

Fibromyalgia Pathogenesis, Diagnosis and Therapeutic Options

Kevin V. Hackshaw, M.D.
Associate Professor of Medicine
Division of Immunology/ Rheumatology
Fellowship Director - Rheumatology
The Ohio State University
Columbus, Ohio

A Major Cause of Disability and Morbidity

- 25.3% of patients received disability payments; (Wolfe, 1996)
- 27.8% of patients were seeking/receiving disability; (Robinson, 2007; J Pain)
- 31% of patients employed prior to onset of their fm reported loss of employment due to their disease (Thorson, 1998)

Fibromyalgia

- A chronic musculoskeletal pain amplification syndrome
- Fatigue
- Wide spread muscular aching
- Sleep disturbance
- Temperature intolerance

Associated Conditions

- Neuralgia
- Neurasthenia
- Muscular Rheumatism
- Psychogenic Rheumatism
- Tension Rheumatism
- Fibrositis/ Myofibrositis
- Chronic Fatigue Syndrome
- Shell Shock
- Post Traumatic Stress Syndrome
- Gulf War Syndrome
- Chemical Hypersensitivity Syndrome
- Sick Building Syndrome

Demographics

- Female > Male (5:1) *
- Age Onset: 9 – 60
- Most commonly between 40 and 60
- All Races
- Between 3 – 7% of the U.S. population is affected
- Inciting events: Trauma (**), Infection, MVA with whiplash, Head or Neck Injury

“Pain”

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage

Pain Mechanisms

Pain Mechanisms

- Nociceptive transmission: arising from inflammation or degeneration of joints and soft tissue
- Examples: Rheumatoid Arthritis and Osteoarthritis

Pain Mechanisms

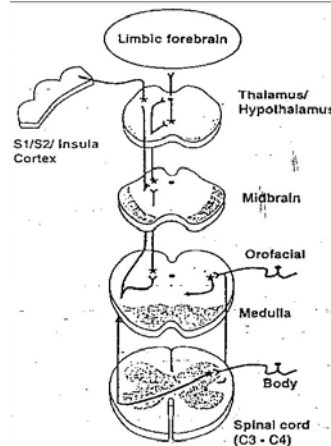
- **Neuropathic transmission:** arising from a primary lesion in the peripheral or central nervous system
- **Hyperresponsiveness to subthreshold stimuli**
- **Examples:** Trigeminal Neuralgia, Diabetic Peripheral Neuropathy, Post herpetic neuralgia, Fibromyalgia (?)
 - ✓ Nociceptive
 - ✓ Inflammatory
 - ✓ Neuropathic
 - ✓ Maladaptive

Peripheral and Spinal Pain Mechanisms

- **Central endings - spinal cord gray matter**
- **Modulating factors** {5HT – High presynaptic levels inhibit NT release, low levels enhance NT release}
- **Neurotransmitters**
 - ✓ Substance P (NK1 receptors; long acting)
 - ✓ Glutamate (NMDA receptors; short acting)
 - ✓ Excitatory Amino Acids
 - ✓ Vasoactive intestinal peptide (visceral organs)
 - ✓ CGRP

Peripheral and Spinal Pain Mechanisms

- **Nociceptive afferents**
 - ✓ A delta myelinated (fast transmission)
 - ✓ C unmyelinated (slow transmission)

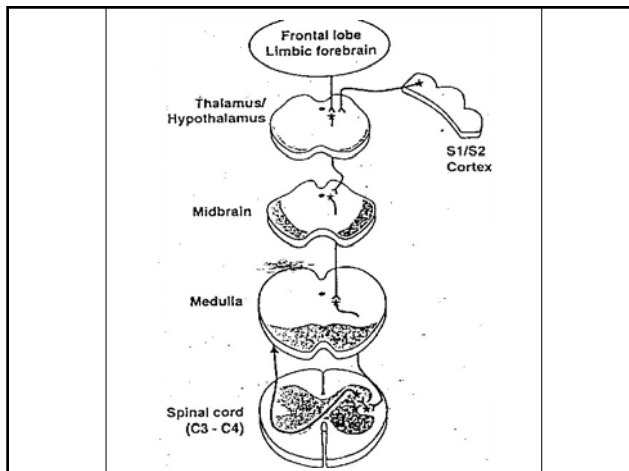


Descending Controls

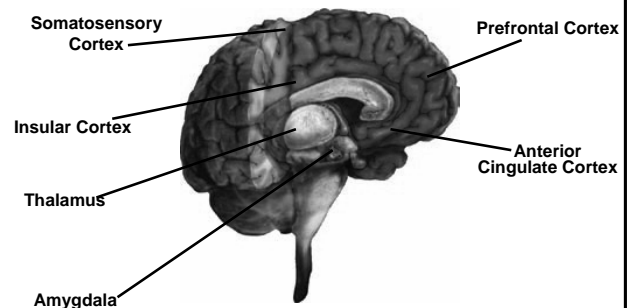
- Modulation of nociceptive processing and pain
 - ✓ Perceptual correlates
 - Placebo effect
 - Hypnosis and suggestion
 - Combat, athletics
 - Ritual analgesia
 - Pharmacological analgesia

