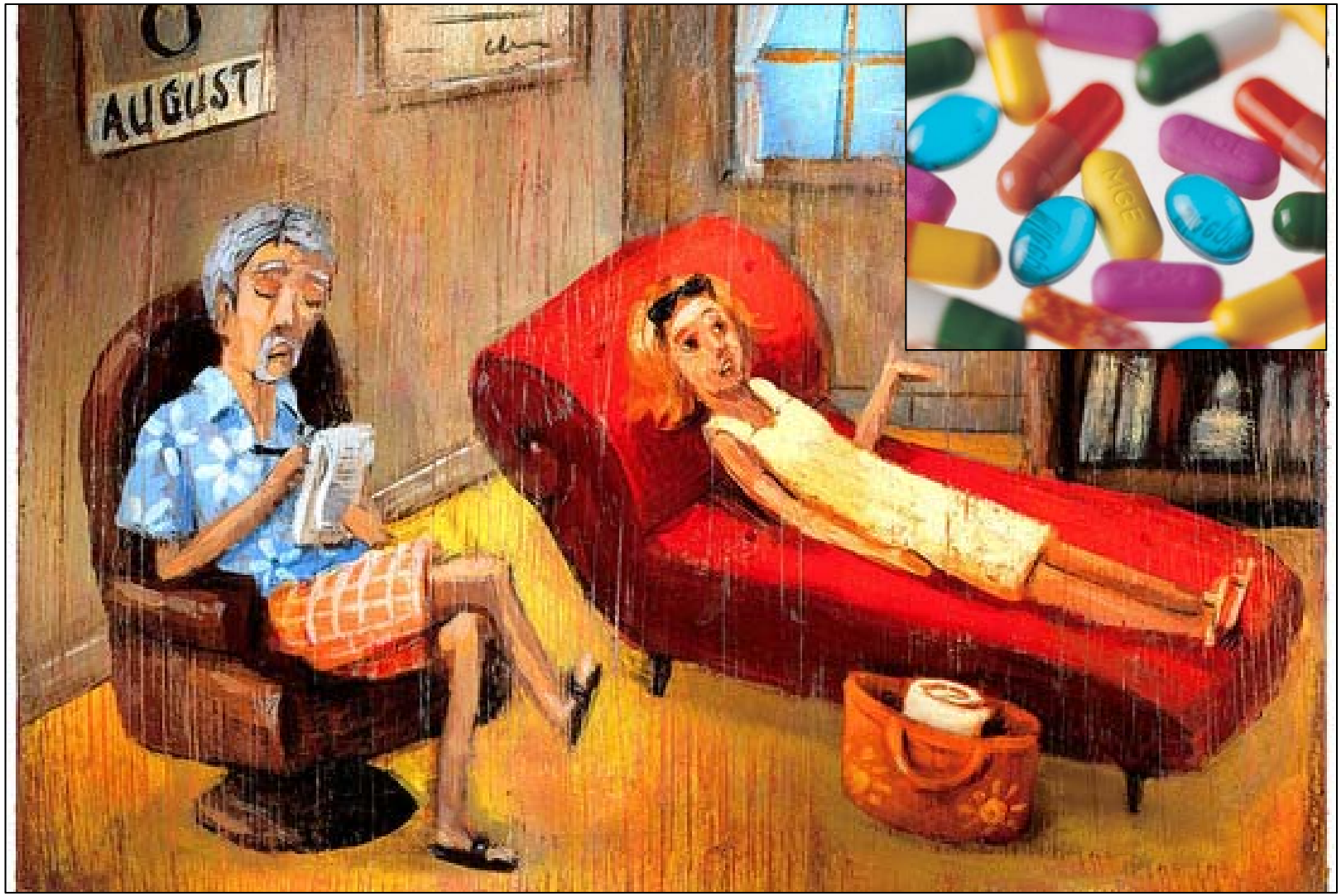
Chronic Regional and Global Pain Syndromes: A Naturopathic and Integrative Approach

David M. Brady, ND, DC, CCN, DACBN

UB Clinics


Coo
Coo!
VAX


AUGUST

Central Sensitivity Syndrome

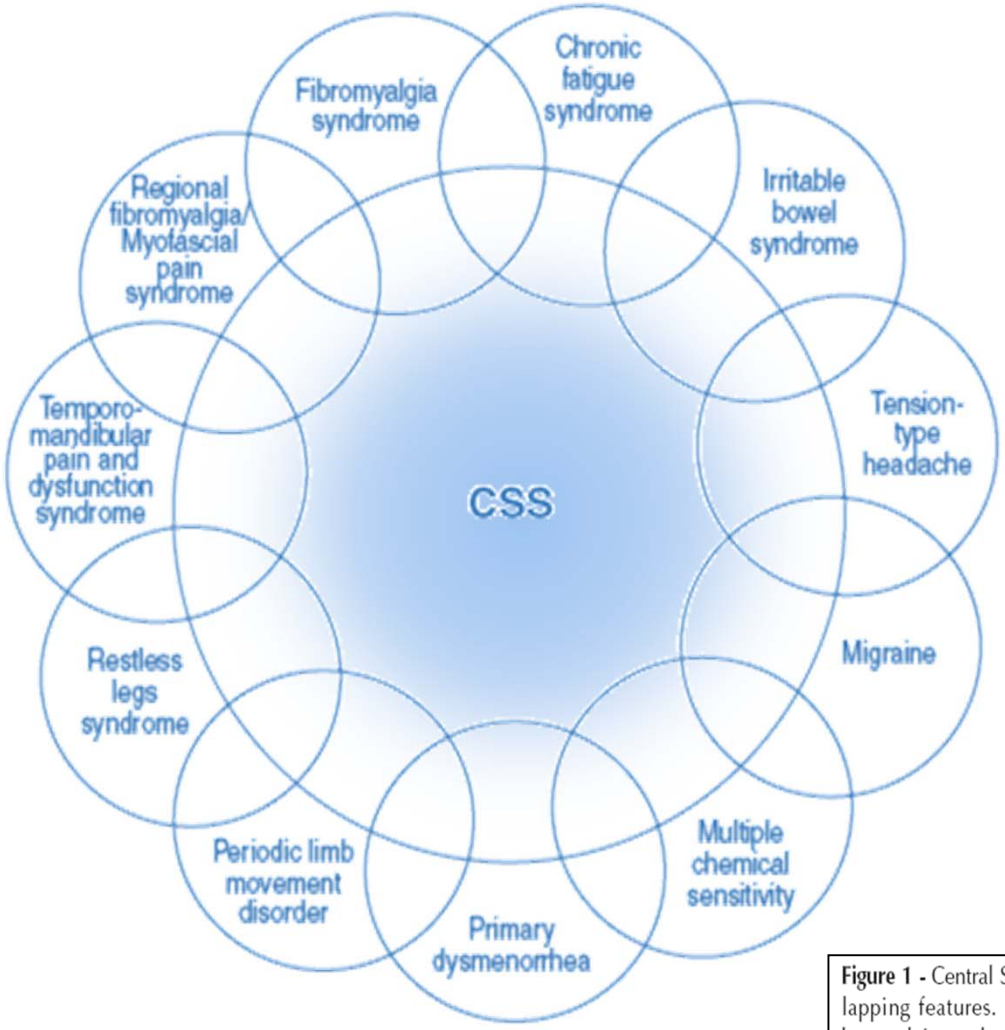


Figure 1 - Central Sensitivity Syndrome and its members with overlapping features. From Yunus MB.Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome. Baillieres Clin Rheumatol. 1994; 8(4): 811-37. In Rachlin ES, Rachlin IS. Myofascial Pain and Fibromyalgia, Trigger Point Management. 2nd ed. St. Louis: Mosby, 2002 (adapted).

Sarzi-Puttini P et al. Chronic widespread pain: from peripheral to central evolution. Best Pract Res Clin Rhematol, 2011 Apr;25(2):133-9

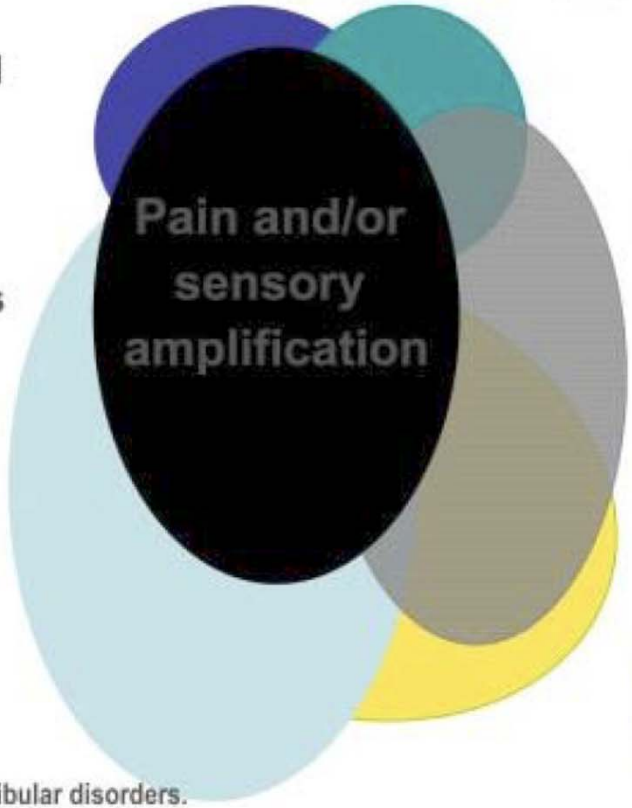
Overlap Between Systemic Syndromes

Chronic Fatigue Syndrome (CFS)

- 1% of population
- Fatigue and 4 of 8 "minor criteria"

Fibromyalgia

- 2%-4% of population
- Defined by widespread pain and tenderness



Psychiatric Disorders

- Major depression
- OCD
- Bipolar
- PTSD
- GAD
- Panic attack

Regional Pain Syndromes

- Irritable bowel [IBS]
- Interstitial cystitis/ Painful bladder syndrome
- TMJD
- Idiopathic low back pain
- Tension HA
- Vulvodynia

Somatoform Disorders

- 4% of population
- multiple unexplained symptoms — no "organic" findings

LBP = low back pain; TMD = temporomandibular disorders.

Clauw and Chrousos. *Neuroimmunomodulation*. 1997;4:134-53.

No Chronic PainTest!

Rheumatology 2003;42:263–267
doi:10.1093/rheumatology/keg075, available online at www.rheumatology.oupjournals.org

Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals

M.-A. Fitzcharles and P. Boulos[1]

At the final evaluation the accuracy of the diagnosis regarding FM by either the referring physician or by the rheumatologist at the time of the initial visit was correct in 34% of patients.

of FM or finally diagnosed with FM. At the final evaluation the accuracy of the

Conclusion. **There is a disturbing inaccuracy, mostly observed to be overdiagnosis, in the diagnosis of FM by referring physicians. This finding may help explain the current high reported rates of FM and caution physicians to consider other diagnostic possibilities when addressing diffuse musculoskeletal pain.**

KEY WORDS: Fibromyalgia, Referral, Misdiagnosis.

Using 2012 US National Health Interview Survey (NHIS) data [7], Walitt et al. [8] have recently reported that more 70% of persons reporting a diagnosis of fibromyalgia do not satisfy NHIS (surrogate) fibromyalgia criteria.

mostly managed by primary care physicians, accuracy in the diagnosis of musculoskeletal complaints is important. Recent reports suggest that FM may be too readily diagnosed and that other medical conditions may be of increasing importance.

The aim of the present study was to determine the accuracy of the diagnosis of FM in patients referred for rheumatology consultation. In addition, we sought to

Division of Rheumatology and McGill Pain Centre, Department of Medicine, Montreal General Hospital, McGill University Health Centre and [1]Division of Rheumatology, Department of Medicine, St. Joseph's Hospital, McMaster University, Canada.

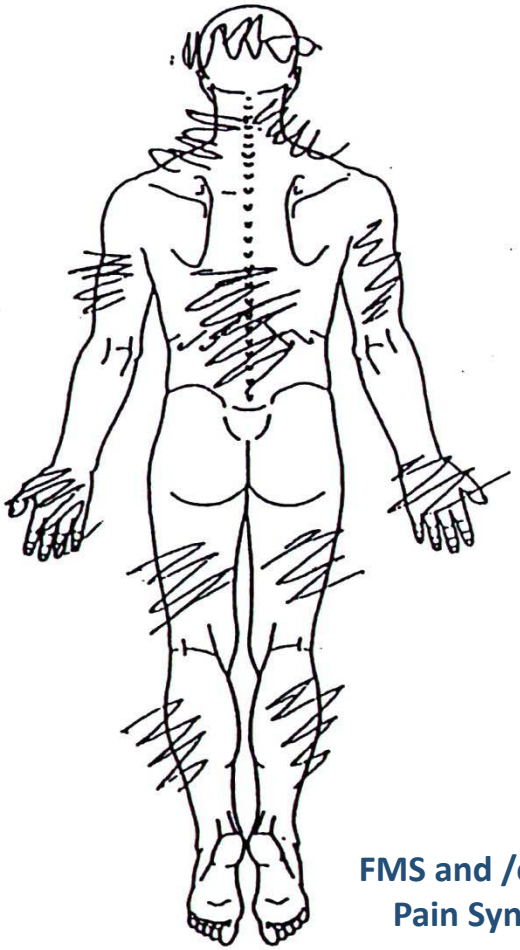
Submitted 14 January 2002; revised version accepted 15 July 2002.

Correspondence to: M.-A. Fitzcharles, Montreal General Hospital, McGill University Health Centre, 1650 Cedar ave, Montreal, Quebec, H3G 1A4. E-mail: mary-ann.fitzcharles@muhc.mcgill.ca

