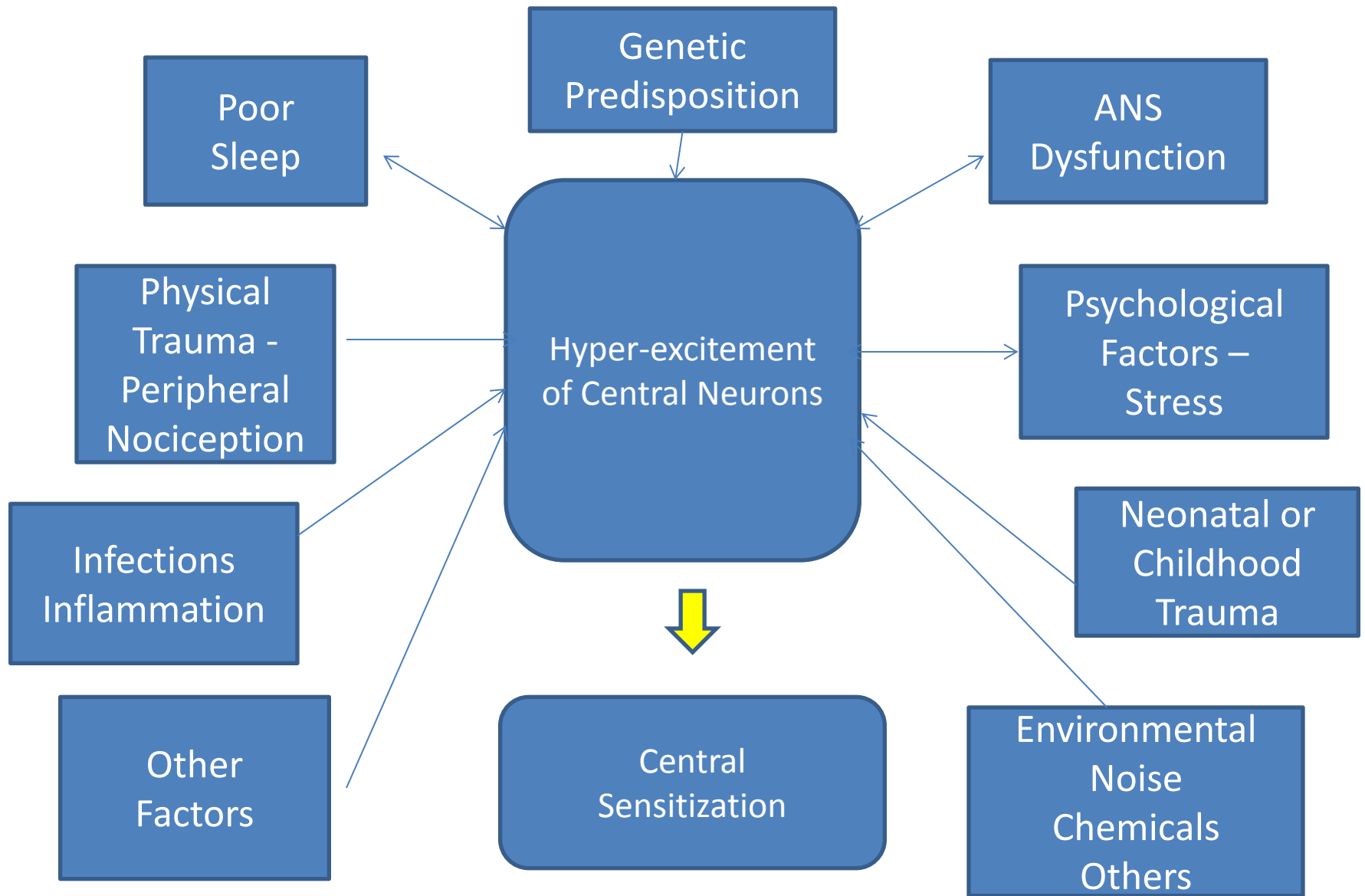
Pain is also common as is altered immune function