Mechanisms of Neuropathic Pain

- Spontaneous discharges either peripherally or centrally
- Localized demyelination, DRG abnormalities or aberrant Sodium or Calcium channels may contribute
- Aberrant expression of neurotransmitters in periphery or centrally leads to "Sensitization"
- Results in more ectopic firing



Pain Processing Areas in the Brain



Clinical Presentation

Fibromyalgia Spectrum

- Seek Medical Care
- Multiple tender points
- Depression *
- Anxiety *
- High frequency of recent stressful experiences

- Don't seek medical care
- Multiple tender points

- Allodynia

- ✓ A non-noxious stimulus elicits pain

- Hyperalgesia

- ✓ An exaggerated response to a painful stimulus

Rheumatic Symptoms

- General aches/ pains
- Articular pains without joint swelling
- Morning stiffness about 1 hour
- Subjective morning swelling

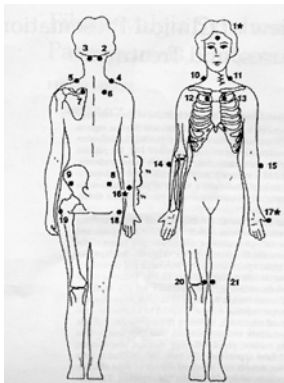
Non-Rheumatic Symptoms

- Anxiety
- Sleep disturbances
- Headaches
- Irritable bowel syndrome
- Irritable bladder
- PMS
- Numbness
- Palpitations
- Mottled skin appearance
- Temperature instability

Diagnostic Criteria

- * Widespread subjective aching for more than 3 months
- *Pain in >11 of 18 tender points *
- Subjective stiffness of more than 3 months
- Pain in all 4 quadrants of body
- “Normal Labs” to include ESR, TSH, ANA, Vitamin D Level, etc.
- Concurrent chronic fatigue, emotional distress, poor sleep, morning stiffness *specific diagnostic criteria

Fibromyalgia Tender Points



Other Considerations...

Pain Catastrophizing -1

- Individuals who catastrophize have difficulty shifting their focus of attention away from painful or threatening stimuli
- They attach more threat or harm to non-painful stimuli (Crombez 1998, 2002)
- Catastrophizing is also associated with affective pain ratings leading to higher evaluations of the experience of pain (Geisser 1994)

Pain Catastrophizing -3

- Describing pain as “awful, horrible or unbearable”
- Early studies suggested these maladaptive responses mirrored responses in depressed individuals
- Later studies have found catastrophizing to be significantly associated with pain related disability independent of depression or negative affect (Keefe 1989, Geiser 1994, 2003)

Pain Catastrophizing -2

- Independent of influence of depression:
- Associated with brain areas associated with anticipation of pain: medial frontal cortex, cerebellum;
- Attention to pain : Dorsal ACC, Dorsal prefrontal cortex;
- Emotional aspects of pain: Claustrum, closely connected to amygdala and motor control

Waddell Signs

- Tenderness
 - ✓ Superficial - skin is tender to light pinch over a wide area of lumbar skin nonanatomic - deep tenderness over a wide area, not localized to one structure
- Simulation Tests - give the impression that an examination is being done, when in fact it is not
 - ✓ Axial loading - vertical loading over the standing patient's skull by the examiner's hands rotation - turn standing patient to one side by rotating lower extremities (not spine)

Waddell Signs

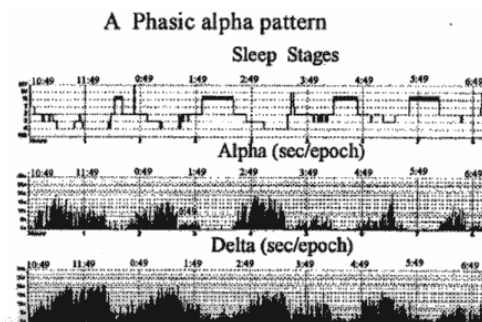
- **Distraction Tests** - reevaluating a positive finding while the patient's attention is not focused on the test
 - ✓ Indirect observation - can patient move the body part without pain when not being directly examined?
 - ✓ Straight leg raise - if positive when examined supine, do "flip test" (sitting SLR)
- **Regional Disturbances** - widespread divergence from accepted neuroanatomy
 - ✓ Weakness - "cogwheeling" or many muscle groups that cannot be explained neuroanatomically
 - ✓ Sensory - "stocking" distribution of sensory changes
- **Overreaction**
 - ✓ Disproportionate verbalization, facial expression, muscle tension and tremor, collapsing, sweating