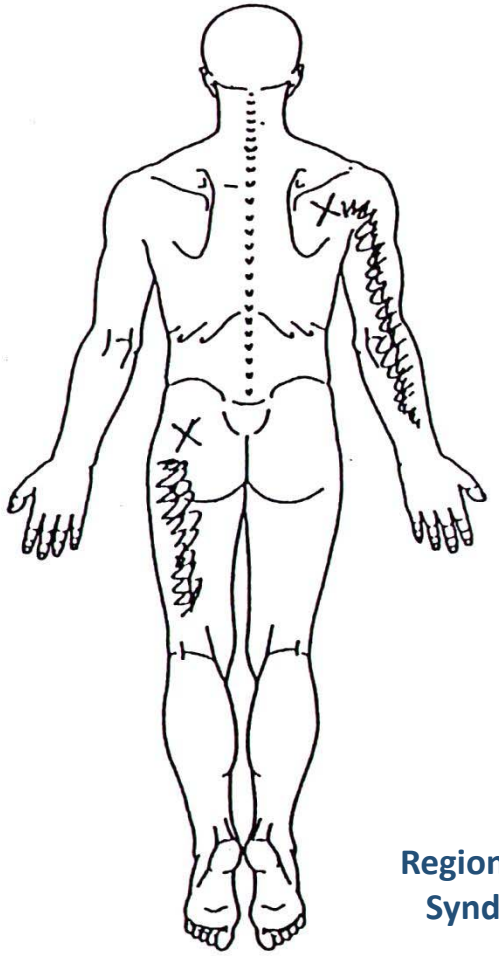
M.-A. Fitzcharles and P. Boulos

Rheumatology 2003;42:263–267

Pain Diagram

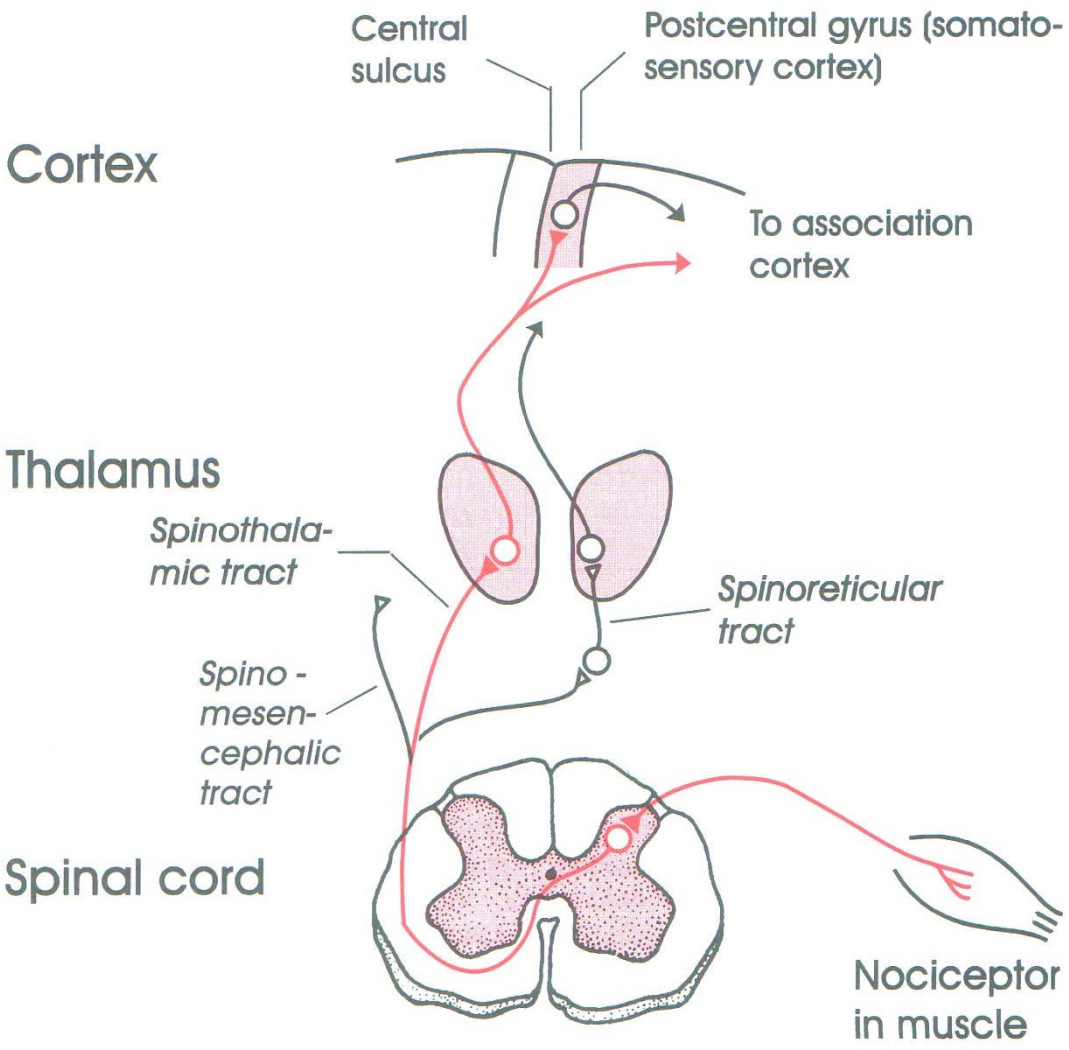


FMS and /or Global Pain Syndrome

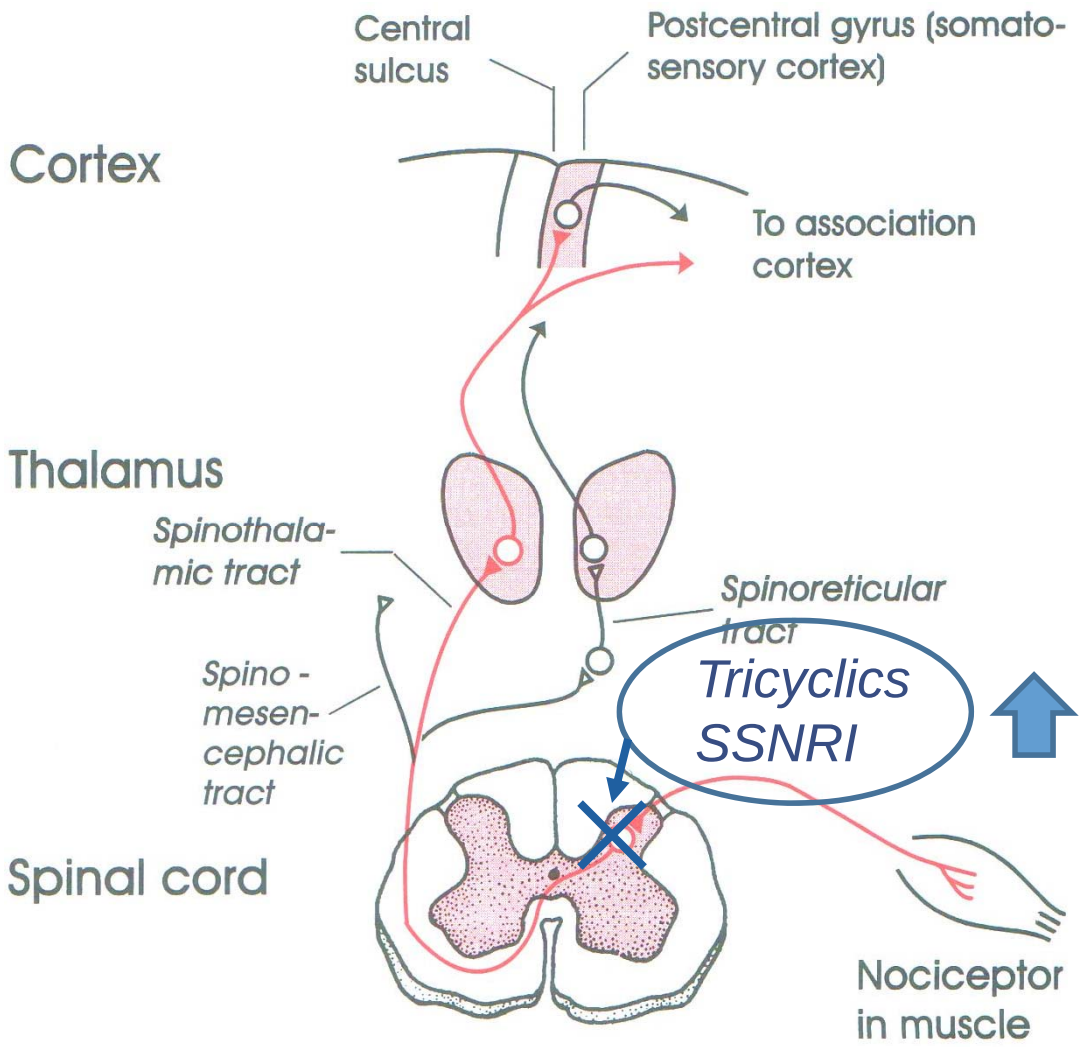


Regional Pain Syndrome

The Muscle Pain Pathway: Spinothalamic Tract

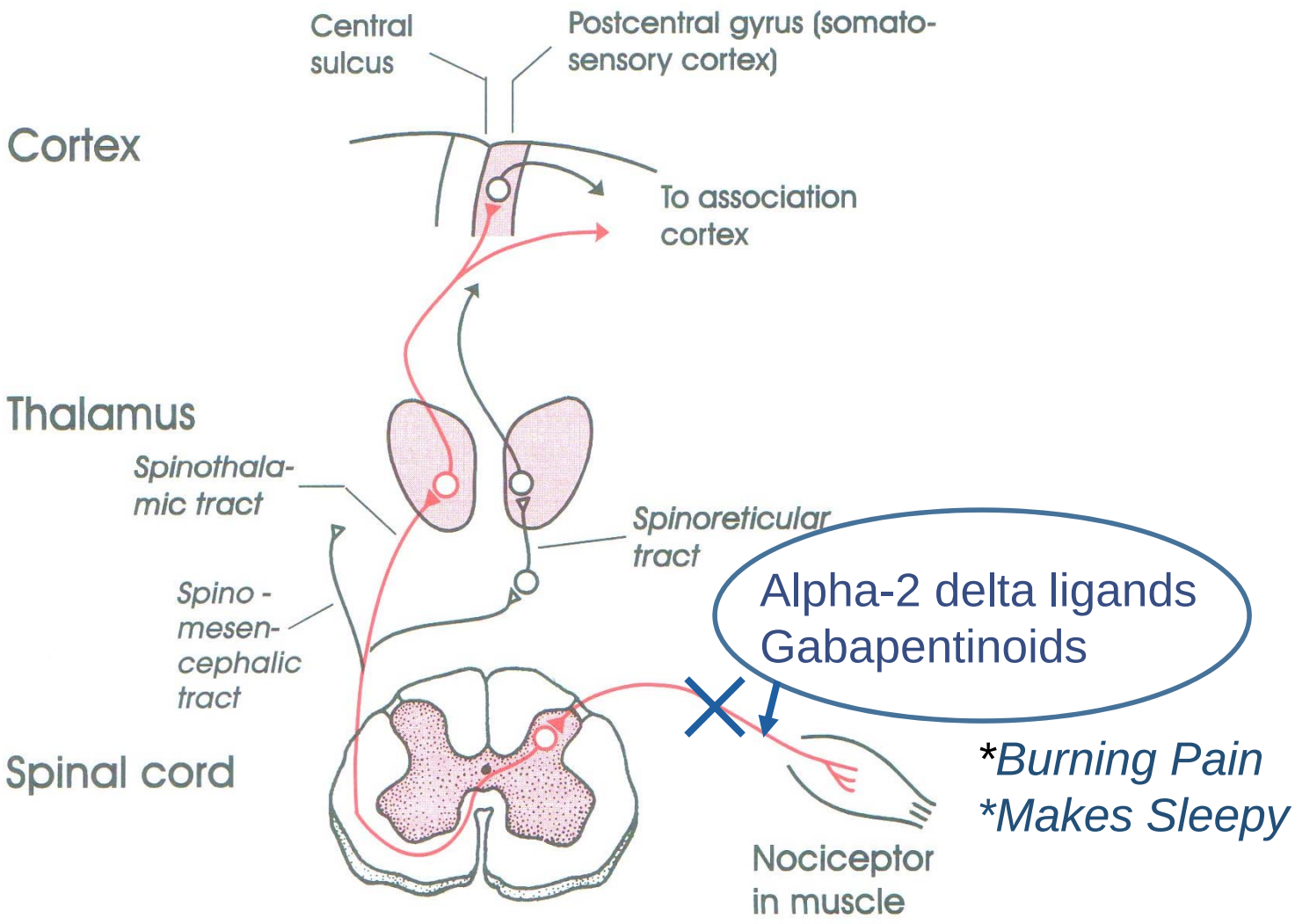


The Muscle Pain Pathway: Spinothalamic Tract



**Seems to have benefit for limited amount of time in about 25% of subjects*

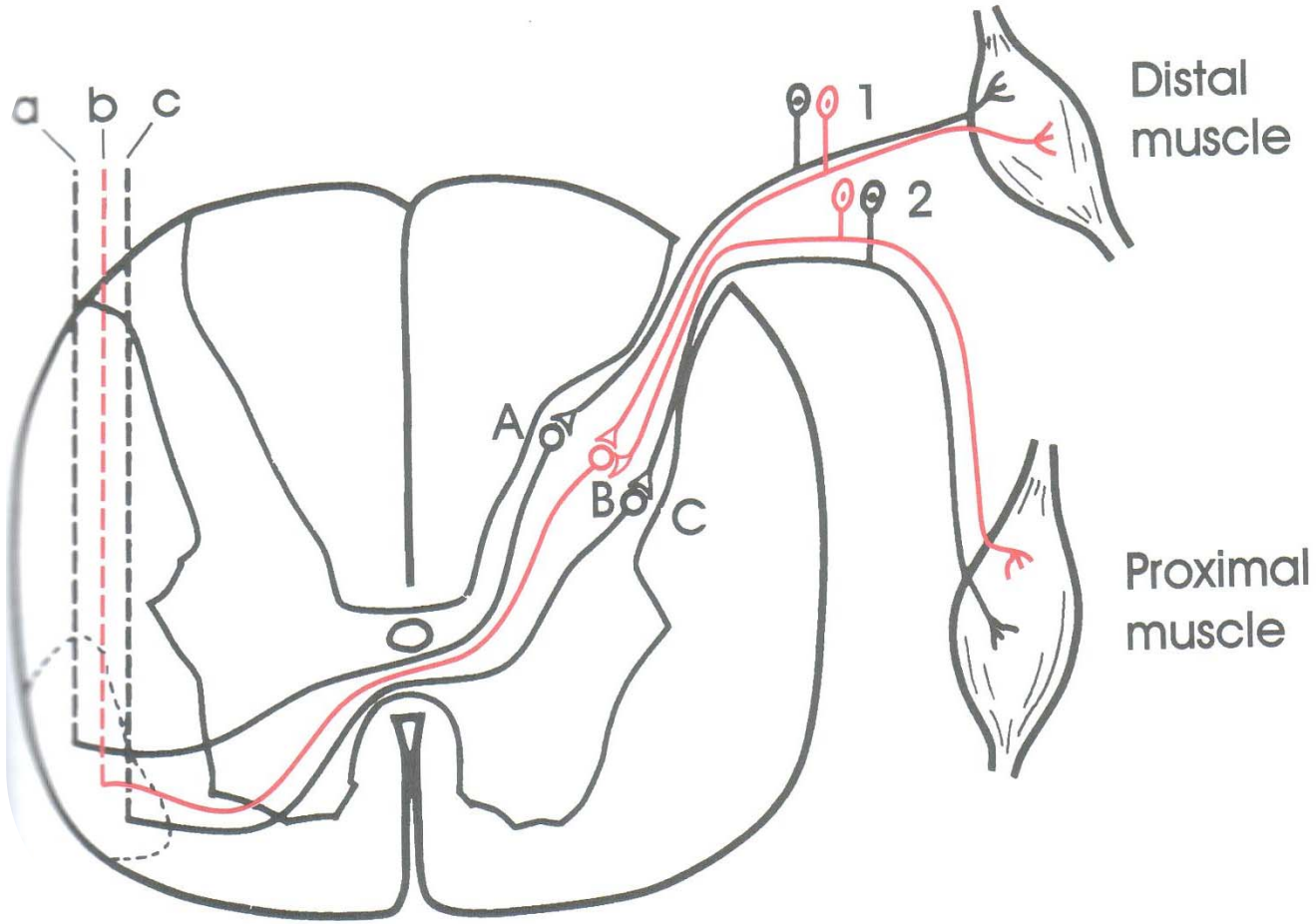
The Muscle Pain Pathway: Spinothalamic Tract



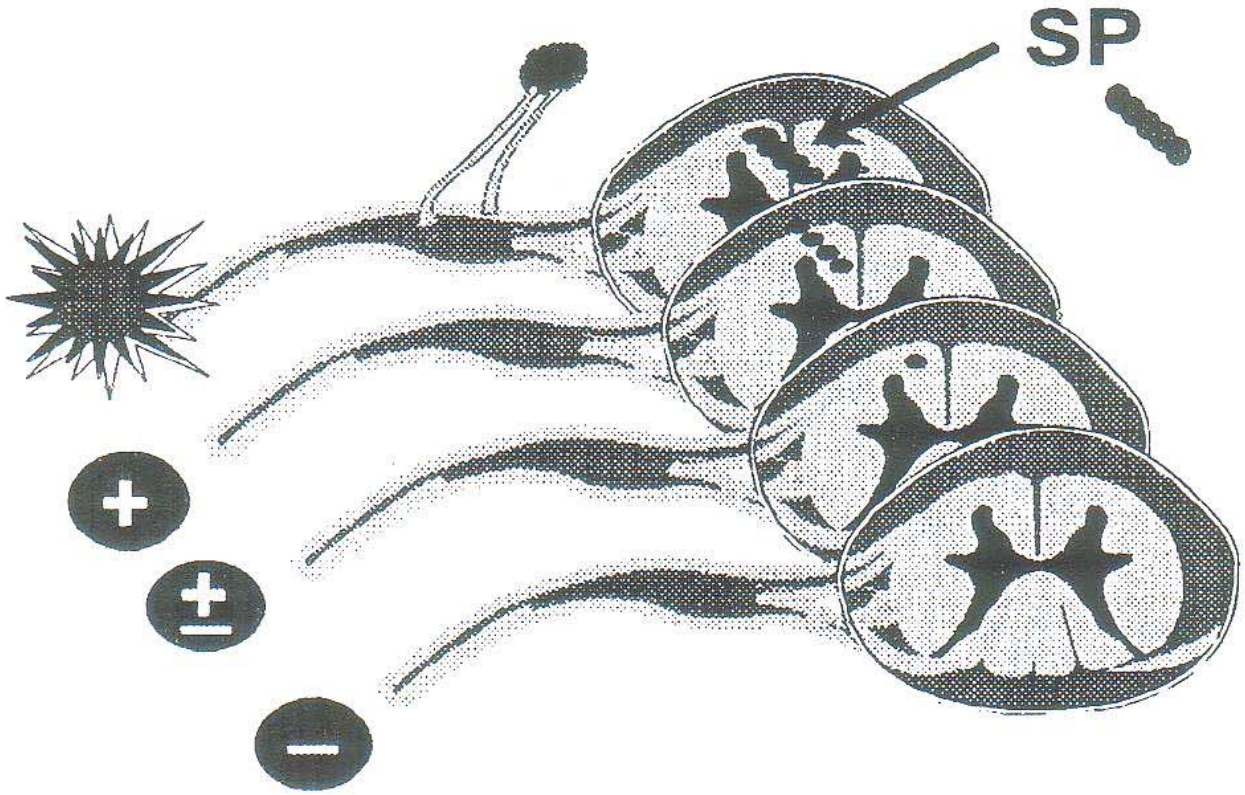
The Spinal Cord

- The spinal cord can be viewed as a “peripheral brain”; it contains both grey and white matter.
- Interneurons within the dorsal horn integrate and modify all incoming sensory input.
- Grey matter of the spinal cord is capable of associative conditioning or “learning.”
- Complexity of the cord’s interneuronal connections allow for the phenomenon of referred pain to occur.

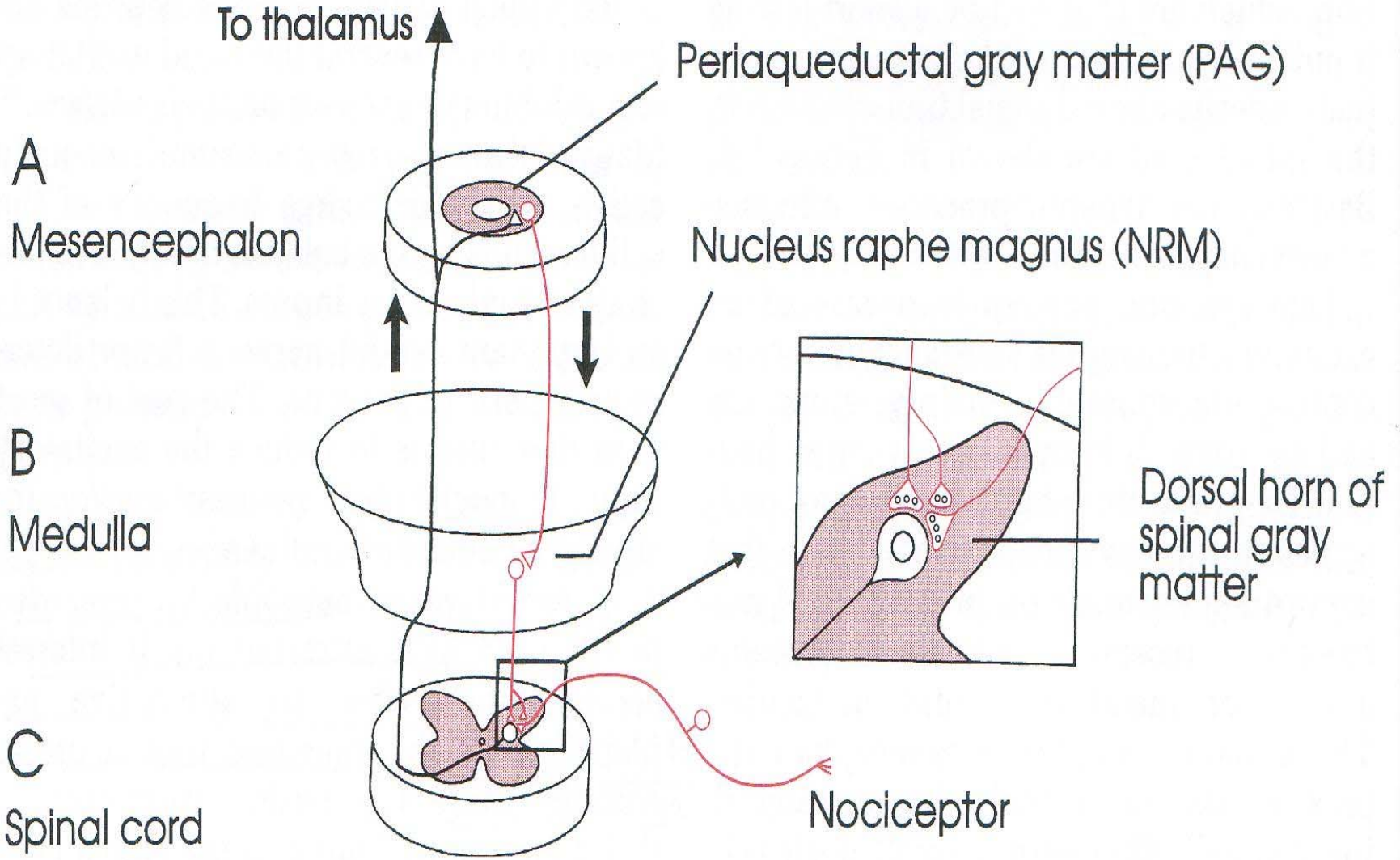
Simplified Convergence-Projection Theory of Referred Pain