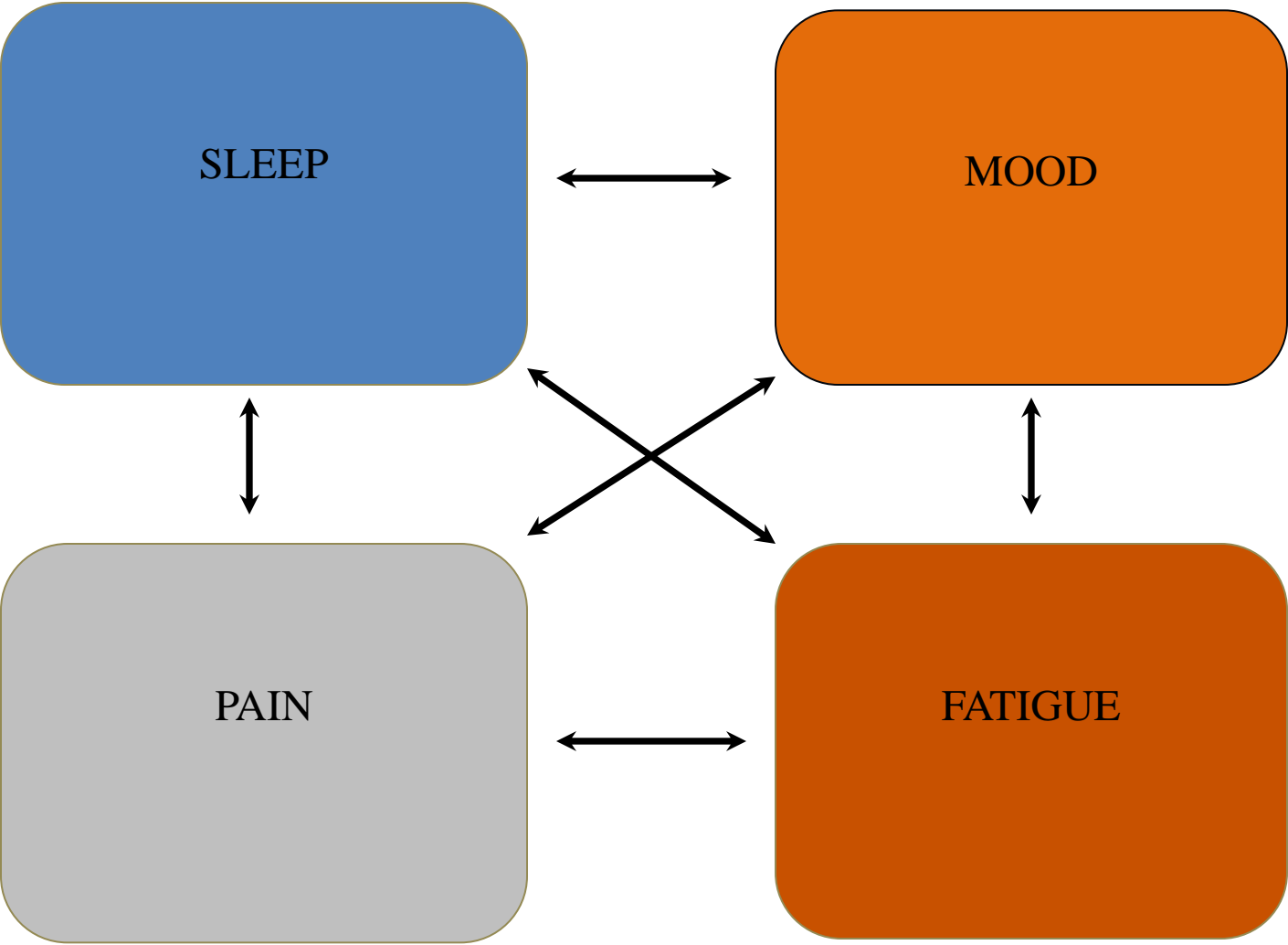
First 3 are required, plus one of * for diagnosis



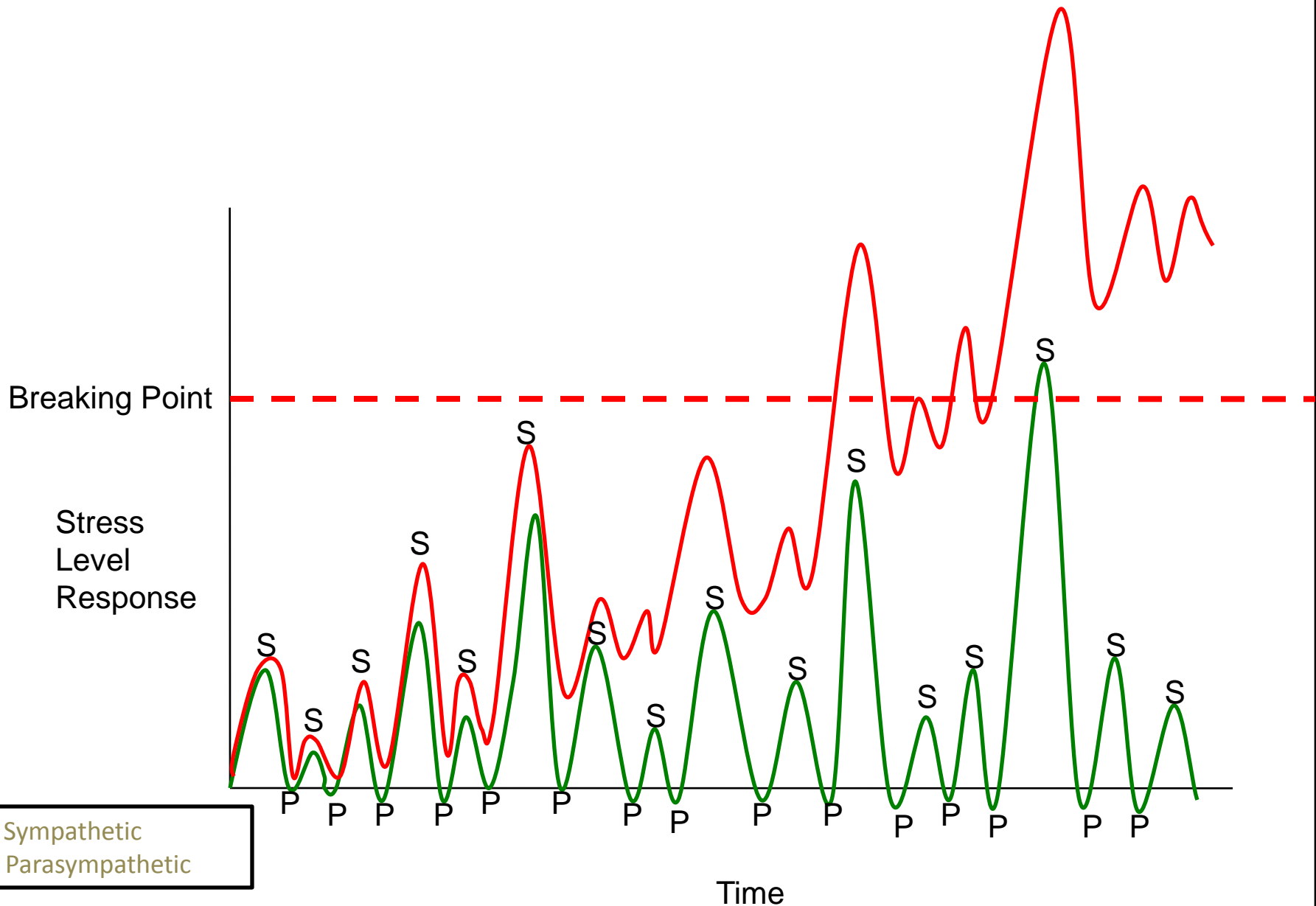
Why the Institute of Medicine is proposing a new name and new criteria