Pathogenesis

Comorbidity

- 25% of RA with FM
- 30% of SLE with FM
- 50% of SS with FM
- 20 -80% of DM with FM
- MS with FM

Phasic alpha wave intrusion patterns correlate with clinical symptoms in fibromyalgia

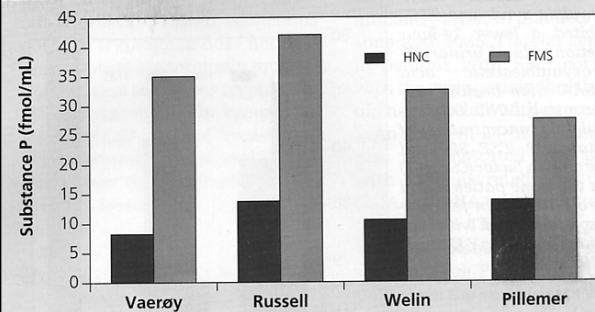


Family and Genetic Studies

- Odds ratio for a family member of a patient with FM to also have FM is 8.5 (Arnold, 2004)
- FM family members have increased pain sensitivity as measured by total myalgic score

Genetic influences on pain sensitivity may in part mediate the relation between somatization and the development of widespread pain

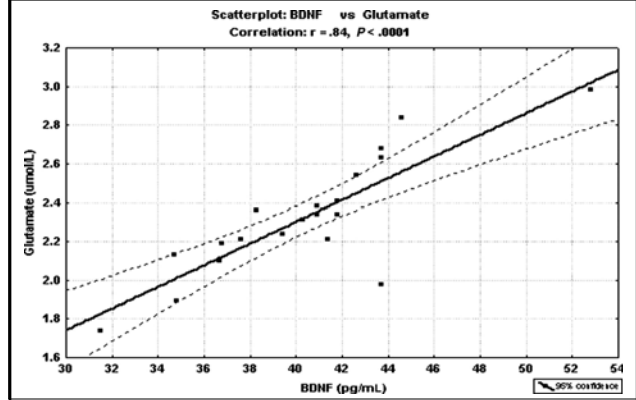
Women with abnormal pain sensitivity or chronic widespread pain show a functional polymorphism in the promoter region of the serotonin transporter gene 5-HTT.



Substance P in CSF

- No significant relationship with depression (Russell , 1994)
- No difference in CSF SP levels between individuals with major depression and normal controls (Deuschle, 2005)
- CSF SP levels are unchanged by antidepressant treatment / response (Deuschle, 2005)

Correlation between levels of CSF BDNF and Glutamate in FM Patients



NGF and BDNF in CSF of FM

Table - CSF Levels of NGF and BDNF (Mean +/- 2 SD) in Patient Groups and Controls

	CM PATIENTS		PFMS		CONTROLS	
NGF (pg/mL)	46.7	4.6	47.2	5.3	13.7	2.7
BDNF (pg/mL)	39.4	6.7	40.4	4.6	11.3	3.4
Glutamate (mol/L)	2.18	0.4	2.36	0.3	1.37	0.3

Abbreviations: CM, chronic migraine; PFMS, primary fibromyalgia syndrome; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor. * = Statistically Significant

Sarchielli et al., 2007

NGF is elevated in CSF of Primary Fibromyalgia

- Primary FM: 41.8 +/- 12.7 pg/ml
- Secondary FM: 8.9 +/- 4.4 pg/ml
- Other : 16.2 +/- 8.4 pg/ml

Giovenco et al., 1999

Changing Glutamate Levels in Insula correlate with Fibromyalgia Pain

H-MRS (proton magnetic resonance spectroscopy)

(Gracely et al., 2008)

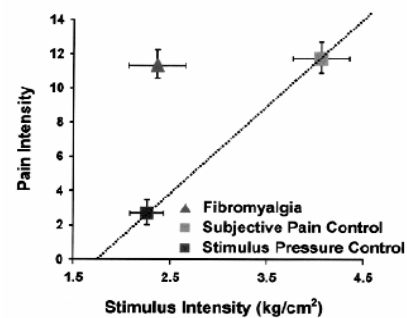
Question?

“Does the pattern of brain activation in FM patients match that produced by equally low stimulus pressures in normal volunteers, or does it match that produced by equally subjectively painful stimuli (produced by significantly greater stimulus pressures) in the normal volunteer group?” A match of equal subjective pain intensities is consistent with a pathologic increase in pain sensitivity in patients.