Spread of Pain to Normal Tissues by Spillover of Substance P



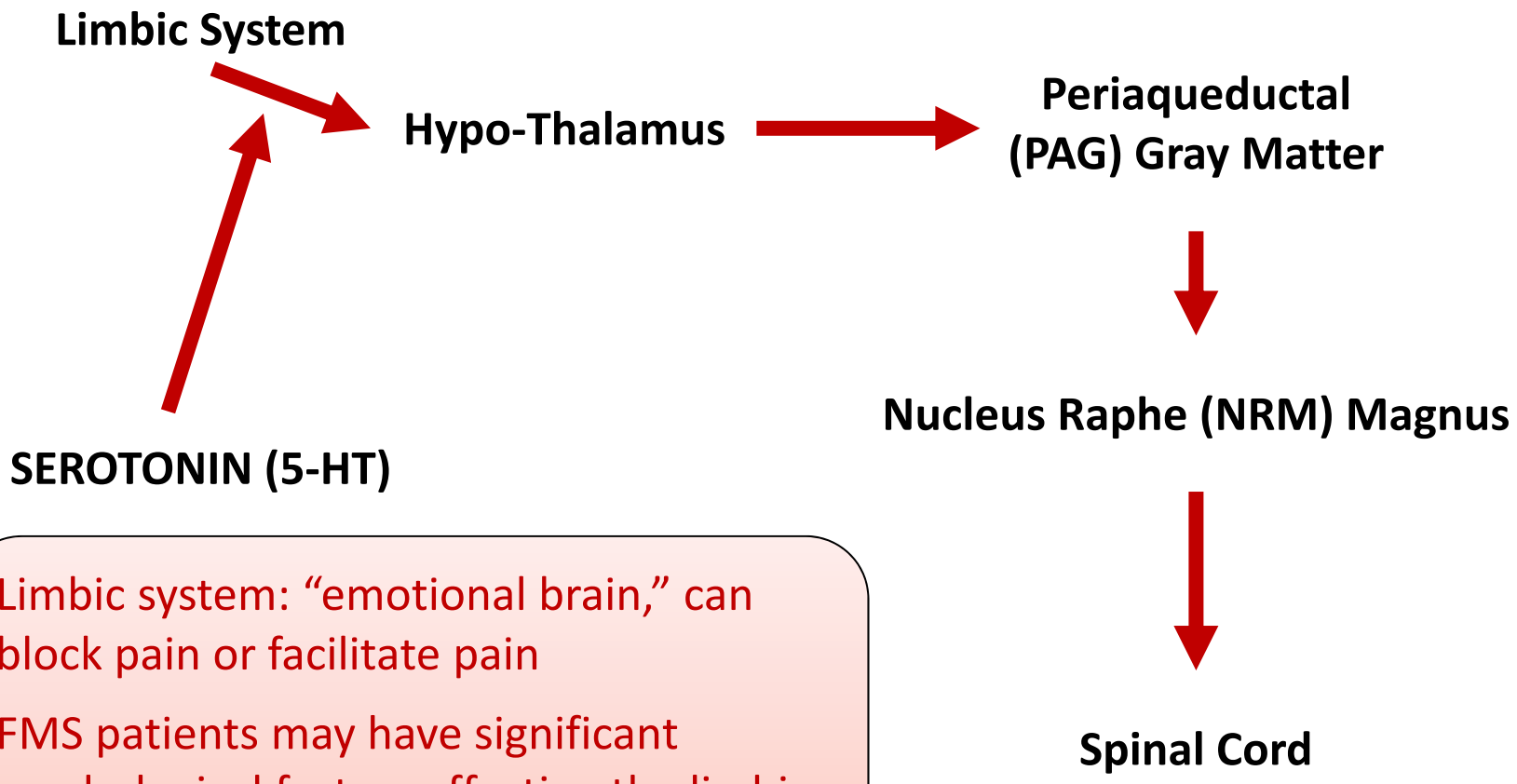
Descending Antinociceptive System



Dysfunction of the DANS is now Thought to be the Major Cause of Non-Responsive Chronic Pain Syndromes by the Major Researchers in the Field

Julien N, et al. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. 2005;114:295-302.

Descending Antinociceptive System

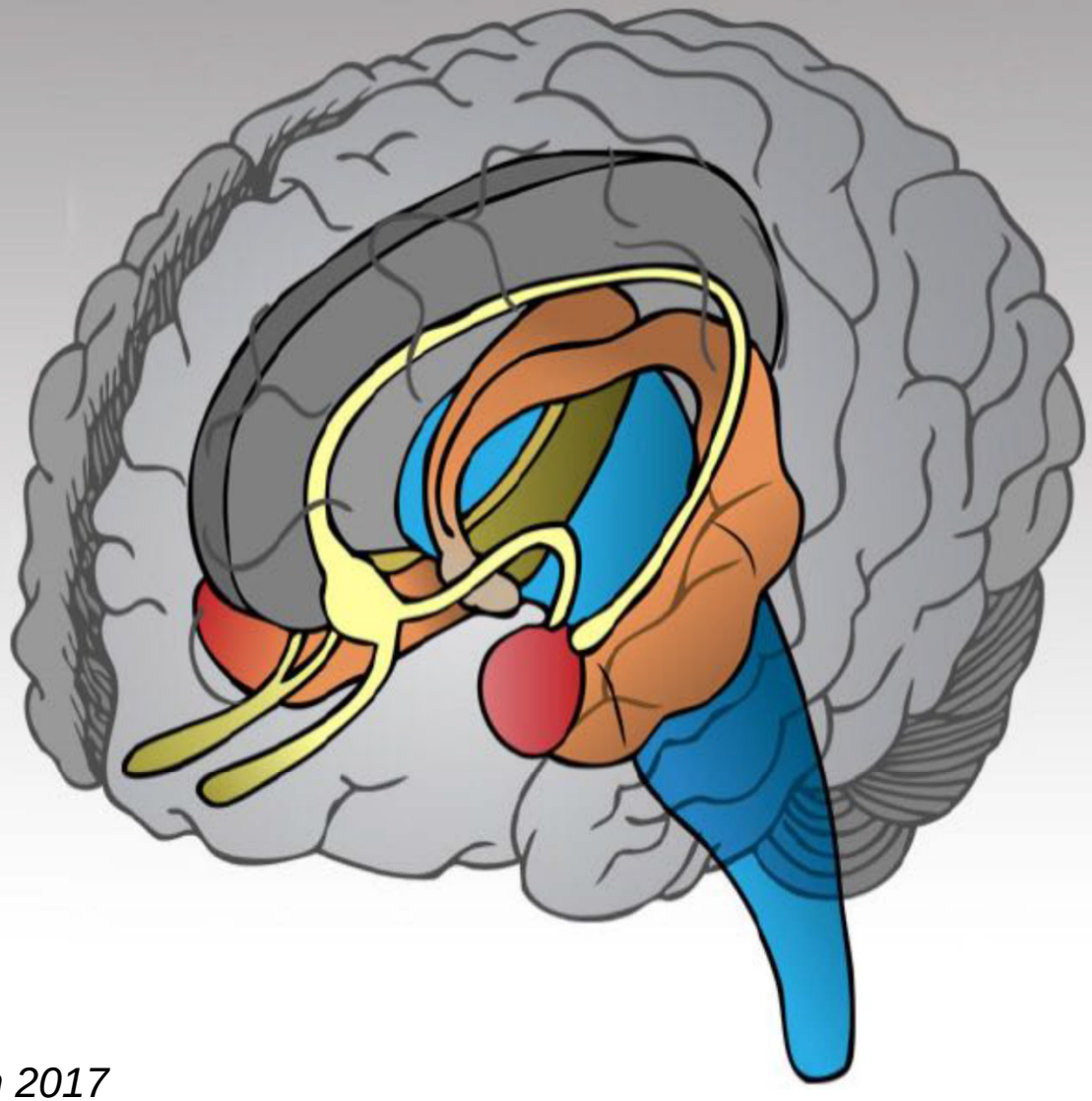


Limbic system: “emotional brain,” can block pain or facilitate pain

FMS patients may have significant psychological factors affecting the limbic system, which may dampen the *DANS.*

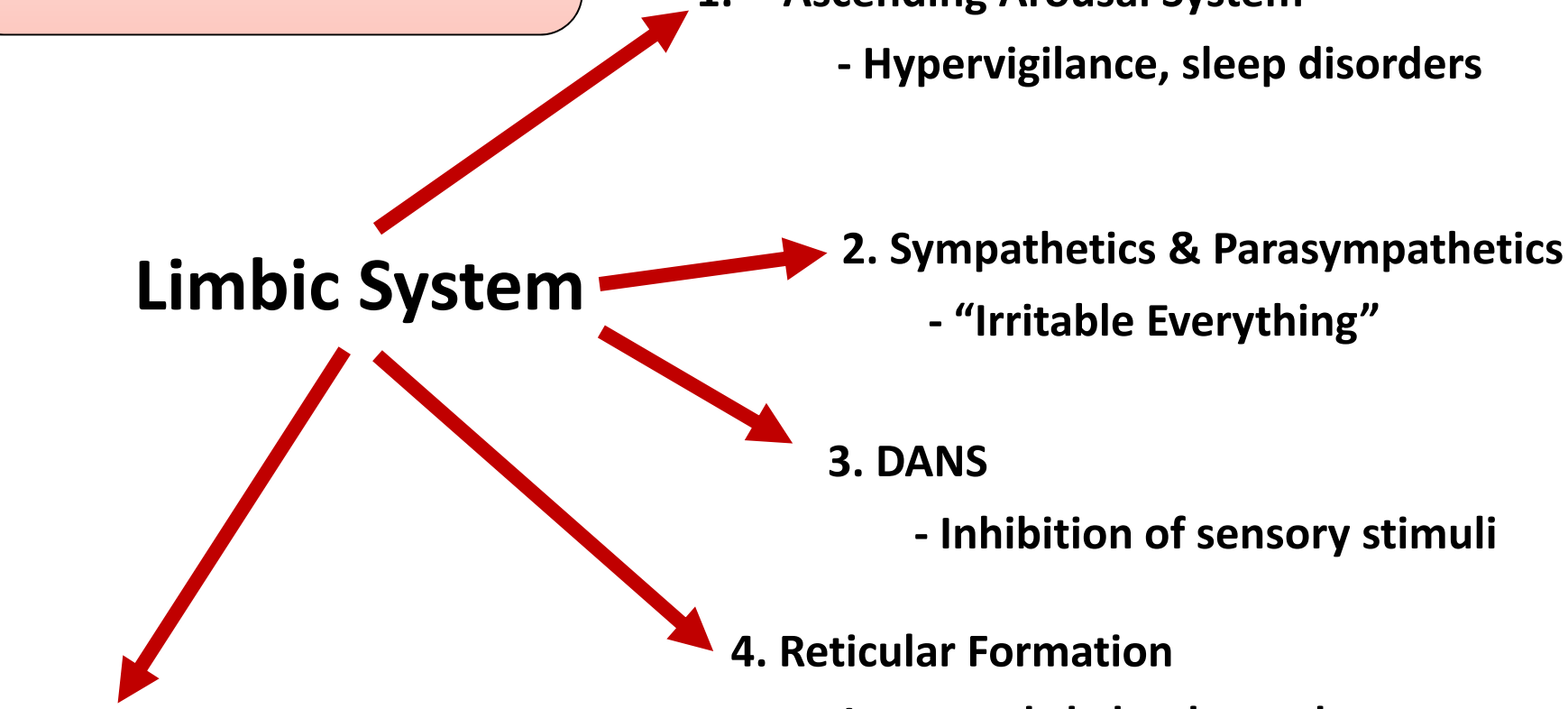
The Limbic System

Our Center for SENSORY Perception



From: Hopper, A.-IFM-AIC Presentation 2017

Every Symptom of FMS!



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Early adverse life events are associated with altered brain network architecture in a sex- dependent manner

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[e] Ahmanson-Lovelace Brain Mapping Center, UCLA, Los Angeles, CA, United States
[f] Department of Integrative Medicine, GLA VHA, Los Angeles, CA, United States
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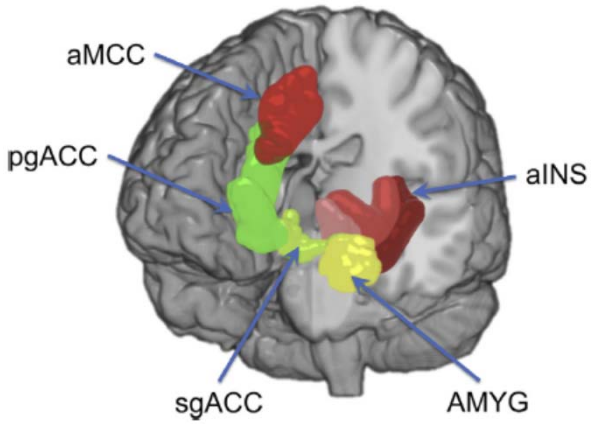

Early adverse life events change the brain in a sex-dependent manner. Childhood traumas affect women much differently than men resulting in altered brain structure leading to psychological issues as an adult as well as a heightened response to pain. When working with female patients who have depression, anxiety, pain, autonomic/HPA axis dysfunction always take a thorough trauma history which will usually reveal a variety of physical and/or emotional traumas when they were young.

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E-mail address: AGupta@mednet.ucla.edu (A. Gupta).

EALs can be associated with early epigenetic changes (Cottrell and Seckl, 2009; Bale et al., 2010; Teicher et al., 2002, 2003; Teicher and Samson, 2016), long lasting changes in brain development, and changes in myelination, neurogenesis, and synaptic branching

http://dx.doi.org/10.1016/j.ynstr.2017.02.003

THE JOURNAL OF FAMILY PRACTICE

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The authors reported no potential conflict of interest relevant to this article.

A new paradigm for pain?

A new way of thinking about pain that occurs in the absence of a pathophysiologic process or injury may alter our approach to conditions like fibromyalgia.

The care of people with pain has been wrought with ineffective and unnecessary treatment, including the misuse of opioids, largely because we do not have an accurate conceptualization of pain. The absence of animal and human models of central nervous system (CNS) pain processing ensures that our understanding of pain will remain incomplete for the foreseeable future, but enough evidence exists to help family physicians develop an understanding of pain that goes beyond what we learned in medical school and that can help us more effectively treat patients with pain.

In this review, we will briefly discuss the established concepts of nociceptive and neuropathic pain. And then, with those concepts in mind, we will explore a third type of pain that for lack of a better term, we will call "pain for psychological reasons." We hypothesize that this pain may be the consequence of changes in nervous system function that arise from developmental trauma, other traumatic experiences in a patient's life, or mental health disorders. It is this third type of pain that may offer us insights into conditions such as fibromyalgia.

While we do not yet have validated diagnostic criteria for this third type of pain, we believe that there is enough information to present initial criteria so that one may distinguish it from nociceptive and neuropathic pain.

Nociceptive and neuropathic pain: The current paradigm

Nociceptive pain. The sensory pain experience, or nociceptive pain, is produced by noxious stimuli that either damage, or are capable of damaging, tissues (eg, burns, cuts, fractures, inflammation, and increased pressure in a hollow viscus). Noxious stimuli are detected at the molecular level by specific pain sensory receptors embedded in our tissues called nociceptors.

The process by which noxious stimuli lead to the experience of sensory pain consists of 4 steps—transduction, transmission, modulation, and perception—which are described in "From periphery to brain: The process of nociceptive pain,"[1-4] on page 600.

Neuropathic pain. While nociceptive pain can be easily traced from a peripheral nociceptive fiber to the brain and typically resolves when the nociceptive stimulus stops, neuropathic pain (NPP) results from changes to the function of the nervous system and is typically caused by injury to the nerves. Such changes, referred to as neuronal sensitization, may not quickly resolve, as is the case with postherpetic neuralgia. In fact, the changes can become permanent. NPP fundamentally differs from nociceptive pain because it results from changes in the central processing of pain that can lead a person to perceive pain sensations even in the absence of tissue pathology.

Common causes of NPP that persists even after tissue damage has healed include trauma (eg, amputation of a limb), ischemia (eg, pressure palsy), disease (eg, the metabolic injury of diabetes or the injury caused by a shingles infection), and drug treatment (eg, chemotherapy). The underlying mechanisms of NPP and the neuronal plasticity (the ability of the nervous system to rewire itself)

TABLE 2

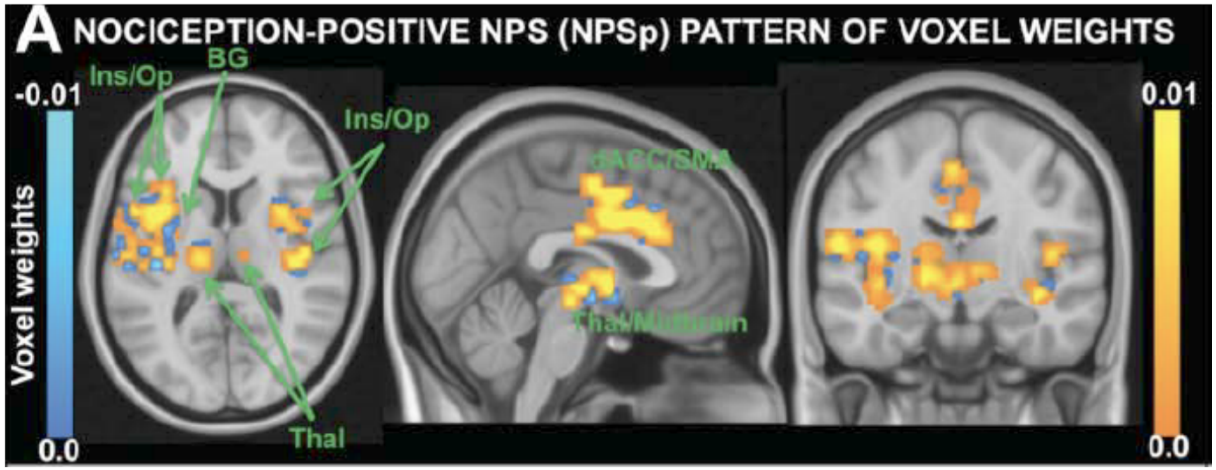
When to suspect ramped-up emotional pain processing[9]

- Patient reports disability that seems out of proportion to physical pathology.
- Pain behaviors seem out of proportion to the physical pathology (eg, grimacing, groaning, crying out with light palpation, protected movement).
- Patient uses emotionally charged language to describe the pain. (Patient says, "I cry in pain.")
- Patient uses emotionally charged pain descriptors such as "sickening," "fearful," and especially "punishing" or "cruel." (For more examples, see the Short-Form McGill Pain Questionnaire available at: https://www.esahq.org/~/media/ESA/Files/ClinicalTrialNetwork/PLATA/Docs/04A%20Appendix4A-PLATAManuscript%20sfMGPQ%20v10%2025FEB2013.ashx.)
- The patient complains of diffuse pain without evidence of a systemic cause.
- The patient describes multiple (and often vague) non-painful somatic complaints across several systems that often include irritable bowel and vague neurologic symptoms.