- Several studies have shown that the term “chronic fatigue syndrome” affects patients’ perceptions of their illness as well as the reactions of others, including medical personnel, family members, and colleagues. This label can trivialize the seriousness of the condition and promote misunderstanding of the illness.
- The term “myalgic encephalomyelitis” is not appropriate because there is a lack of evidence for encephalomyelitis (brain inflammation) in patients with this disease, and myalgia (muscle pain) is not a core symptom of the disease.
- The Institute of Medicine (IOM) committee recommends the name systemic exertion intolerance disease (SEID) for this disease. This new name captures a central characteristic of this disease—the fact that exertion of any sort (physical, cognitive, or emotional)—can adversely affect patients in many organ systems and in many aspects of their lives.





Effects of Chronic Stress



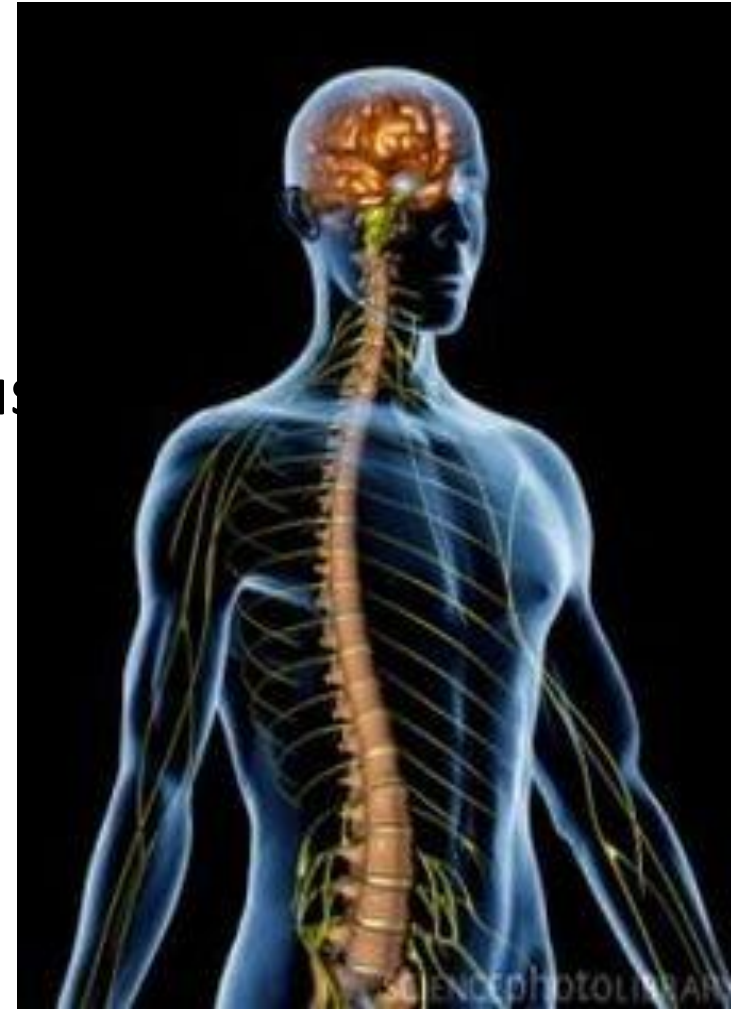
Stress Signals

Physical	Emotional	Cognitive	Behavioral
<ul style="list-style-type: none"> *increased sweating *increased heart rate *increased blood pressure palpitations *short, shallow respirations *muscle tension body aches *clench jaw/teeth TMJ symptoms headaches *change in appetite irritable bowel irritable bladder insomnia constantly tired fatigue weight loss/gain decrease sexual desire/function skin changes Sensitivities Dizziness/lightheadedness Sense of imbalance 	<ul style="list-style-type: none"> *anxiety *nervousness *feeling overwhelmed crying easily mood swings impatience irritability sensitivity anger depression worry guilt fear 	<ul style="list-style-type: none"> poor concentration memory lapse forgetfulness confusion difficulty with word find “fogginess” 	<ul style="list-style-type: none"> unhealthy eating patterns sleeping habits change increased focus on symptoms negative attitude negative thoughts irritability no longer fun to be with withdrawal/isolation decreased activity and/or exercise scattered activity procrastination unrealistic expectations spend more hours doing less work increased chemical use (meds, caffeine, alcohol, nicotine) addictive behaviors neglecting appearance

Research Suggests....