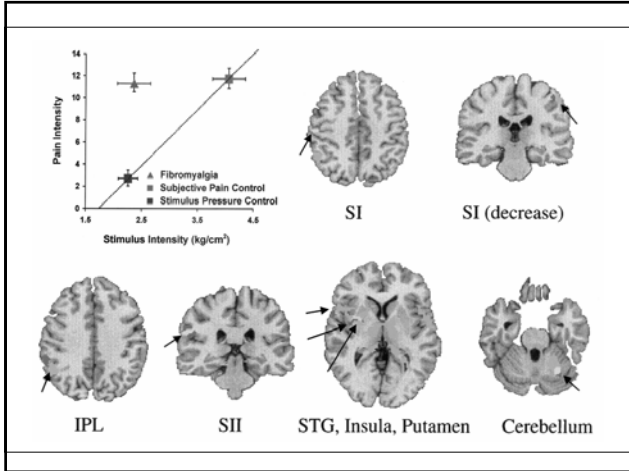
Functional Imaging Techniques

- PET Scanning
- Functional MRI
- Studies by K. Casey, Peyron
- Pain is associated with activation in the Secondary Somatosensory (SII), Insular Region, Anterior Cingulate Cortex (ACC), contra lateral thalamus and primary somatosensory cortex (SI)
- Activation is characterized by an increase in Regional Cerebral Blood Flow

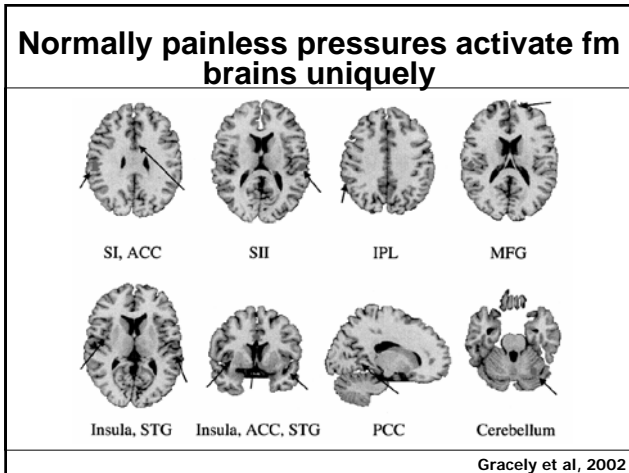
FM patients report pain at normally painless pressures



Gracely et al, 2002



Treatment



Treatment Options

(after exercise program has been established *)

<ul style="list-style-type: none"> • <i>Medication Class</i> • 1-Tricyclic Antidepressants • 2-Analgesics • 3-SNRI's * • 4-SSRI's • 5-Anticonvulsants (A2D) * • 6-Other anticonvulsants (Na channel) • * FDA approved 	<ul style="list-style-type: none"> • <i>Study Results</i> • 1-8 and 12 week trials: Some +, Most - • 2-All - except tramadol • 3-All + • 4-All - • 5-All + • 6-Most have not been tested • * FDA approved
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Treatment Regimens

- | | |
|--|---|
| <ul style="list-style-type: none">• Pregabalin 50 qhs x 1 wk• 50 bid wk 2• 50/100 wk 3; etc.• Duloxetine 30 mg qAM wk 1• 60 qAM thereafter | <ul style="list-style-type: none">• Milnacipran 12.5 mg day 1• 12.5 mg bid days 2 and 3• 25 bid days 4 – 7• 50 bid thereafter• Treat symptom domains for most patients; ie., sleep, fatigue, pain, etc. |
|--|---|

Summary

- The pathogenesis of FM has more in common with neuropathic pain spectrum disorders than the typical inflammatory or degenerative musculoskeletal pain disorders
- Treatments should be directed towards CNS mechanisms
- FM and classical neuropathic pain syndromes respond similarly to drugs of several different chemical classes with different MOA consistent with shared pathogenic mechanisms

Other Treatment Considerations

- Cognitive Behavioral Therapy
- Local Trigger Point Injections
- Topical Capsaicin
- Muscle Relaxants / Anti inflammatories
- NMDA Antagonists (Dextromethorphan) – C-fiber second pain (Windup) dependent on NMDA mechanisms – not effective

References

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- Arth Rheum 46: 1333 – 1343, 2004
- J Rheum 26: 1564 – 1569, 1999
- J Pain 8: 737 – 745, 2007
- Arth Rheum 58: 903 – 907, 2008
- J Pain 5: 323 – 332, 2005
- Brain Res 1041: 38 – 47, 2005
- Spine 5: 117 – 125, 1980