This third type of pain may be the consequence of changes in nervous system function that arise from developmental trauma, other traumatic experiences in a patient's life, or mental health disorders.

Neural signature for fibromyalgia may aid diagnosis, treatment

A brain signature that identifies fibromyalgia sufferers with 93 percent accuracy has been discovered by researchers, a potential breakthrough for future clinical diagnosis and treatment of the highly prevalent condition.



An MRI image showing the multivariate brain pattern that predicts fibromyalgia status on the basis of brain activation during multisensory stimulation.

Marina López-Solà, Choong-Wan Woo, Jesus Pujol, Joan Deus, Ben J. Harrison, Jordi Monfort, Tor D. Wager. **Towards a neurophysiological signature for fibromyalgia**. *PAIN*, 2016; 1 DOI: 10.1097/j.pain.0000000000000707

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 529–538
DOI 10.1002/art.37734

Low-Dose Naltrexone for the Treatment of Fibromyalgia

Findings of a Small, Randomized, Double-Blind, Placebo-Controlled, Counterbalanced, Crossover Trial Assessing Daily Pain Levels

Jarred Younger,

Objective. **To determine wh**
(4.5 mg/day) of naltrexone reduce fi
as compared with the nonspecific ef
this replication and extension study
ical trial, we tested the impact of low
daily self-reported pain. Secondary
general satisfaction with life, positiv
ity, and fatigue.

Methods. **Thirty-one women**
participated in the randomized, dou
controlled, counterbalanced, crosso
the active drug phase, participants
oral naltrexone daily. An intensive
was used to measure daily levels of

Results. **When contrasting**
points, we observed a significantly g
baseline pain in those taking low-d
in those taking placebo (28.8% reduction versus 18.0%
reduction; $P = 0.016$). Low-dose naltrexone was also
associated with improved general sa
($P = 0.045$) and with improved mo
not improved fatigue or sleep. Th
participants met the criteria for res
significant reduction in pain plus a
tion in either fatigue or sleep proble

ClinicalTrials.gov identifier: NCT005
Supported by a grant from the Ame
drome Association, with additional support
Binns, the Oxnard Foundation, the Chris
Endowment Fund, and the Rosekrans Pain
Fund.

Jarred Younger, PhD, Noorulain No
BA, Sean Mackey, MD, PhD: Stanford Univer
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Submitted for publication January
vised form September 27, 2012.

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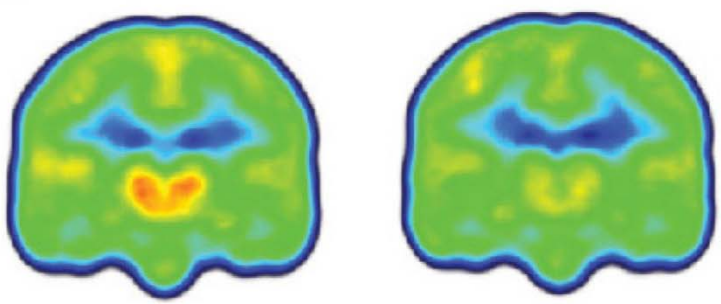
Conclusion. **The preliminary evidence continues to show that low-dose naltrexone has a specific and clinically beneficial impact on fibromyalgia pain. The medication is widely available, inexpensive, safe, and well-tolerated. Parallel-group randomized controlled trials are needed to fully determine the efficacy of the medication.**

sclerosis (6). The use of naltrexone at this dosage range

naltrexone may work to reduce disease severity by attenuating inflammatory processes (8). This antiinflammatory effect is distinct from the better-known effect of naltrexone in the blockade of neuronal opioid receptors and may instead involve the antagonism of immune cell receptors, including microglia in the central nervous system (9,10).

Imaging study finds first evidence of neuroinflammation in brains of chronic pain patients

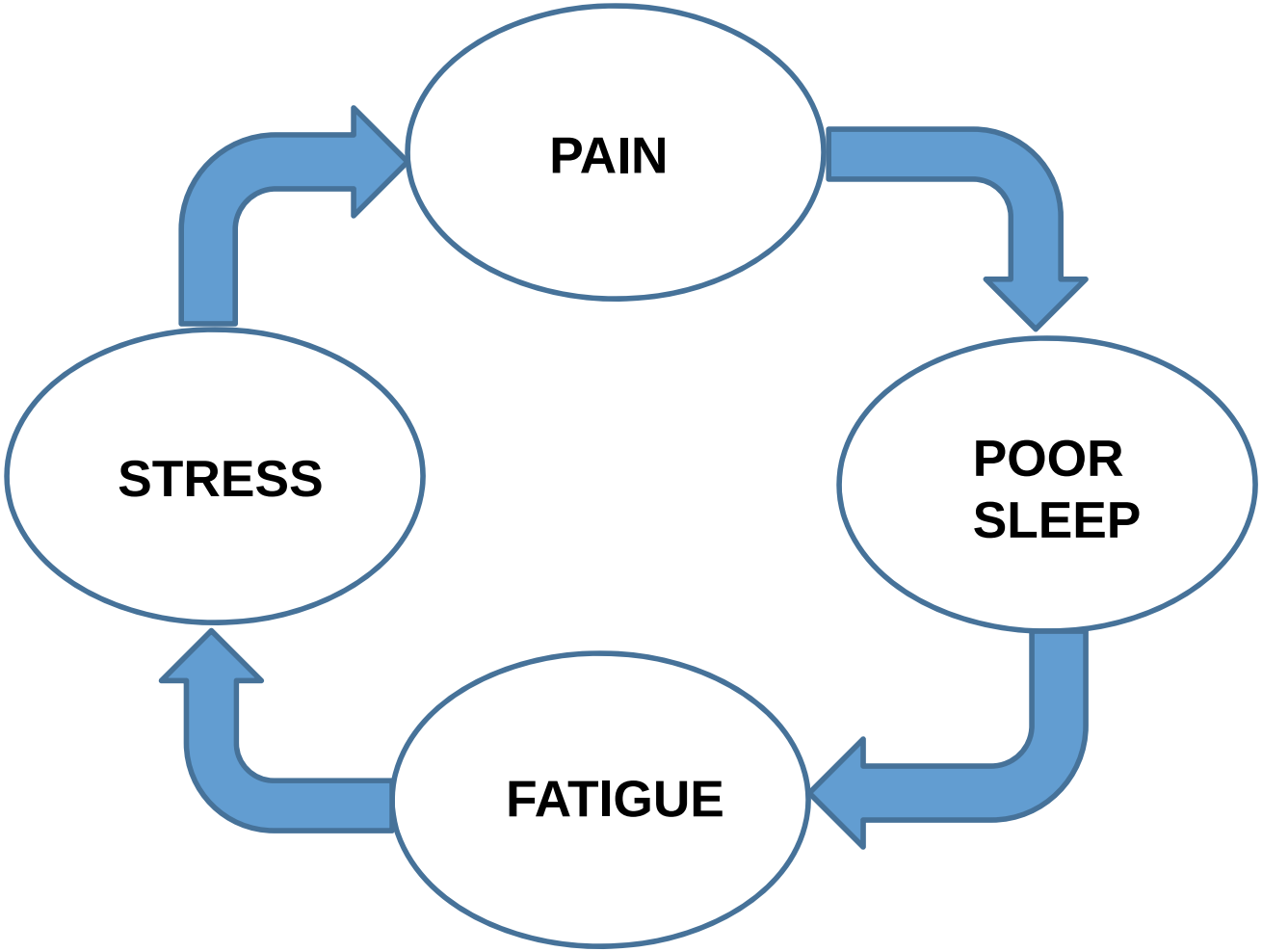


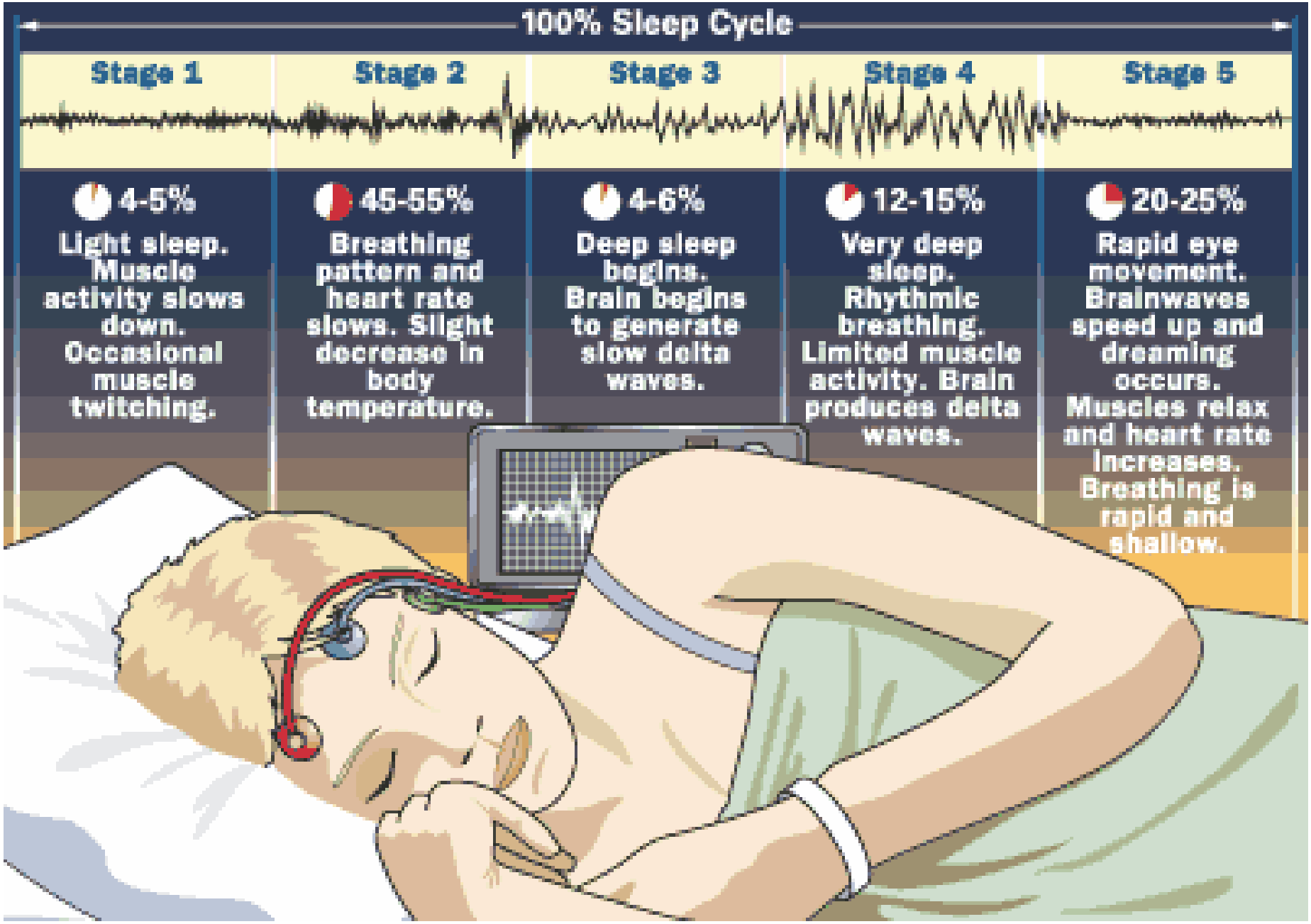
Images created by averaging PET scan data from chronic pain patients (left) and healthy controls (right) reveals higher levels of inflammation-associated translocator protein (orange/red) in the thalamus and other brain regions of chronic …more

"Finding increased levels of the translocator protein in regions like the thalamus - the brain's sensory gateway for pain and other stimuli - is important, since we know that this protein is highly expressed in microglia and astrocytes, the immune cells of the central nervous system, when they are activated in response to some pathologic event," says Marco Loggia, PhD, of the MGH-based Martinos Center for Biomedical Imaging, lead author of the report.

A new study from Massachusetts General Hospital (MGH) investigators has found, for the first time, evidence of neuroinflammation in key regions of the brains of patients with chronic pain. By showing that levels of an inflammation-linked protein are elevated in regions known to be involved in the transmission of pain, the study published online in the journal *Brain* paves the way for the exploration of potential new treatment strategies and identifies a possible way around one of the most frustrating limitations in the study and treatment of chronic pain - the lack of an objective way to measure the presence or intensity of pain.

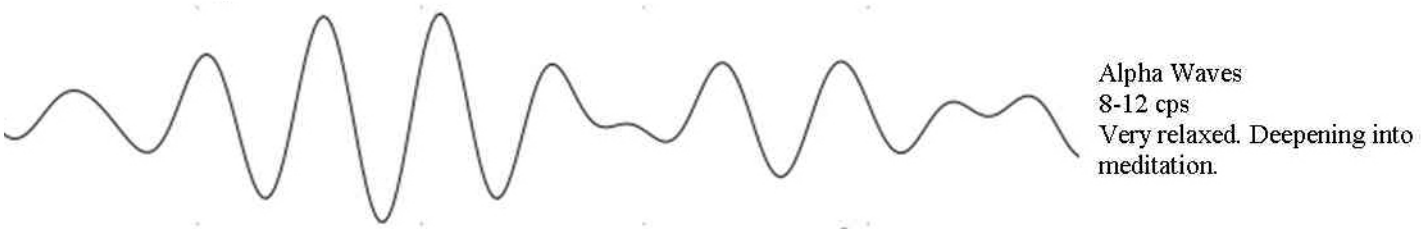
Loggia M et al. Evidence for brain glial activation in chronic pain. Brain, 2015, Jan 12.


PAIN
POOR SLEEP
FATIGUE
STRESS


100% Sleep Cycle
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
4-5%
Light sleep. Muscle activity slows down. Occasional muscle twitching.
45-55%
Breathing pattern and heart rate slows. Slight decrease in body temperature.
4-6%
Deep sleep begins. Brain begins to generate slow delta waves.
12-15%
Very deep sleep. Rhythmic breathing. Limited muscle activity. Brain produces delta waves.
20-25%
Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate increases. Breathing is rapid and shallow.

Sleep Dysfunction in FM and Other Chronic Pain Syndromes

- Non-restorative sleep is a major symptom of FM and correlates with the global achiness/TPI
- Typical EEG pattern of "alpha wave intrusion" during non-REM delta wave sleep
- Most intense delta activity is in the frontal lobes of the cortex
- Frontal lobe hypoactivity during waking state is associated with inability to concentrate or focus attention (i.e., Fibro-Fog).



Blocking Blue Light Helps Sleep

Nighttime exposure to artificial light disrupts sleep.

Shift workers are at especially high risk for circadian rhythm disruptions, because of their non-traditional schedules. In a study by scientists at Quebec's Universite Laval, nightshift workers used (http://www.ncbi.nlm.nih.gov/pubmed/19637050) blue-light blocking glasses at or near the end of their overnight shifts for 4 weeks. At the end of study period, their overall sleep amounts increased, as did their sleep efficiency.

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Chronobiology International, 26(8): 1602–1612, (2009)

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DOI: 10.3109/07420520903523719

informa
healthcare

AMBER LENSES TO BLOCK BLUE LIGHT AND IMPROVE SLEEP: A RANDOMIZED TRIAL

Kimberly Burkhart[1] and James R. Phelps[2]

[1]*Graduate Student in Clinical Psychology, University of Toledo, Ohio, USA*
[2]*Samaritan Mental Health, Corvallis, Oregon, USA*

All light is not equal: blue wavelengths are the most potent portion of the visible electromagnetic spectrum for circadian regulation. Therefore, blocking blue light could create a form of physiologic darkness. Because the timing and quantity of light and darkness both affect sleep, evening use of amber lenses to block blue light might affect sleep quality. Mood is also affected by light and sleep; therefore, mood might be affected by blue light blockade. In this study, 20 adult volunteers were randomized to wear either

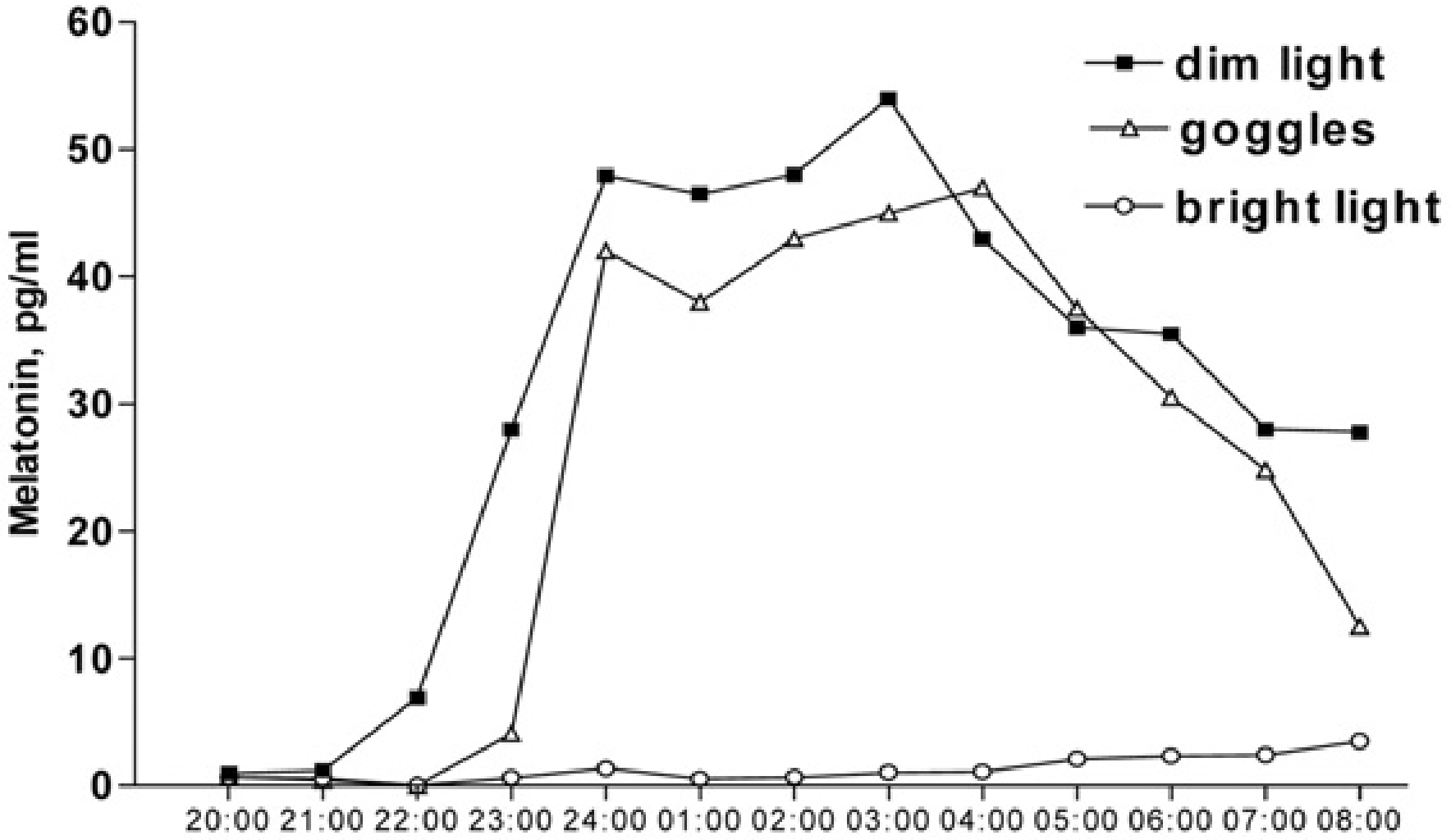
At the end of the study, **the amber lens group experienced significant ($p < .001$) improvement in sleep quality relative to the control group and positive affect ($p = .005$). Mood also improved significantly relative to controls."**

Keywords Insomnia, Sleep quality, Amber lenses, Blue light, Dark therapy

INTRODUCTION

Sleep-onset insomnia (difficulty falling asleep) and mid-sleep insomnia (difficulty staying asleep) are common problems, affecting as many as 30% of the world's population (Mai & Buysse, 2008). In anxiety and mood disorders, insomnia is a prominent and distressing symptom that often exacerbates the condition, and in bipolar disorder, insomnia can be the primary cause of severe mood episodes (Plante & Winkelman, 2008).