CENTRAL SENSITIZATION:

- Increase in the excitability of neurons within the central nervous system
- Results in an abnormal enhancement of pain and general hypersensitivity

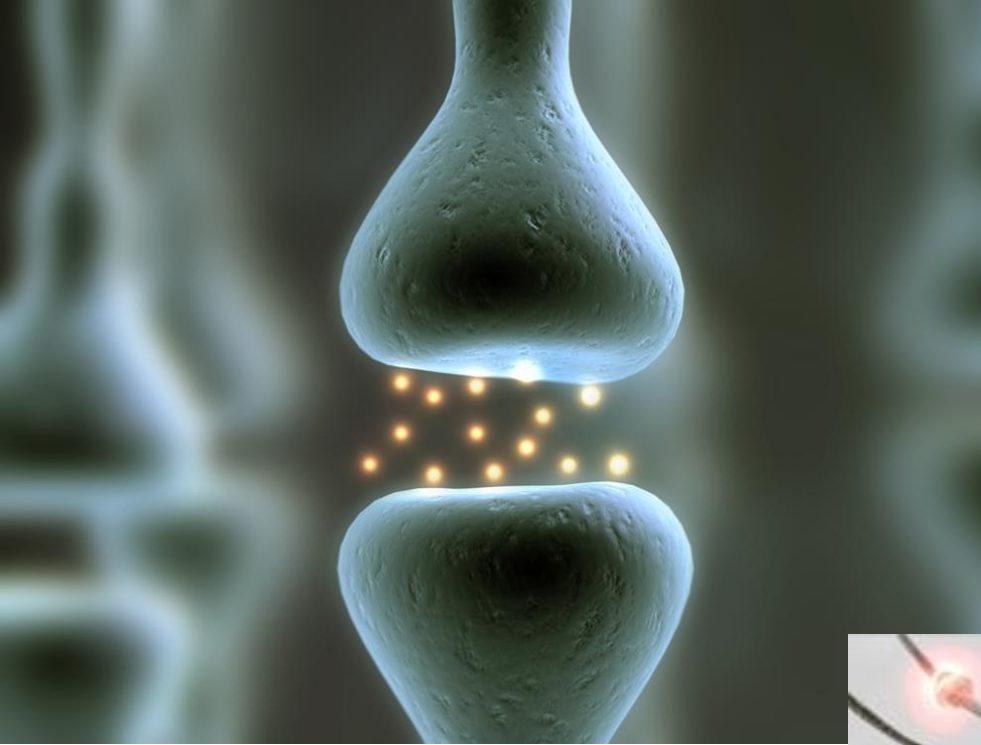


Sensitivities

Heightened response to any stimuli:

- Light
- Sounds
- Smells
- Stress
- Touch
- Pain
- Foods
- Medications





In our brains, neurons fire and synapse with one another....

...and repeated signals can create memory pathways.



Managing Symptoms

- Dampeners

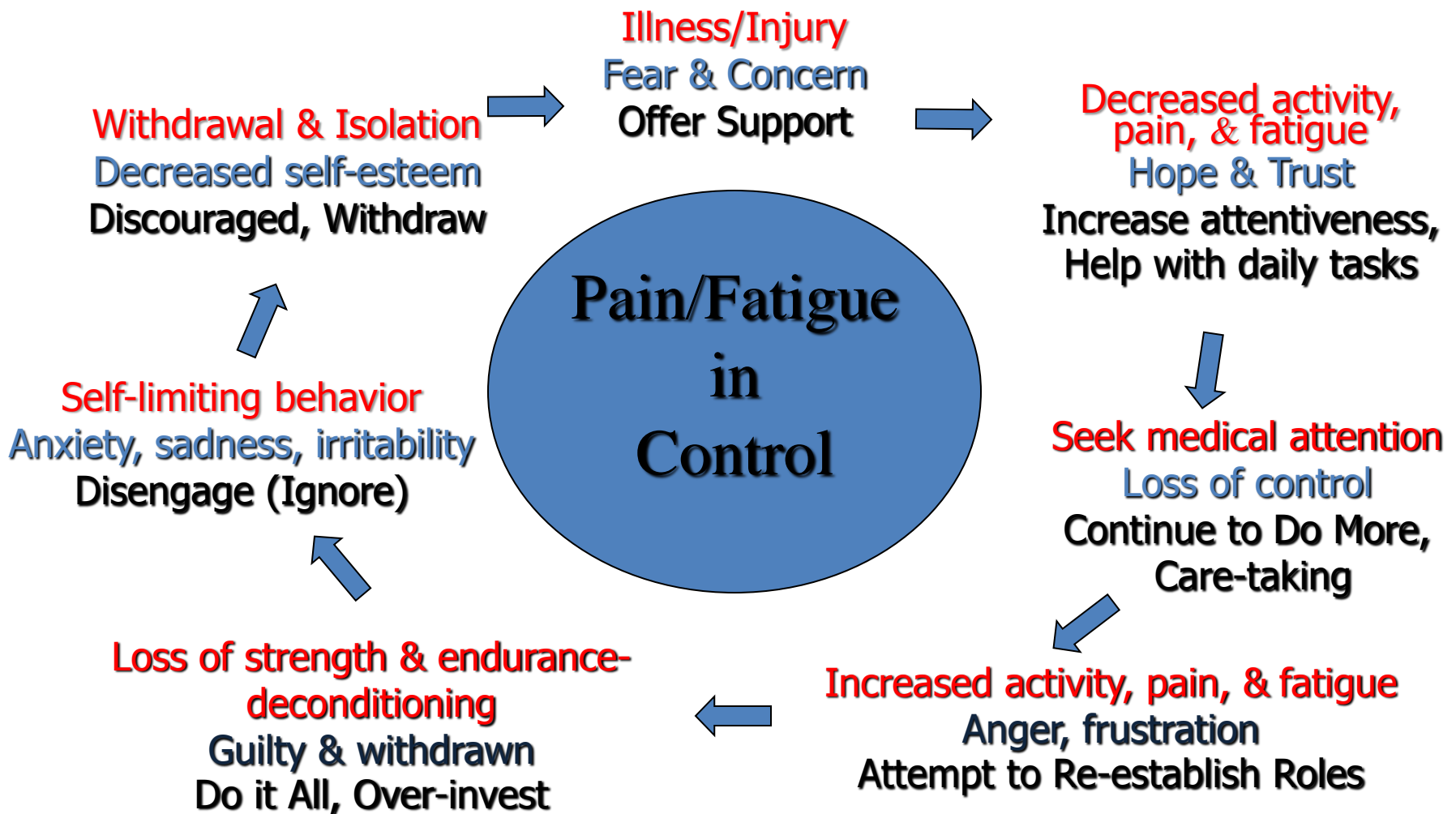
- Relaxation
- Regular exercise
- Good sleep hygiene
- Decreasing perfectionism
- Positive outlook
- Humor
- Balanced nutrition
- Healthy boundaries
- Meaningful free time activities