PHILIPS


60
50
40
30
20
10
0
Melatonin, pg/ml
dim light
goggles
bright light
20:00 21:00 22:00 23:00 24:00 01:00 02:00 03:00 04:00 05:00 06:00 07:00 08:00

Sleep Hygiene

- In bed by 10pm, up by 7am consistently
- Limit bright/blue-light and electronics 3 hrs. prior to bed
- Dark quiet bedroom with no pets
- No TV, reading or activities in bedroom (other than two!)
- Prayer and progressive relaxation 30 mins. prior to bed

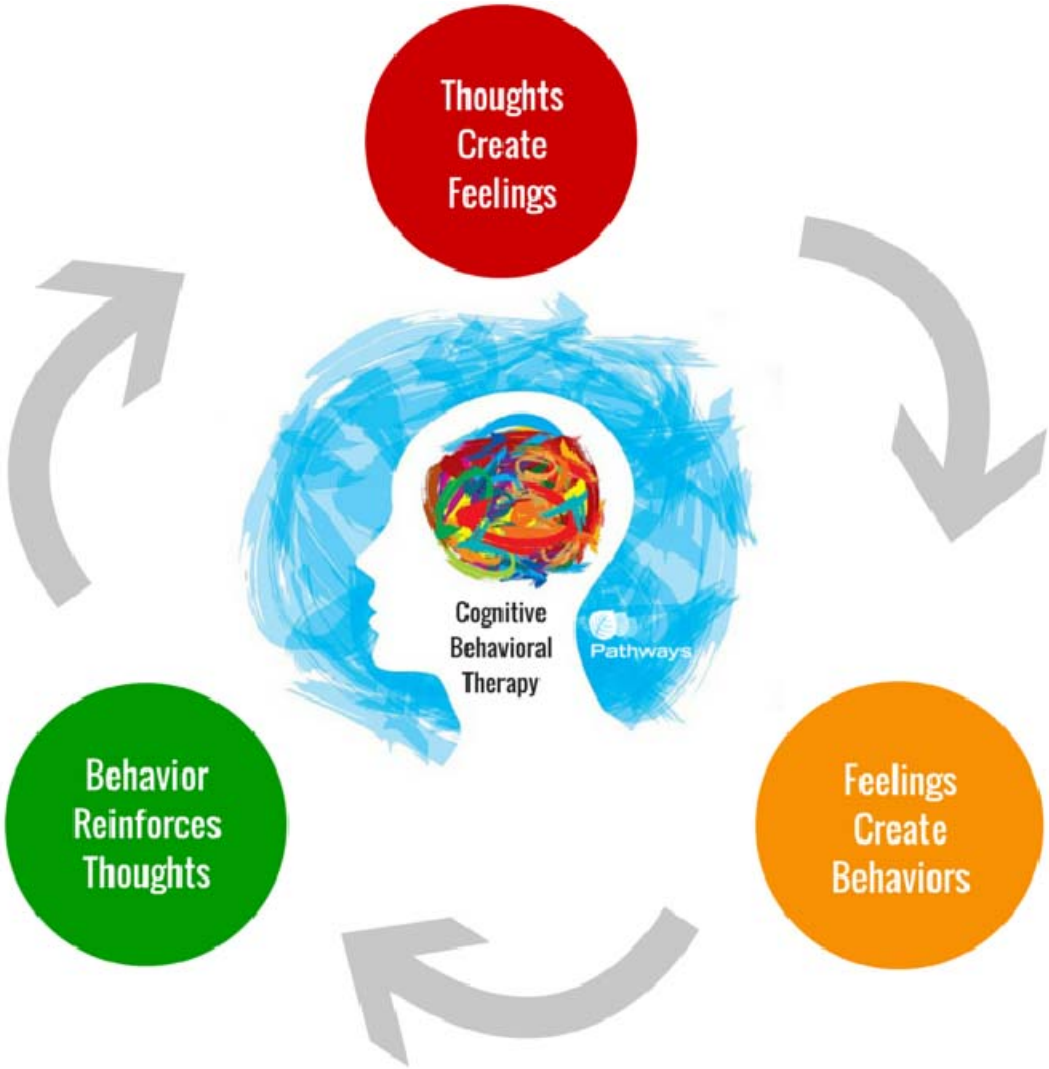
Light Box Therapy

Generally, the light box should:

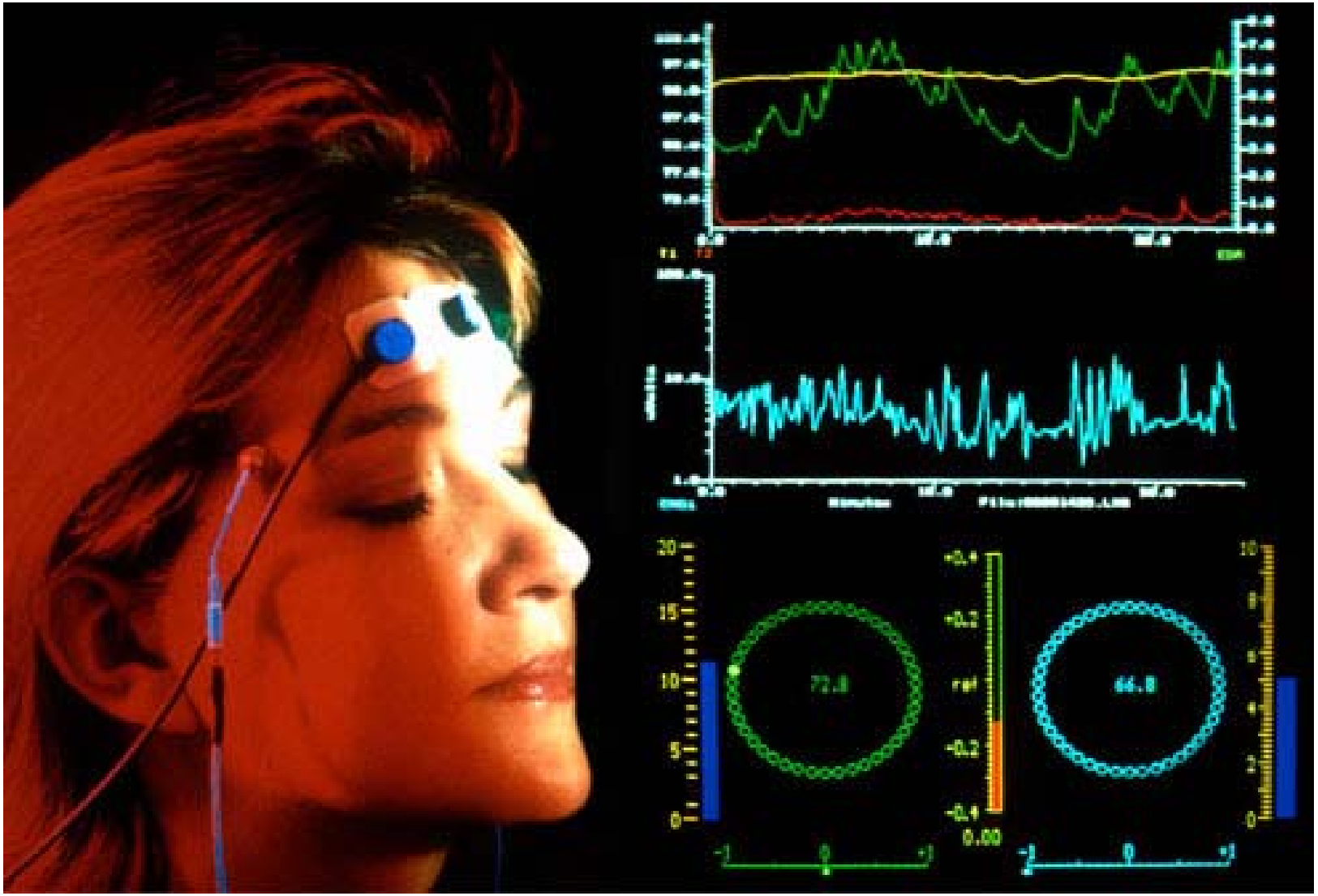
- Provide an exposure to 10,000 lux of light
- Emit as little UV light as possible

Typical recommendations include using the light box:

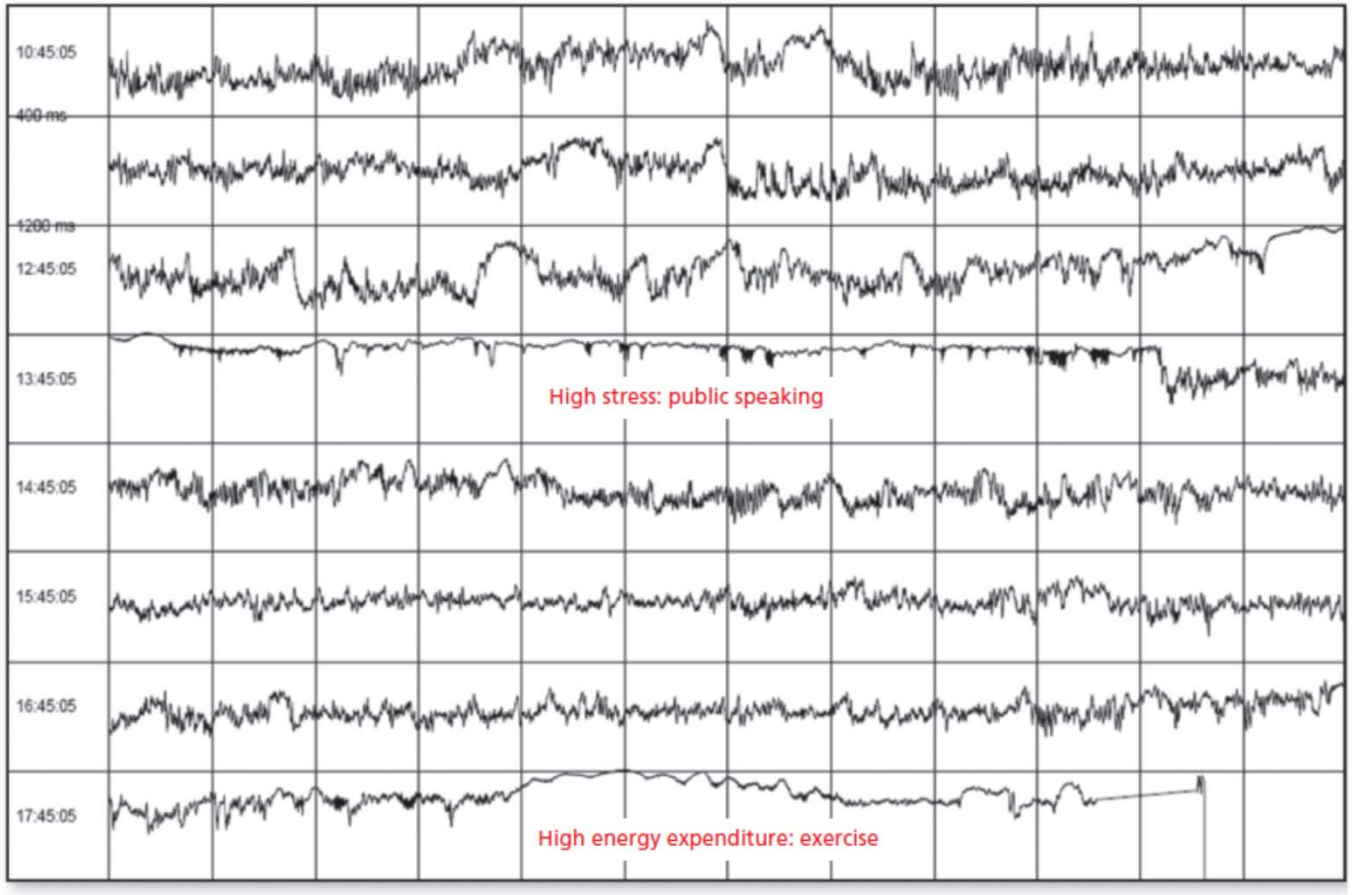
- Within the first hour of waking up in the morning
- For about 20 to 30 minutes
- At a distance of about 16 to 24 inches (41 to 61 centimeters) from the face
- With eyes open, but not looking directly at the light


Thoughts Create Feelings
Feelings Create Behaviors
Behavior Reinforces Thoughts
Cognitive Behavioral Therapy
Pathways

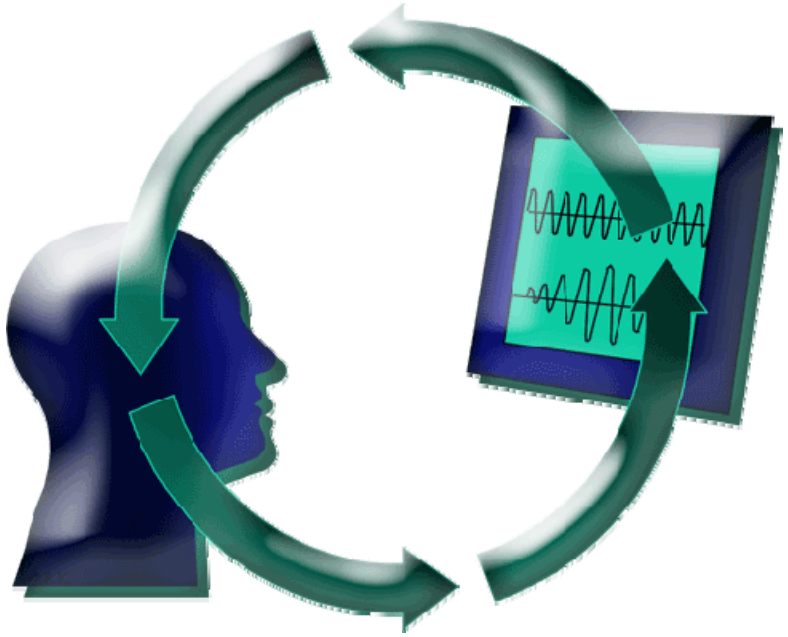
Biofeedback



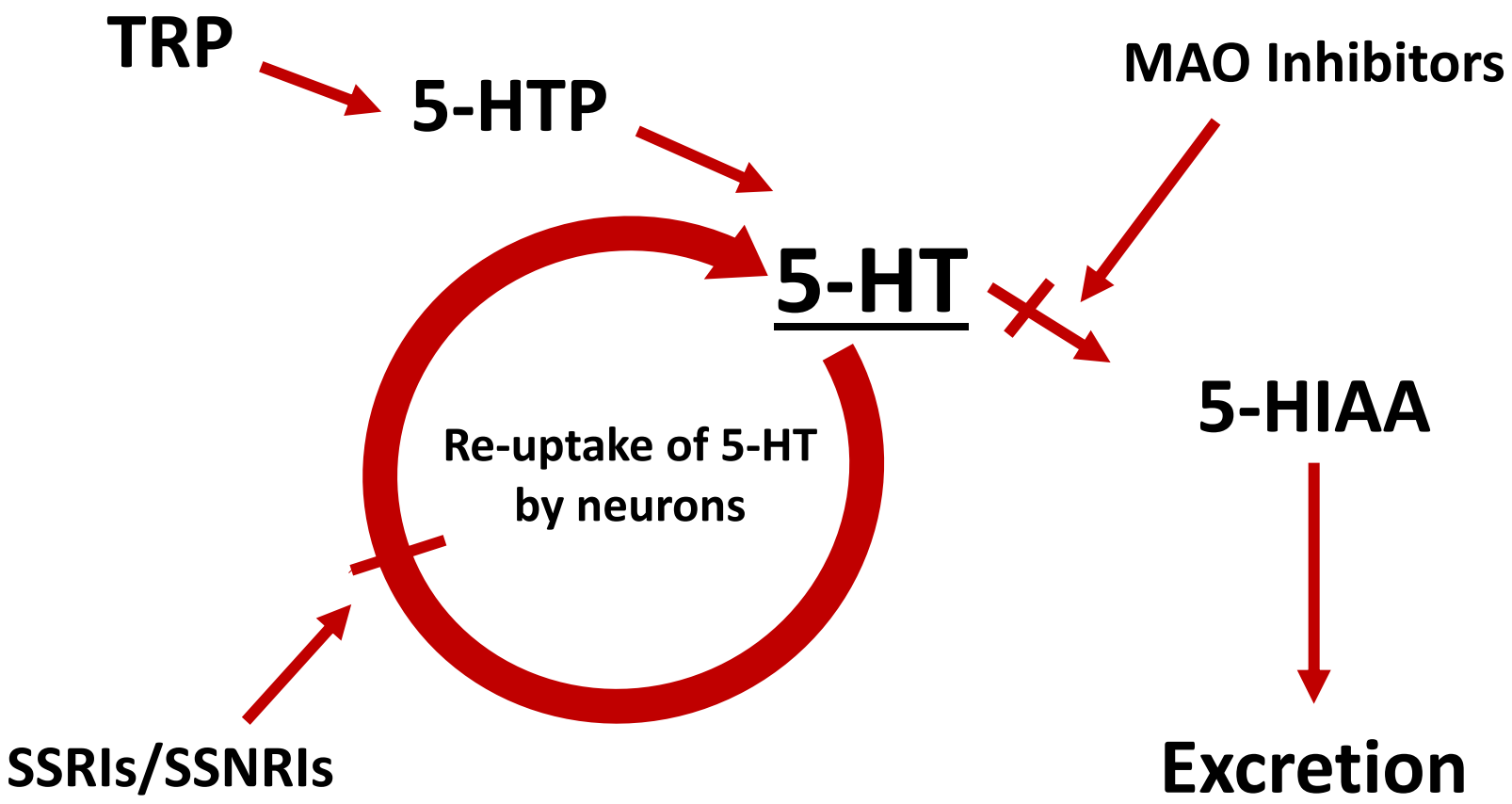
Heart Rate Variability



Biofeedback Made Simple at Home

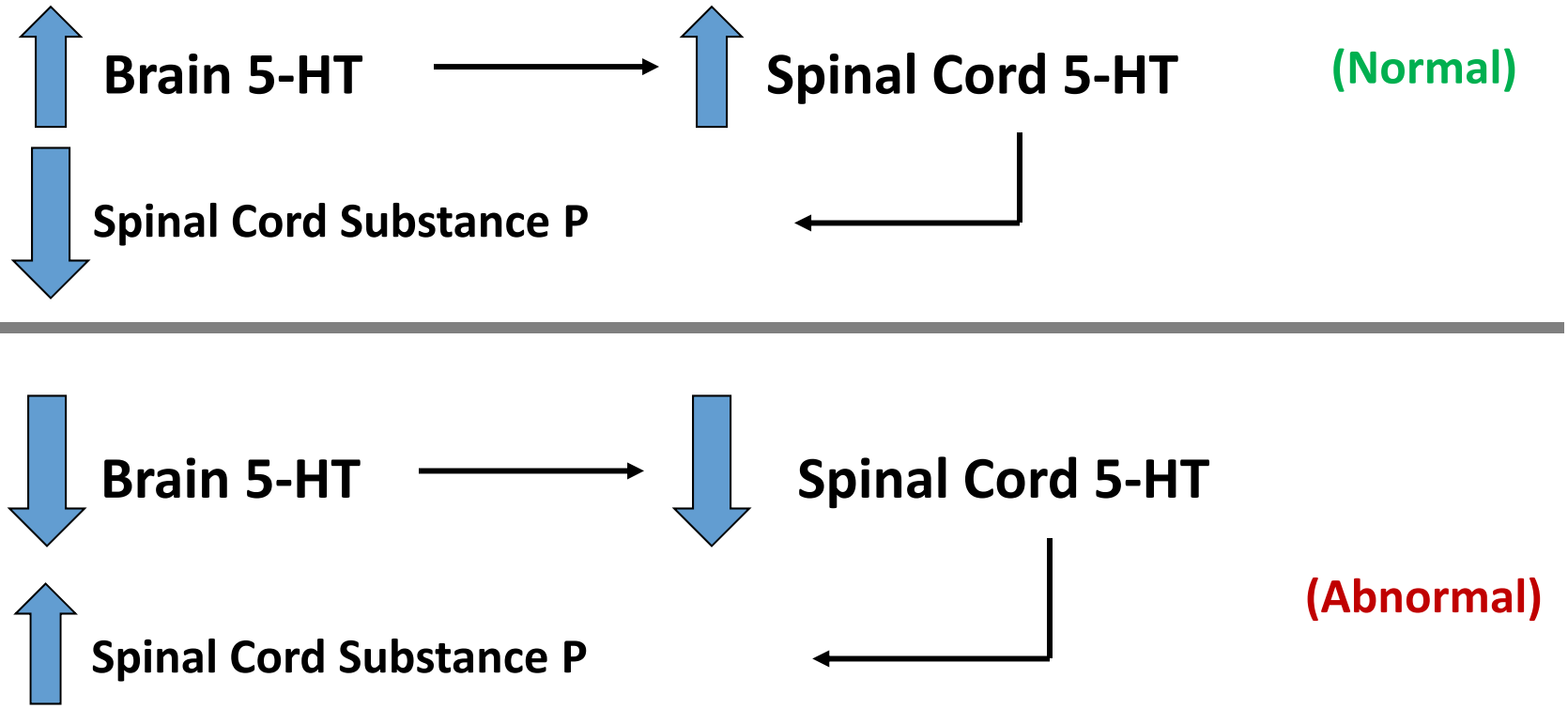


Biochemistry of Serotonin



Serotonin and Substance P

Descending Inhibitory System



FMS = Failure of Descending Inhibitory System?

Classic CRP Treatment

- Serotonin Modulators
  - 5-HTP, melatonin, etc.
  - Antidepressant medications – Tricyclics, SSRIs, SSNRIs, MAOIs, etc.
- Stress & Anxiety Management Management
  - Biofeedback, guided imagery, prayer, meditation, yoga, adrenal therapy, proper sleep, etc.
  - GABA, L-theanine, inositol, calming adaptogenic botanicals
- Nutritional Supplementation
  - Mg, malic acid, etc.

Rossy L A, Buckelew S P, Dorr N, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med. 1999; 21:180-191.

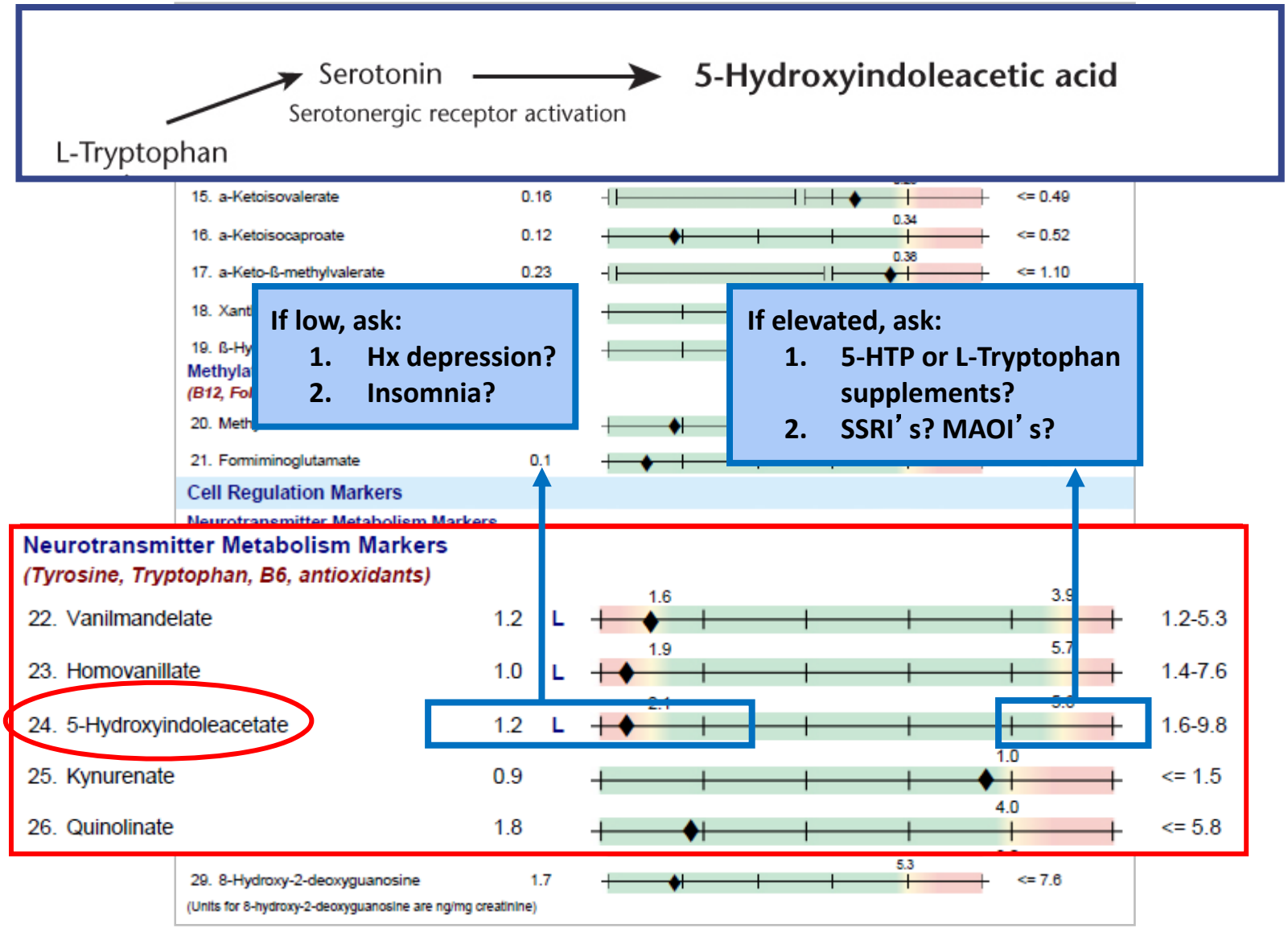
Sim J, Adams N. Systematic review of randomized controlled trials of non-pharmacological interventions for fibromyalgia. Clin J Pain. 2002;18:324-36.

Treatment with 5-HTP

In a randomized, placebo-controlled study of 200 fibromyalgia patients who were also migraine sufferers, 5-HTP (400 mg/d) was compared to a tricyclic drug (amitriptyline) and an MAOI (pargyline or phenelzine). The combination of 5-HTP (200 mg/d) with an MAOI was also evaluated. Patients were treated for a total of 12 months and kept a daily pain dairy by means of a visual analog scale. At the end of the 12-month trial period, all treatment regimens showed significant improvement over placebo ($p < 0.0001$), although the combination of 5-HTP with the MAOI was the most effective. 5-HTP alone was as effective as the tricyclic or MAOI drugs. No patients withdrew from the study due to side effects; 8% of patients taking 5-HTP alone reported some degree of stomach upset.

Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. Serotonin as the common clue for pathogenesis and therapy. Adv Exp Med Biol. 1996;398:373-379.

Neurotransmitter Metabolism



Pharmacopsychiatry. 2016 Oct 4. [Epub ahead of print]

Crocus sativus L. versus Citalopram in the Treatment of Major Depressive Disorder with Anxious Distress: A Double-Blind, Controlled Clinical Trial.

Ghajar A[1], Neishabouri SM[2], Velayati N[1], Jahangard L[2], Matinnia N[3], Haghighi M[2], Ghaleiha A[2], Afarideh M[1], Salimi S[4], Meysamie A[5], Akhondzadeh S[1].

Author information

Abstract

Introduction: Saffron (*Crocus sativus L.*) has demonstrated antidepressant effects in clinical studies and extensive anxiolytic effects in experimental animal models. **Methods:** 66 patients with major depressive disorder accompanied by anxious distress were randomly assigned to receive either saffron (30 mg/day) or citalopram (40 mg/day) for 6 weeks. Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) were used to assess treatment effect during the trial. **Results:** 60 participants finished the study. Patients who received either saffron or citalopram showed significant improvement in scores of the Hamilton Rating Scale for Depression (P-value<0.001 in both groups) and Hamilton Rating Scale for Anxiety (P-value<0.001 in both groups). Comparison of score changes between the 2 trial arms showed no significant difference (P-value=0.984). Frequency of side effects was not significantly different between the 2 groups. **Discussion:** The present study indicates saffron as a potential efficacious and tolerable treatment for major depressive disorder with anxious distress.

Sceletium tortuosum

- The South African plant *Sceletium tortuosum* has been used by the indigenous people for hundreds of years for: Relaxation, Stress, Thirst and Hunger (before long hunting trips), soothing infants from: Colic and teething. Modern science has proven its benefits in: increasing mood state, cognitive function, reducing stress, inducing a calm but not sedative effect. It appears to achieve this by a dual inhibition action, by acting both as an SSRI and by its inhibitory effects on PDE4 (phosphodiesterase 4). PDE4 inhibitors are known to possess procognitive (including long-term memory-improving), wakefulness-promoting,] neuroprotective, and anti-inflammatory effects It has been shown in the research to be non-addictive, as well as showing no dependency or withdrawal symptoms, after 3 months of continuous use.

Terburg D, Syal S, Rosenberger LA, et al. Acute Effects of Sceletium tortuosum (Zembrin), a Dual 5-HT Reuptake and PDE4 Inhibitor, in the Human Amygdala and its Connection to the Hypothalamus. Neuropsychopharmacology. 2013;38(13):2708-2716.

The FASEB Journal article fj.13-246546. Published online February 20, 2014.

The FASEB Journal • Review

Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism

Rhonda P. Patrick[1] and Bruce N. Ames[1]

Nutrition and Metabolism Center, Children's Hospital Oakland Research Institute, Oakland, California, USA

ABSTRACT **Serotonin and vitamin D have been proposed to play a role in autism; however, no causal mechanism has been established. Here, we present evidence that vitamin D hormone (calcitriol) activates the transcription of the serotonin-synthesizing gene tryptophan hydroxylase 2 (*TPH2*) in the brain at a vitamin transcri barrier explains the low elevated brain ba hormon the high of mate peptide associat cin-neu tor, an VDREs and tryp help pr sympto Vitamin 1: relev www.fas**

Here, we present evidence that vitamin D hormone (calcitriol) activates the transcription of the serotonin-synthesizing gene tryptophan hydroxylase 2 (*TPH2*) in the brain at a vitamin D response element (VDRE) and represses the transcription of *TPH1* in tissues outside the blood-brain barrier at a distinct VDRE.

Key Wo munity

AUTISM SPECTRUM DISORDERS (ASDs) cover a range of neurodevelopmental disorders affecting >1% of children born in the United States and are characterized by 3 primary behavioral symptoms: impaired reciprocal social interactions, communication deficits, and propensity for repetitive behaviors (1). Autism prevalence is currently 1 in 88, and the incidence has grown by 600% since the 1970s; however, the fundamental cause of this rapid growth is unknown (2, 3). Better diagnostics and environment.

Four observations are consistently associated with ASD: tissue-specific aberrant serotonin concentrations; low plasma concentrations of the vitamin D hormone precursor 25-hydroxyvitamin D [25(OH)D_3]; high male incidence; and presence of maternal antibodies to fetal brain tissue. This report first presents a brief review of current scientific evidence relevant to the roles of serotonin and vitamin D in autism. The main body of the article presents a unifying mechanistic

Abbreviations: 25(OH)D_3, 25-hydroxyvitamin D; *AVPR1A*, arginine vasopressin receptor 1A; *AVPR1B*, arginine vasopressin receptor 1B; ASD, autism spectrum disorder; BH4, tetrahydrobiopterin; GI, gastrointestinal; 5-HTP, 5-hydroxytryptophan; IDO, indoleamine 2,3-dioxygenase; *OXT*, oxytocin/neurophysin I prepropeptide; *OXTR*, oxytocin receptor; RXR, retinoid X receptor; SSRIs, serotonin reuptake inhibitors; TPH, tryptophan hydroxylase; *TPH1*, tryptophan hydroxylase 1; *TPH2*, tryptophan hydroxylase 2; T_{reg}, regulatory T; UCSC, University of California–Santa Cruz; UV, ultraviolet; UVB, ultraviolet B; VDR, vitamin D receptor; VDRE, vitamin D response element

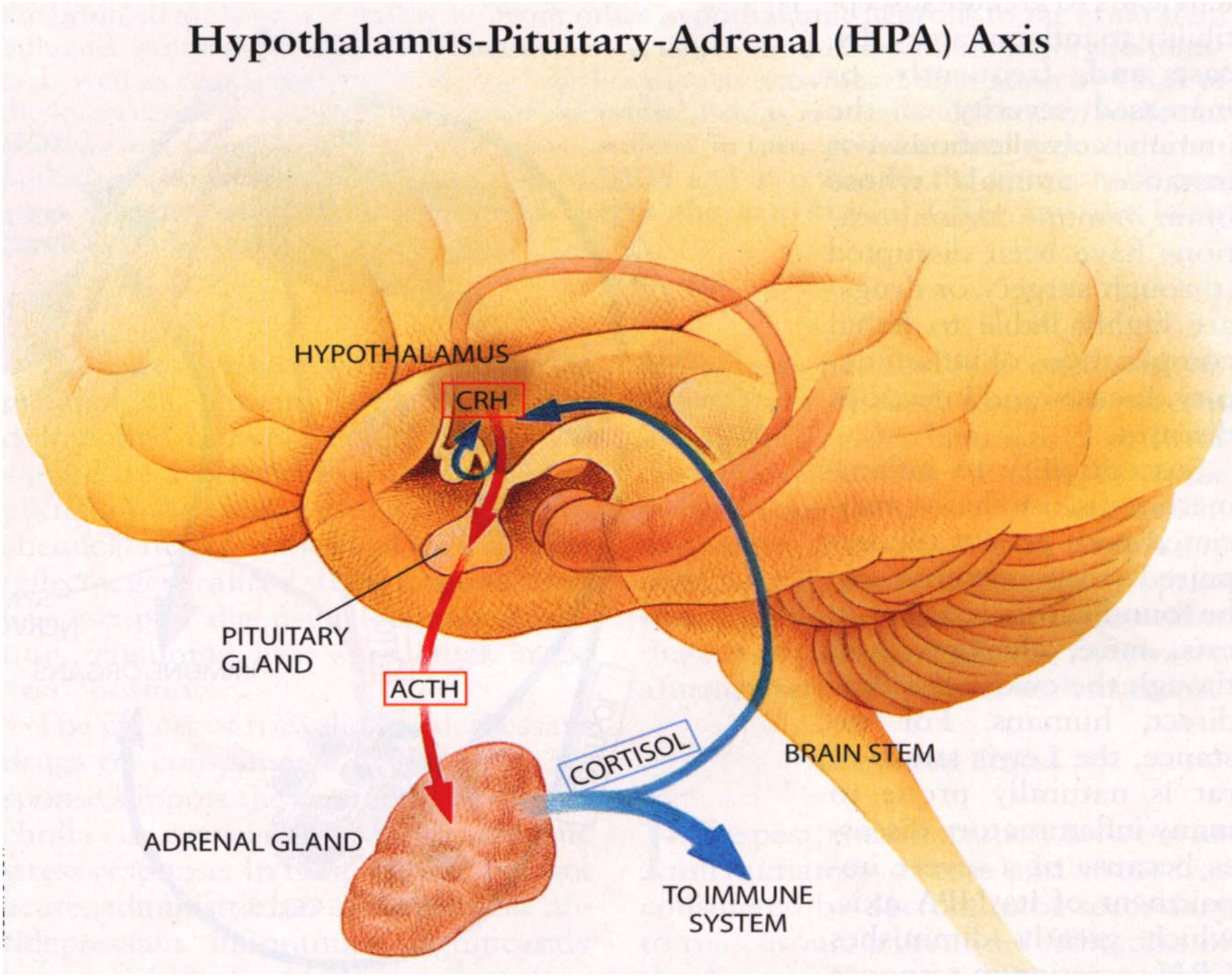
[1] Correspondence: Nutrition and Metabolism Center, Children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr. Way, Oakland, CA 94609, USA. E-mail: R.P.P., rpatrick@chori.org; B.N.A., bames@chori.org