- Amplifiers

- Muscle tension
- Decreased activity/exercise
- Poor sleep hygiene
- Unrealistic expectations
- Procrastination
- Negative thinking
- Symptom focus
- Unhealthy eating
- Withdrawal/isolation

Cycle of Chronic Pain/Chronic Fatigue

(Behaviors, Emotions, Family Response)



Benefits of Exercise

Blood vessels

- Increased number of blood vessels in active muscles

Blood

- Increased blood volume and total hemoglobin
- Improved blood flow

Lungs

- Increased lung muscle strength and endurance

Gastrointestinal system

- Improved digestion
- Improved motility

Brain

- Improved mental alertness
- Improved overall feeling of well-being
- Reduced risk of stroke

Active muscle

- More efficient oxygen use
- Increased strength
- Increased flexibility

Heart

- Increased ability to pump blood
- Reduced risk of heart disease

Fat

- Increased use of body fat for energy during exercise
- Decreased body fat stores

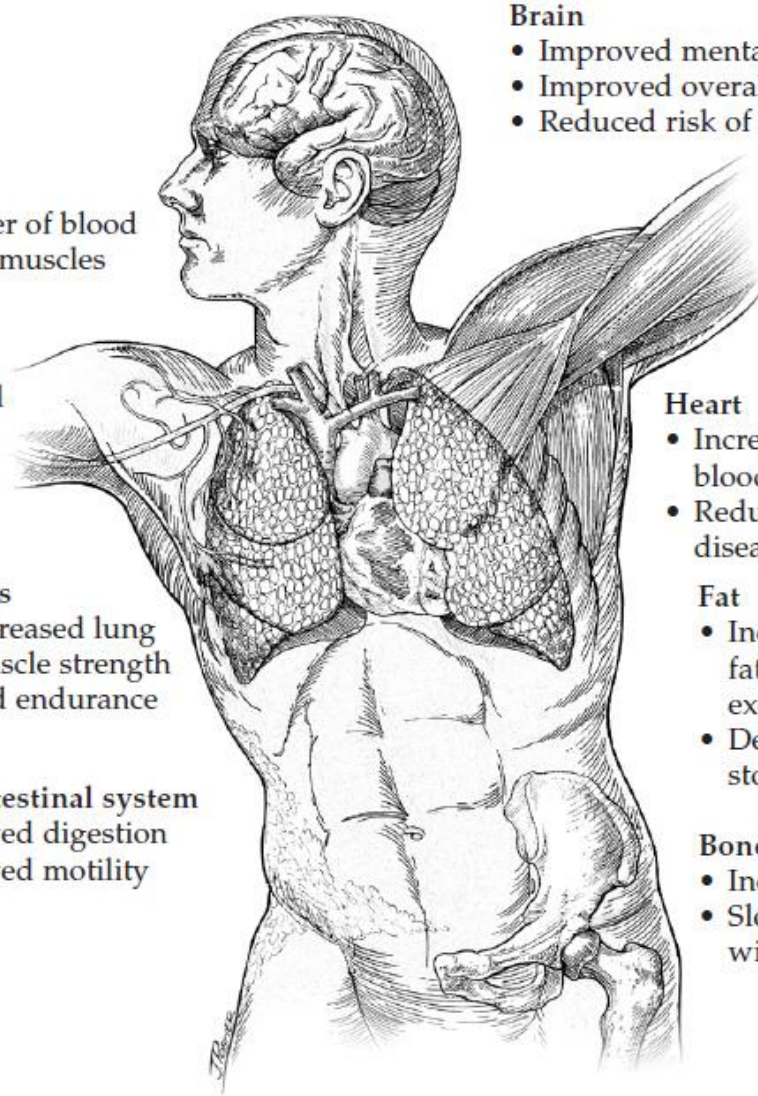
Bone

- Increased bone mass
- Slower loss of mass with aging

Additional benefits

- Reduced risk of certain cancers
- Reduced risk of chronic diseases such as diabetes and heart disease
- Improved posture
- Improved sleep
- Increased energy
- Decreased stress
- Improved mood and self-confidence
- Improved appearance