doi: 10.1096/fj.13-246546

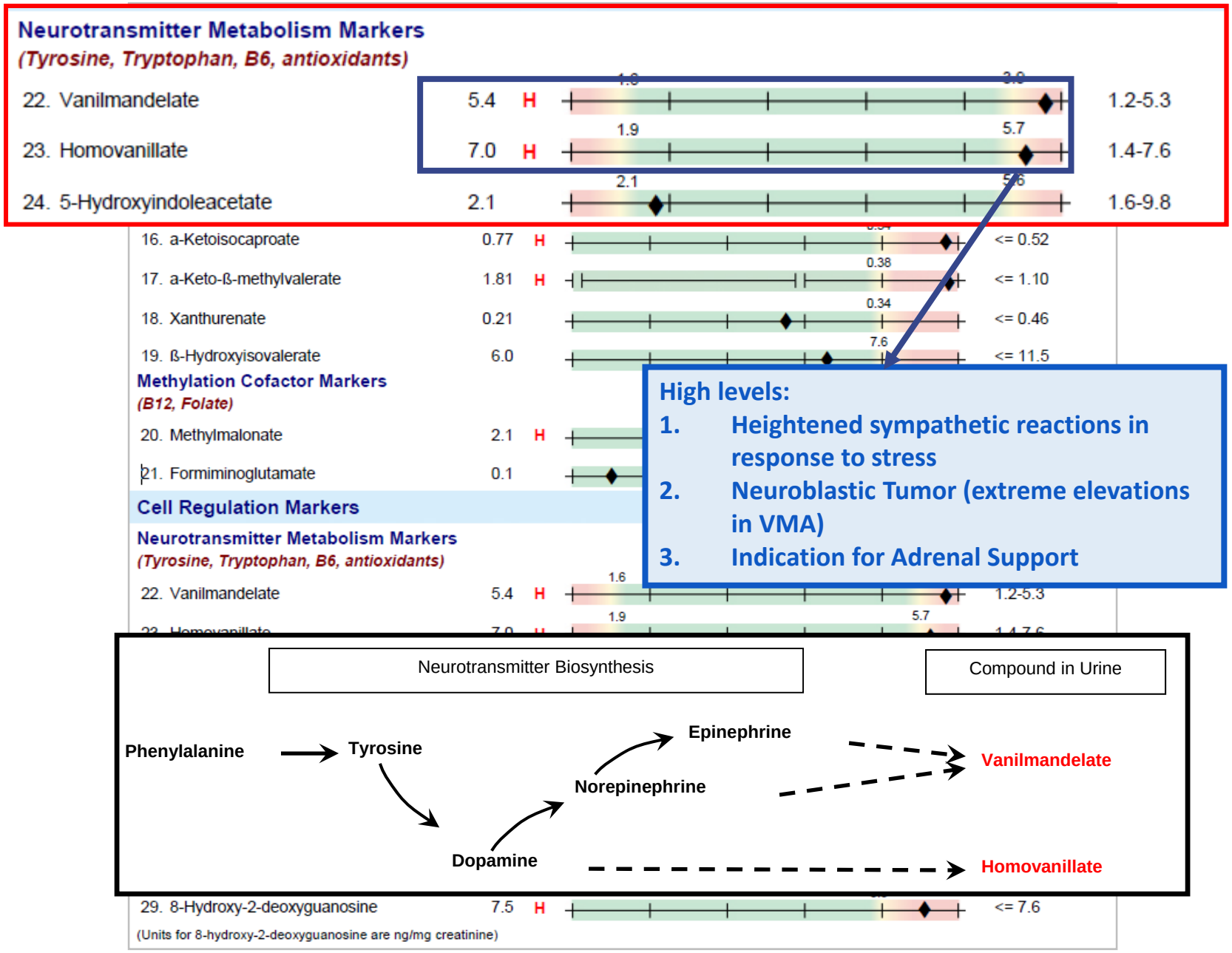
Rhonda P. Patrick[1] and Bruce N. Ames[1]

The FASEB Journal article fj.13-246546. Published online February 20, 2014.

Hypothalamus-Pituitary-Adrenal (HPA) Axis



Neurotransmitter Metabolism



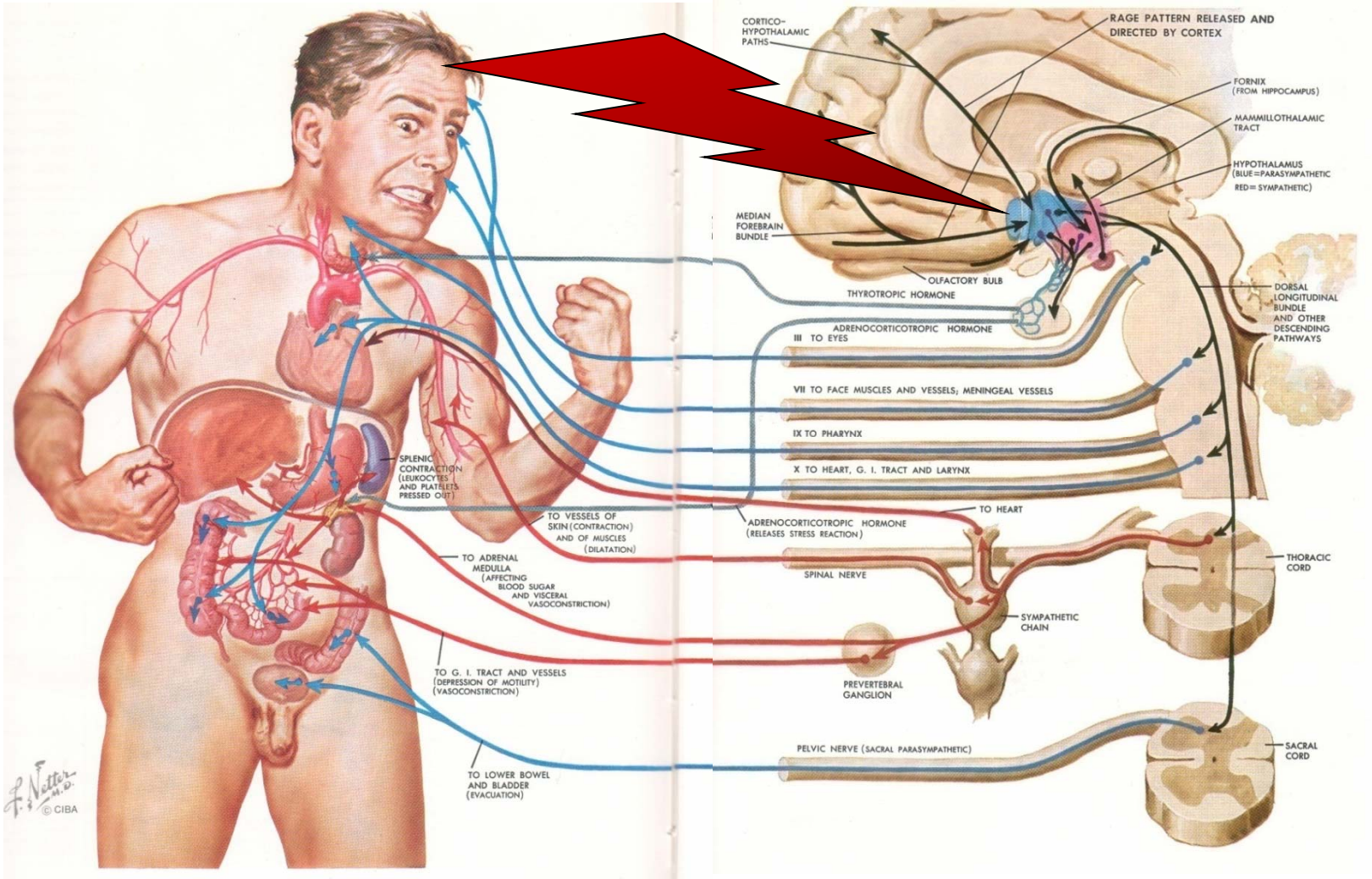
Sympathetic Compensation

"Patients with posttraumatic stress disorder (PTSD) have decreased cortisol and increased catecholamine secretion."

Baker DG, et al. Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder [abstract]. Neuroimmunomodulation. 2001;9:209-217.

This phenomenon can occur in those who may not meet the diagnostic criteria of PTSD, but also those with "Distressing Life Events." (See work of Peter Mol, et al)

Is a Sustained Fight/Flight State One Mechanism Behind FM?



Netter FH. The CIBA Collection of Medical Illustrations. Volume 1: The Nervous System. 1977.

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PLOS ONE

Stress-Induced Allodynia – Evidence of Increased Pain Sensitivity in Healthy Humans and Patients with Chronic Pain after Experimentally Induced Psychosocial Stress

Benjamin Crettaz[1], Martin Marziniak[2], Peter Willeke[3], Peter Young[4], Dirk Hellhammer[5], Astrid Stumpf[1], Markus Burgmer[1]*

1 Department of Psychosomatics and Psychotherapy, University Hospital Münster, Münster, Germany, **2** Department of Neurology and Department of Inflammatory Disorders of the Nervous System and Neurooncology, University Hospital Münster, Münster, Germany, **3** Department of Medicine D, Section of Rheumatology, University Hospital Münster, Münster, Germany, **4** Department of Sleep Medicine and Neuromuscular Disorders, University Hospital Münster, Münster, Germany, **5** Department of Psychology, Trier University, Trier, Germany

Abstract

Background: Experimental stress has been shown to have analgesic as well as allodynic effect in animals. Despite the obvious negative influence of stress in clinical pain conditions, stress-induced alteration of pain sensitivity has not been tested in humans so far. Therefore, we tested changes of pain sensitivity using an experimental stressor in ten female healthy subjects and 13 female patients with fibromyalgia.

Methods: Multiple sensory aspects of pain were evaluated in all participants with the help of the quantitative sensory testing protocol before (60 min) and after (10 and 90 min) inducing psychological stress with a standardized psychosocial stress test ("Trier Social Stress Test").

Results: Both healthy subjects and patients with fibromyalgia showed stress-induced enhancement of pain sensitivity in response to thermal stimuli. However, only patients showed increased sensitivity in response to pressure pain.

Conclusions: Our results provide evidence for stress-induced allodynia/hyperalgesia in humans for the first time and suggest differential underlying mechanisms determining response to stressors in healthy subjects and patients suffering from chronic pain. Possible mechanisms of the interplay of stress and mediating factors (e.g. cytokines, cortisol) on pain sensitivity are mentioned. Future studies should help understand better how stress impacts on chronic pain conditions.

Funding: No external funding existed for the study. But we acknowledge financial publication support by Deutsche Forschungsgemeinschaft and Open Access Publication Fund of University of Muenster. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

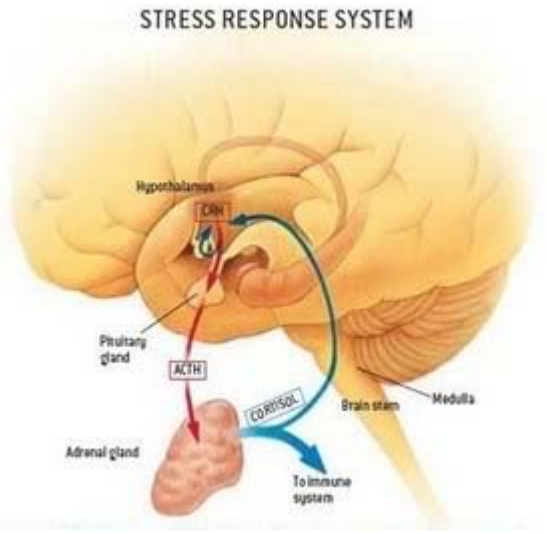
* E-mail: burgmem@mednet.uni-muenster.de

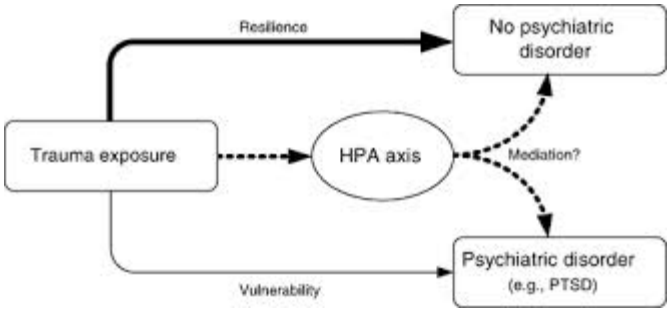
Introduction

Stress is defined as the physiological reaction to real or potential life-threatening conditions [1] and is accompanied by changes in the associated neural, endocrinological and immunological systems [2]. Studies on animals have shown that experimentally induced short-term stress has not only an analgesic effect of [3,4] but also elicits reactions of hyperalgesia and allodynia [5–9]. The differences in pain sensitivity seem to be influenced by the strength of the stressor and the physiological state of the animals' stress-system [6,7]. Situations in need of a fight-or-flight-reaction seem to favor hyperalgesia while analgesia dominates in situations in which such an active reaction is impossible [6]. Chronic experimental stress [5,8] and prior pain experience [7] favor stress-induced hyperalgesia/allodynia [10]. Although these animal studies suggest that stress may enhance the pain processing under certain conditions, no study has tested the concept of stress-induced

In humans, the onset and course of clinical pain conditions such as headache, migraine and fibromyalgia are influenced by stress [11–14] and are associated with changes in the hypothalamic-pituitary-adrenal axis, the core pathway of the human stress system [15–17]. Newer studies in animals and humans exposed to experimental stress suggest a causal relationship of cortisol levels to changes in pain sensitivity [18–20].

The present study describes changes pain thresholds occurring in healthy subjects under conditions of experimental stress. Because of the obvious impact of stress in clinical pain conditions, a sample of patients suffering from fibromyalgia was also investigated. The findings on the two groups were not compared due to the explorative character of our study. In line with the reports in literature, we expected to observe stress-induced analgesia in healthy subjects and stress-induced hyperalgesia/allodynia in the group of fibromyalgia patients.





Citation: Crettaz B, Marziniak M, Willeke P, Young P, Hellhammer D, et al. (2013) Stress-Induced Allodynia – Evidence of Increased Pain Sensitivity in Healthy Humans and Patients with Chronic Pain after Experimentally Induced Psychosocial Stress. PLoS ONE 8(8): e69460. doi:10.1371/journal.pone.0069460

Calming Adrenal Botanicals

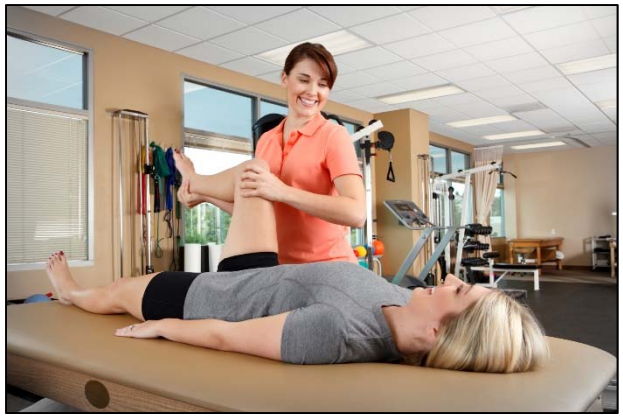
Ashwagandha (*Withania somnifera*) 15% withanolides	**100–200 mg**
German chamomile (Matricaria recutita) 1.2% apigenin	**100-200 mg**
Valerian root (*Valeriana officinalis*)	**100–200 mg**
Passion flower (*Passiflora incarnate*)	**100–200 mg**
Lemon balm (*Melissa officinalis*)	**100–200 mg**

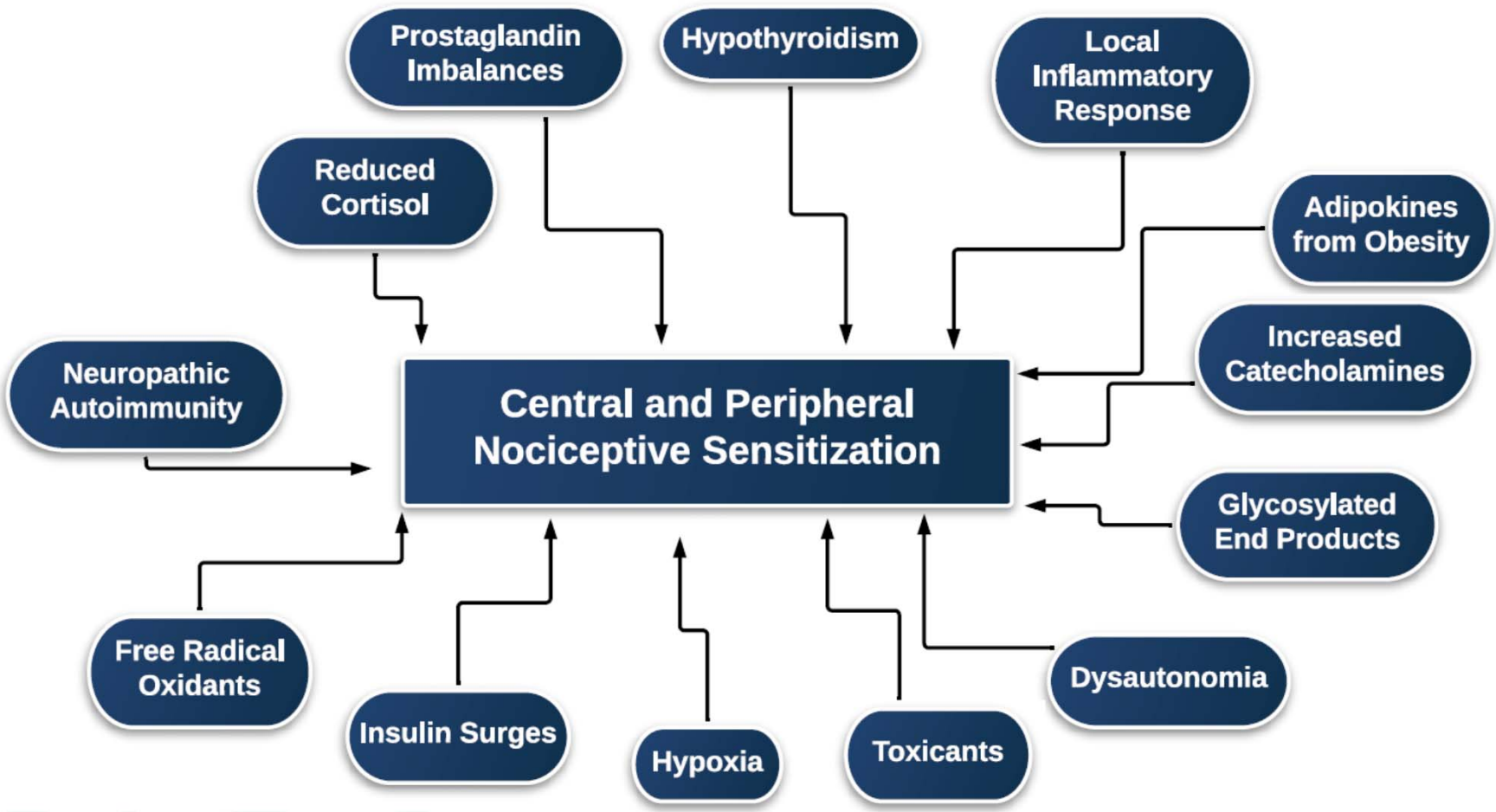
1. Archana R, Namasivayam A. Antistressor effect of Withania somnifera. J of Ethnopharmacol 1999; 64(1): 91-3
2. Kennedy DO et al. Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (Lemon Balm). *Psychosomatic Med*. 2004;68(4):607-613.
3. Groff JL, Gropper SS. Advanced Human Nutrition and Human Metabolism (3rd ed.). Belmont, CA: Wadsworth: 2000

Calming Adrenal Nutrients

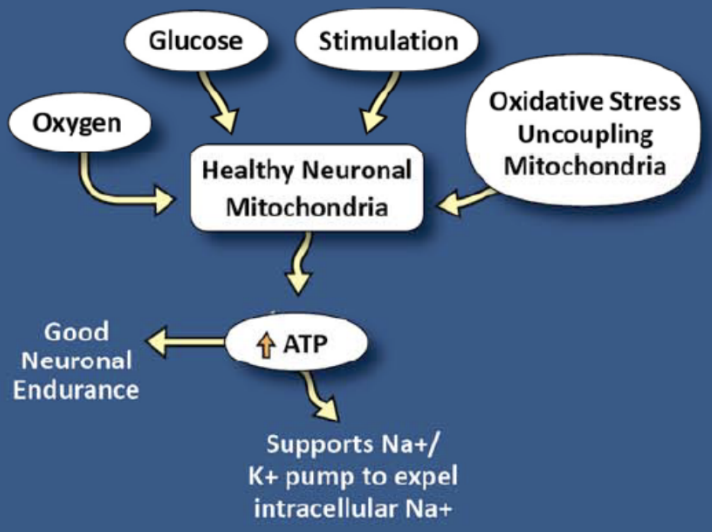
L-theanine	**100–200 mg**
L-taurine	**100–200 mg**
Phosphatidylserine	**50–100 mg**
GABA	**100 mg**
Magnesium-L-threonate	**150 mg**
Vitamin C (ascorbic acid)	**500 mg**
Thiamine (B1)	**50 mg**
Riboflavin (B2) (riboflavin-5-phosphate)	**10 mg**
Pantothenic acid (vitamin B5)	**250 mg**
Pyridoxal 5'-phosphate (coenzyme B6)	**10 mg**
Folate (5-MTHF)	**500 mcg**
B12 (methyl, hyroxy, adenosyl-cobalamin)	**2 mg**

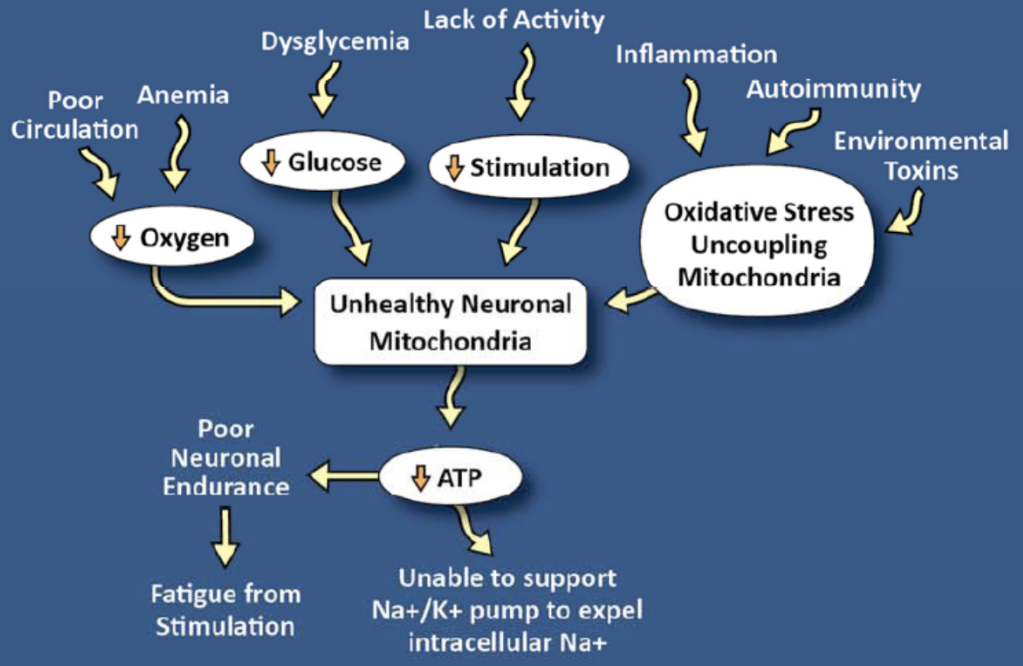
1. Hellhammer J et al. Effect of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress. *Stress:The International Journal on the Biology of Stress*. 2004;7(2):119-126.
2. Frosini M et al. Interactions of taurine and structurally related analogues with the GABAergic system and taurine binding sites of rabbit brain. *Br J Pharmacol*. 2003;138:1163-1171.
3. Driskell JA. Vitamin B6 requirements of humans. Nutr Res 1994; 14: 293-324.
4. Groff JL, Gropper SS. Advanced Human Nutrition and Human Metabolism (3rd ed.). Belmont, CA: Wadsworth: 2000

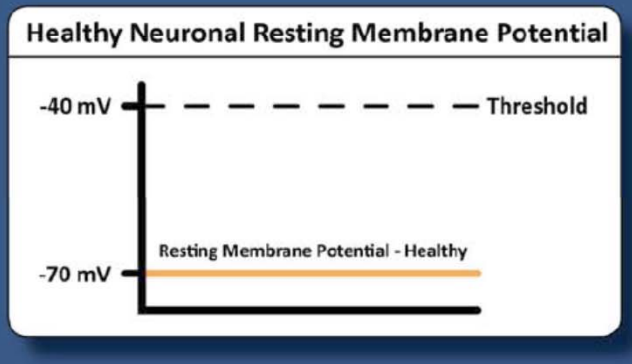


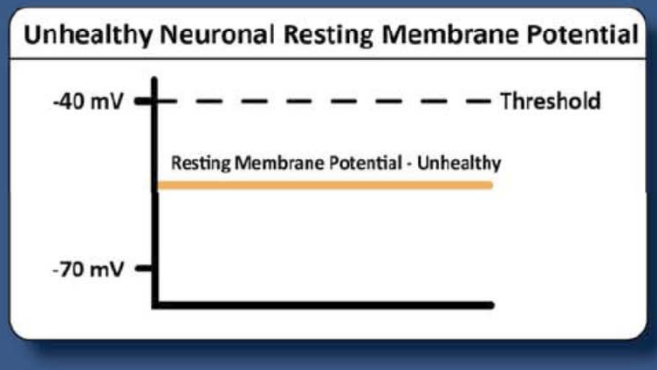

Prostaglandin Imbalances
Hypothyroidism
Local Inflammatory Response
Reduced Cortisol
Adipokines from Obesity
Increased Catecholamines
Neuropathic Autoimmunity
Central and Peripheral Nociceptive Sensitization
Glycosylated End Products
Free Radical Oxidants
Insulin Surges
Hypoxia
Toxicants
Dysautonomia

HEALTHY AND UNHEALTHY RESTING MEMBRANE POTENTIALS

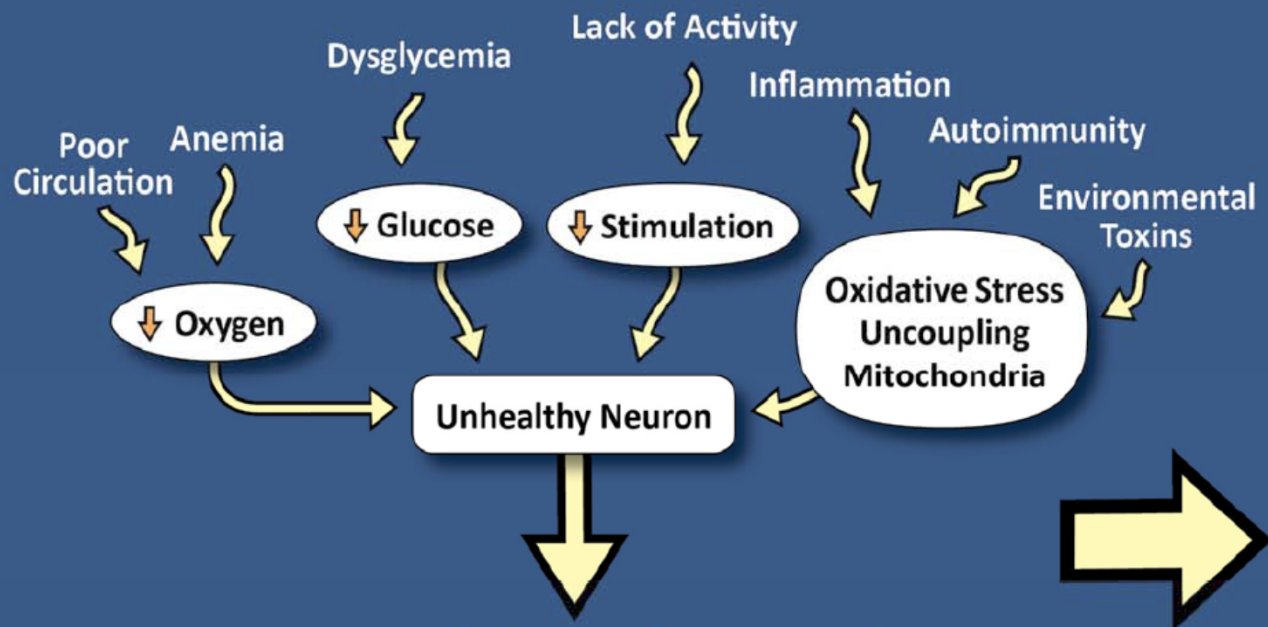








SIGNS AND SYMPTOMS OF UNHEALTHY RESTING MEMBRANE POTENTIALS



- Neuronal resting membrane potential close to threshold
- Decreased production of ATP, leading to poor neuronal endurance

Signs and Symptoms

- Reaction to MSG in foods
- Reaction to electromagnetic fields
- Reaction to smells
- Reaction to flashing lights
- Reaction to high-pitched noise
- Car sickness or seasickness from trivial stimulation
- Reaction to mental changes
- Fear for minor reasons
- Feelings of nausea from minimal stimulation of movement
- Tinnitus
- Hypersensitivity to touch or pain
- Mental fatigue after minor cognitive tasks
- Inability to stand for extended periods of time

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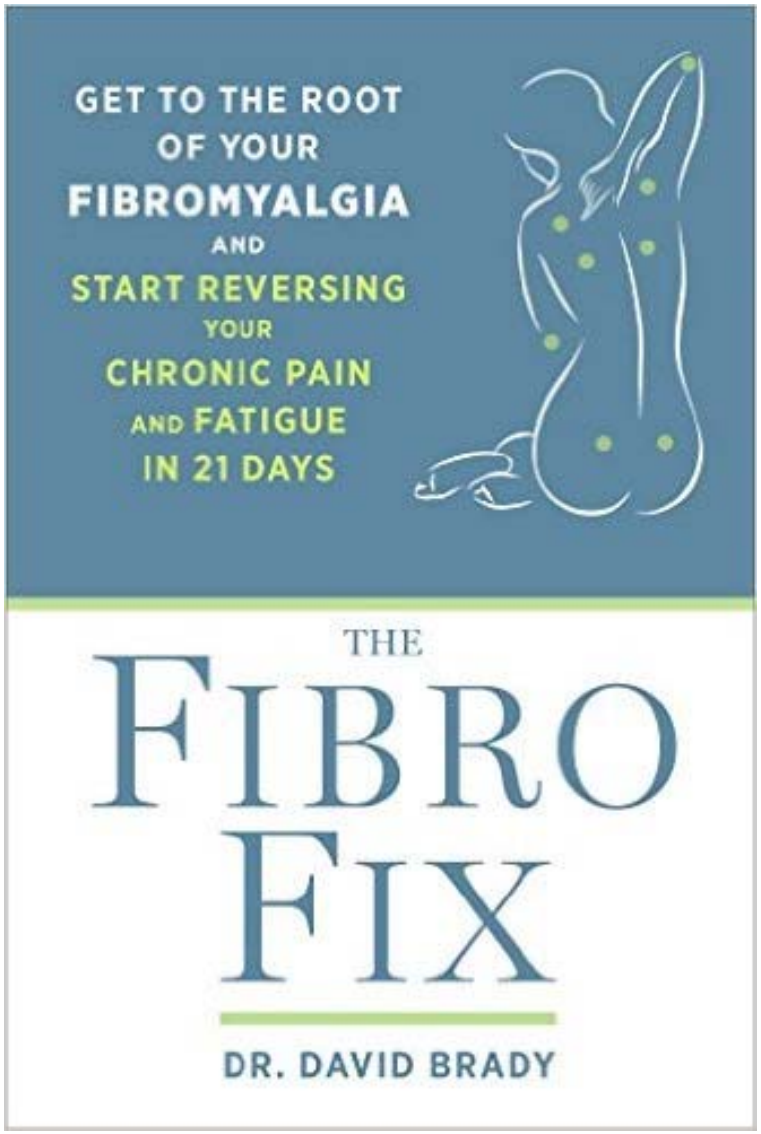

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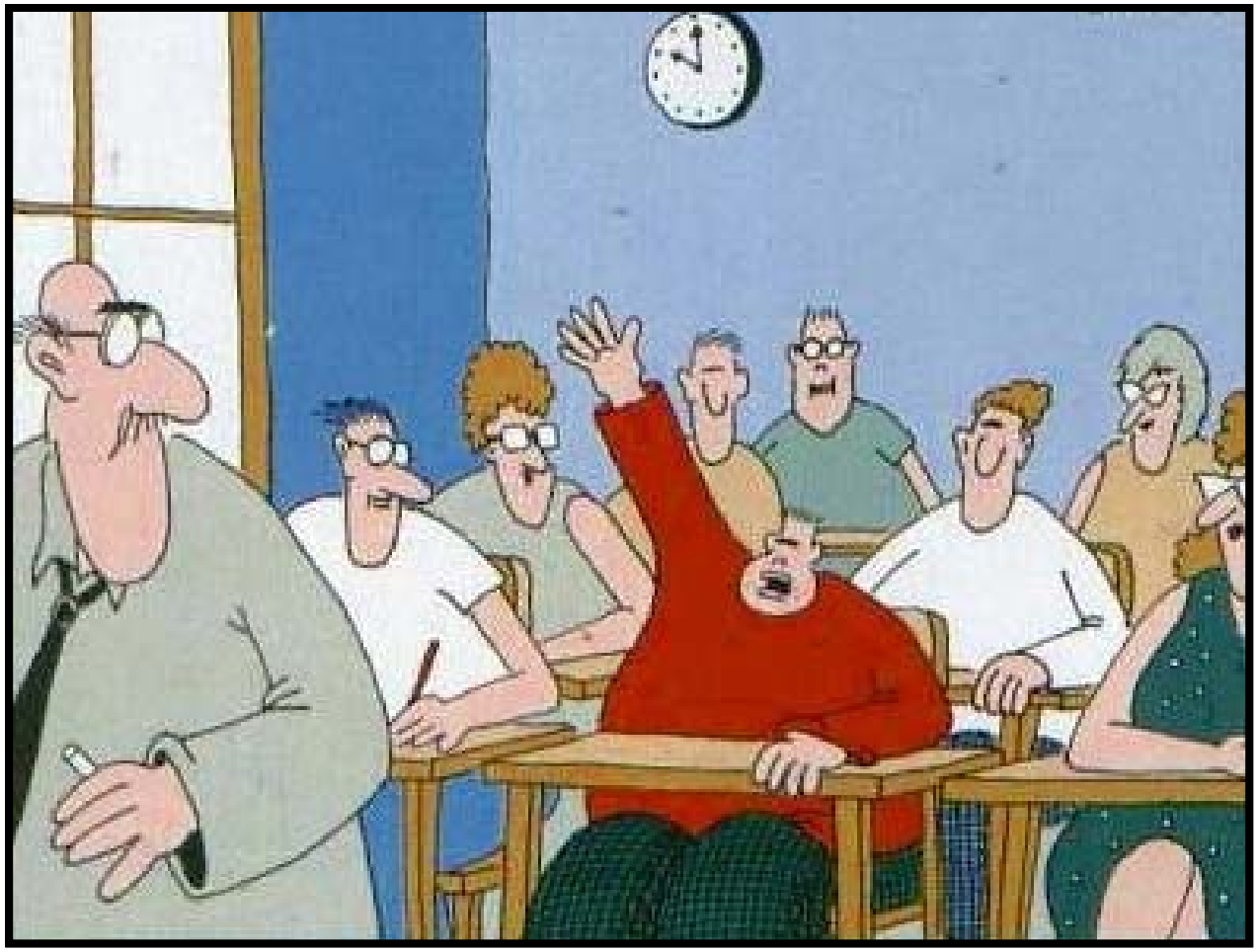
RODALE



"Dr. Brady, may I be excused? My brain is full."

DrDavidBrady.com