- 1) Decreased pain (endorphins)
- 2) Release of chemicals that block pain signals from reaching your brain
- 3) Decreased symptoms of fatigue
- 4) Increased muscle tone, strength, and flexibility: reverses deconditioning

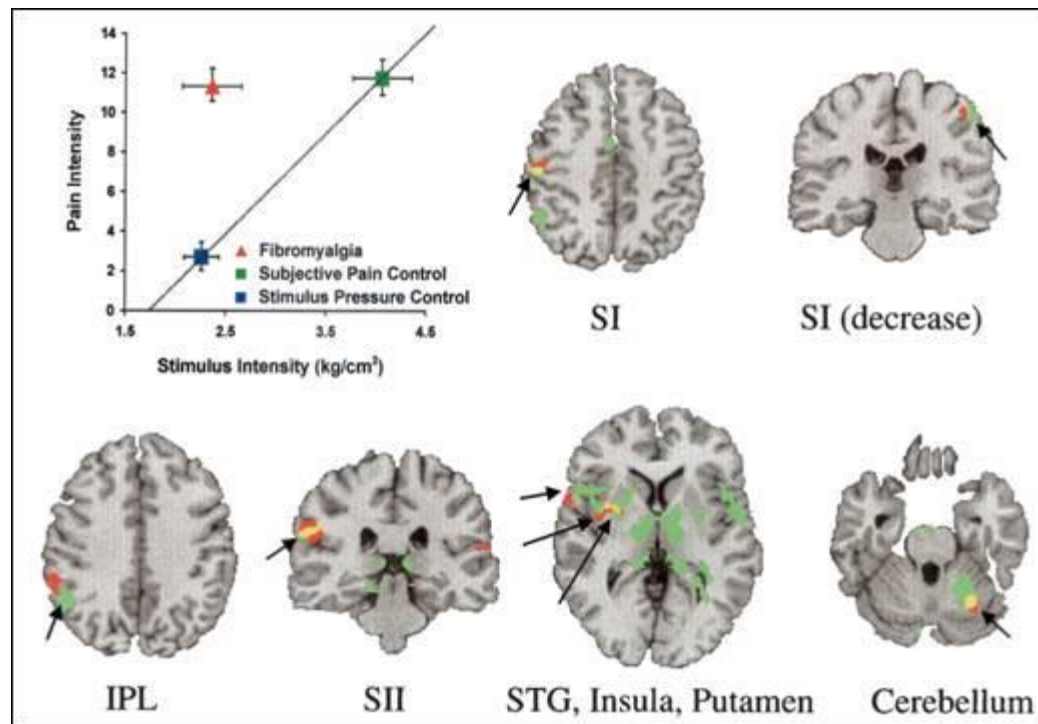
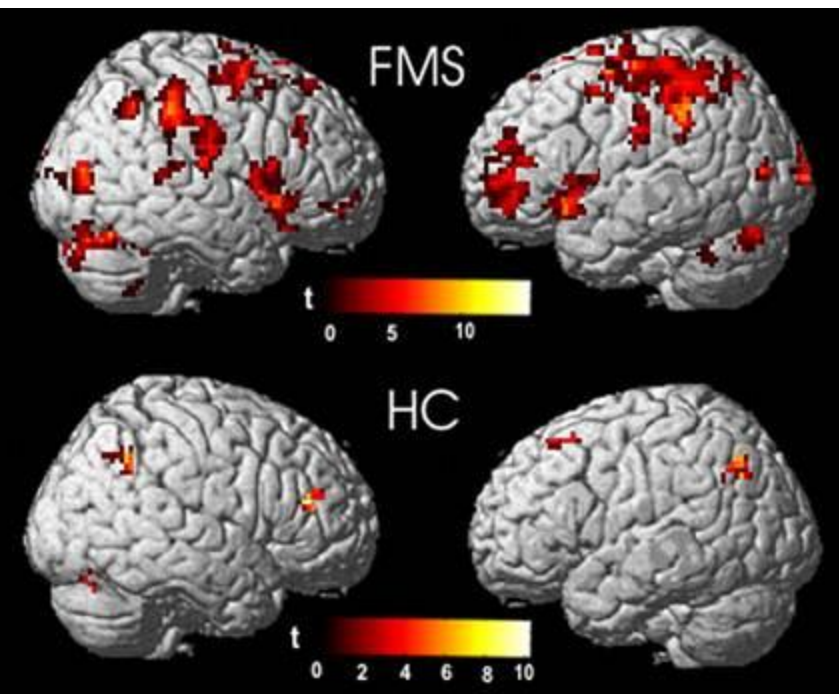


101 Benefits of exercise

http://www.healthlibrary.com/book14_chapter420.htm

- 1) There is a definite link between high premature death rates and chronic inactivity. Exercise promotes longevity by reducing the risk of premature mortality.
- 2) Exercise retards the process of aging, thus preserving vitality and youth.
- 3) Exercise reduces the risk of developing hypo-kinetic diseases (those associated with lack of movement). It prevents the incidence of and/or helps control such disease processes.
- 4) Exercise helps prevent or control coronary artery disease and most cardiovascular diseases, as lack of exercise is the number 1 risk factor for developing these diseases.
- 5) Exercise helps prevent cerebro-vascular disease (Strokes).
- 6) Exercise helps control Tri-glycerides in blood. Tri-glycerides are as harmful as cholesterol and lead to heart disease.
- 7) Regular aerobic exercise helps control/prevent hypertension.
- 8) Exercise prevents clotting of blood, thus reducing the risk of heart attacks and strokes.
- 9) Exercise increases the elasticity of blood vessels, which reduces the resistance to blood flow. This in turn helps prevent hypertension and heart disease.
- 10) Blood viscosity is decreased as a result of regular exercise. This reduces the stress on the heart, as thinner blood is easier to pump, and also prevents clotting.
- 11) Exercise increases HDL (Good Cholesterol) levels in the body, which prevents plaque build-up on the inner walls of arteries. This in turn prevents heart attacks and strokes.
- 12) Exercise strengthens the heart muscle, and cause left ventricular enlargement, thus improving cardiac output, and endurance.
- 13) Exercise improves overall glucose tolerance and insulin sensitivity, thus reducing the risk for type II diabetes mellitus.
- 14) Exercise increases muscle mass, which is linked to various vital physiological functions. Increased muscle mass helps optimize these functions thus promoting good health and vitality.
- 15) Exercise increases muscular strength and endurance, which improves your ability to perform work and function optimally in day-to-day life.
- 16) Exercise improves the body's ability to control its internal temperature, thus making it better suited to cope with heat stress.
- 17) Exercise improves the body's hydration status. This helps prevent dehydration for strenuous exertion, or heat stress.
- 18) Exercise helps improve/maintain bone density, reducing the risk of developing osteoporosis (hollowing of bones).
- 19) Exercise boosts immunity, helping the body to combat infectious disease.
- 20) Regular light to moderate exercise helps reduce the symptomatic pain caused by arthritis.
- 21) Exercise helps reduce the risk of developing cancer.
- 22) Regular endurance exercise helps reduce the risk for testicular and prostate cancer in men.
- 23) Regular endurance exercise helps reduce the risk for breast, cervix, ovarian, and uterine cancers in women.

Etc.



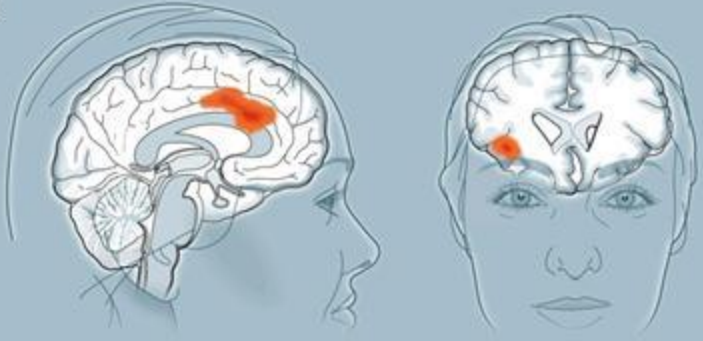
Differential central pain processing following repetitive intramuscular proton-prostaglandin E2 injections in female fibromyalgia patients and healthy controls
Martin Diers, Marcus T. Schley, et al. European Journal of Pain 15 (2011) 716–723

Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia; Gracely, et al, [Arthritis Rheum.](#) 2002 May;46(5):1333-43

Social
Pain

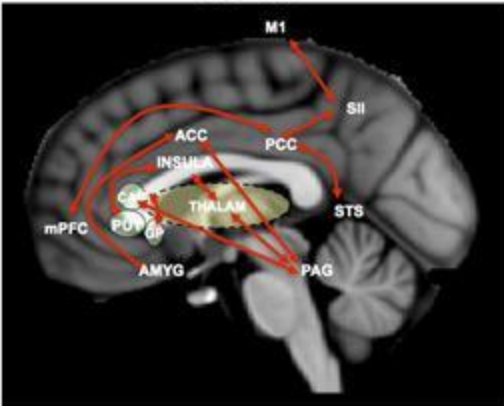


Physical
Pain

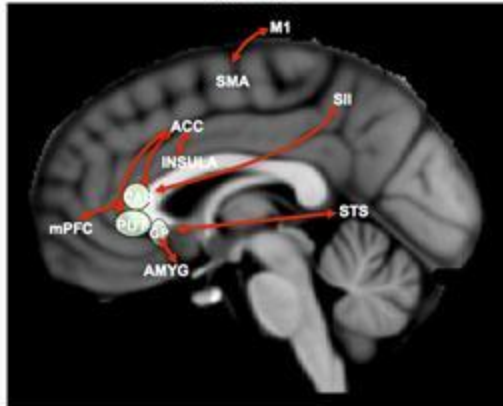


The neural correlates of placebo effects: a disruption account. Lieberman MD¹, Jarcho JM, Berman S, Naliboff BD, Suyenobu BY, Mandelkern M, Mayer EA. *Neuroimage*. 2004 May;22(1):447-55.

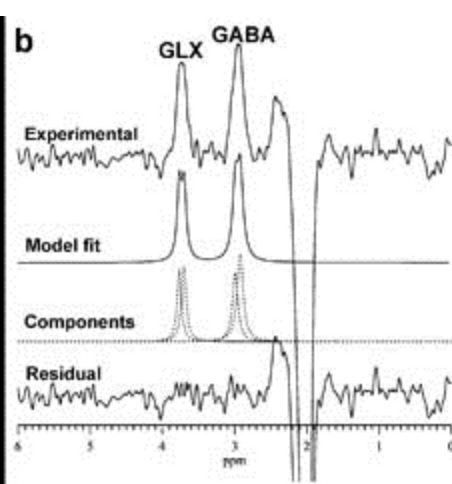
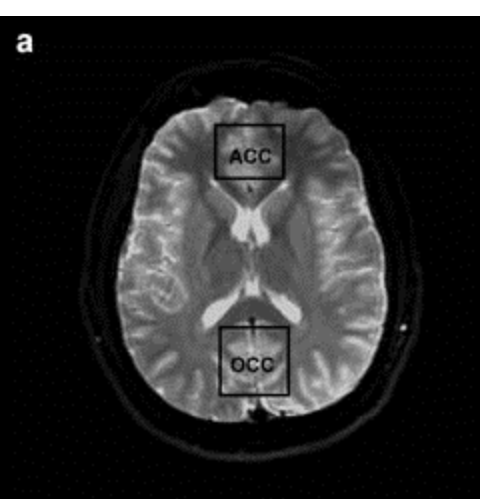
HC > FM



FM > HC



Disrupted Functional Connectivity of the Pain Network in Fibromyalgia. *Psychosomatic Medicine*: Volume 74(1), January 2012, p 55–62



Increased ventricular lactate in chronic fatigue syndrome measured by 1H MRS imaging at 3.0 T. II: comparison with major depressive disorder. Murrough JW1, Mao X, Collins KA, Kelly C, Andrade G, Nestadt P, Levine SM, Mathew SJ, Shungu DC. NMR Biomed. 2010 Jul;23(6):643-50.

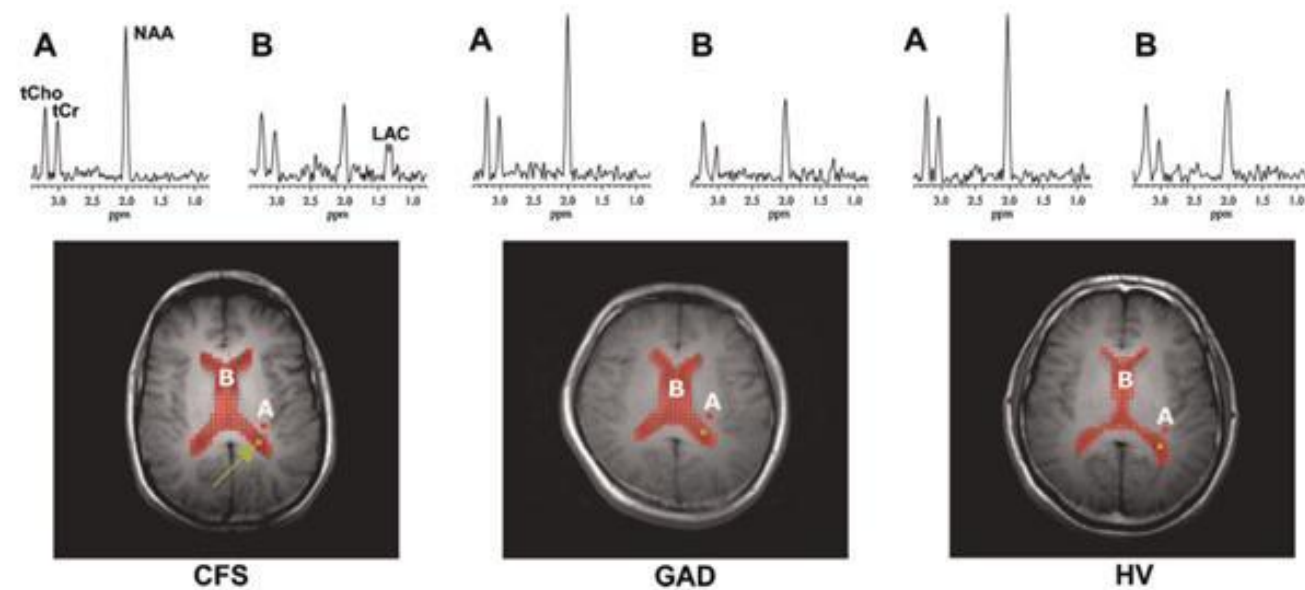


Figure 2. T₁-weighted MR brain images showing (A) brain parenchyma and (B) the lateral ventricular voxels of interest, with corresponding ¹H spectra directly above the panels for a patient with CFS, a patient with GAD, and a medically healthy volunteer (HV). To achieve a smooth representation and

Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: an in vivo 3.0 T 1 H MRS imaging study. Sanjay J. Mathewa, Xiangling Maob, Kathryn A. Keegana, Susan M. Levinec, Eric L. P. Smith, Linda A. Heierb, Viktor Otcheretkoa, Jeremy D. Copland and Dikoma C. Shungu. NMR Biomed. 2009; 22: 251–258