Presentation 5 – Daniel Clauw

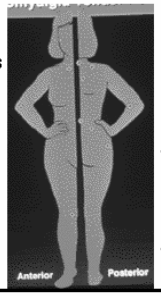
The Pathophysiological Basis of Fibromyalgia

Daniel J. Clauw, MD

Professor of Medicine, Division of Rheumatology
Assistant Dean for Clinical and Translational Research
Director, Chronic Pain and Fatigue Research Center
University of Michigan Medical Center

Paradigm Shift in Fibromyalgia

- Discrete illness
- Pain, focal areas of tenderness
- Psychological and behavioral factors nearly always present



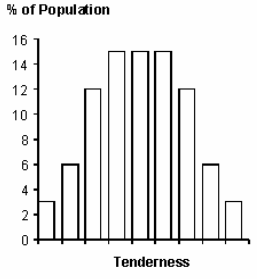
American College of Rheumatology Criteria

- Chronic widespread pain
- Tenderness in ≥ 11/18 tender points

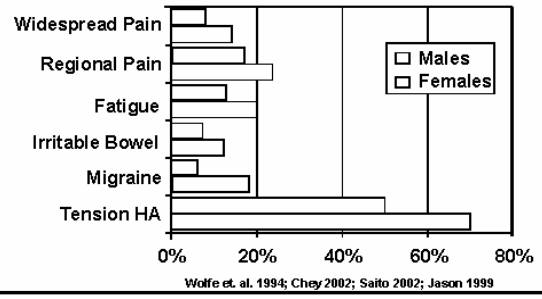
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychological and behavioral factors play roles in some individuals

Tenderness in the General Population

- Pain and other somatic symptoms occur as a continuum rather than as "yes" or "no"
- In fact, all of the defining features of somatic syndromes such as FM, IBS, etc. occur as a continuum
- In the absence of a peripheral injury tenderness throughout the body is highly correlated

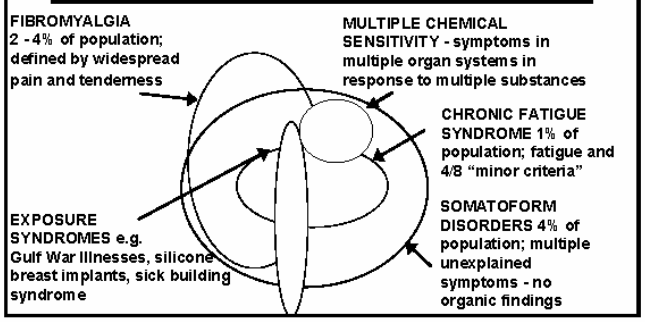


Prevalence of Chronic Somatic Symptoms/Syndromes in U.S.

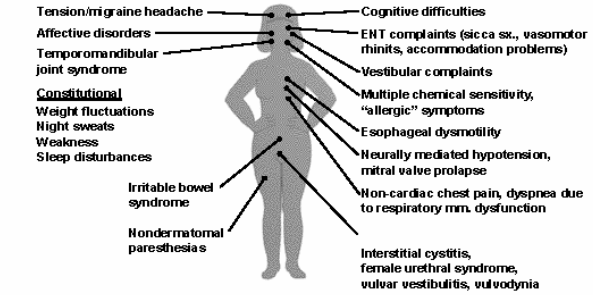


Wolfe et. al. 1994; Chey 2002; Saito 2002; Jason 1999

Overlap between Fibromyalgia and other "Systemic" Syndromes



Symptoms and Syndromes Related to Fibromyalgia



Summary : What is Fibromyalgia?

- A discrete disorder
- The prototypical chronic central pain state, that can help us understand central mechanisms that may play a role in pain and other symptoms seen in chronic multisymptom illnesses

Summary

- *Peripheral (nociceptive)*
  - Primarily due to *inflammation* or mechanical damage in periphery
  - NSAID, opioid responsive
  - Responds to procedures
  - Behavioral factors minor
  - Examples
    - OA
    - Acute pain models (e.g. third molar, post-surgery)
    - RA
    - Cancer pain
- *Central (non-nociceptive)*
  - Primarily dues to a central disturbance in pain processing
  - Tricyclic, neuroactive compounds most effective
  - Behavioral factors more prominent
  - Examples
    - Fibromyalgia
    - Irritable bowel syndrome
    - Tension headache
    - Idiopathic low back pain
    - Interstitial cystitis / vulvodynia, non-cardiac chest pain / etc.

What causes fibromyalgia?

- Genetics
- "Triggers"
- Mechanisms
  - Relationship between physiologic and psychologic factors
  - Disordered sensory processing
  - Autonomic/neuroendocrine dysfunction

Genetics of Fibromyalgia

- Clearly is a strong *familial* predisposition
  - Most recent work by Arnold, Hudson, et. al. suggest
    > 8 OR for first degree relatives, and much less familial aggregation (OR 2) with affective disorders
- Genes that may be involved
  - 5 HT 2A receptor polymorphism T/T phenotype (Bondy 1999)
  - Serotonin transporter (Offenbaecher 1999)
  - COMT (Catecholamine O-Methyl Transferase)
    - Shown to be involved in pain transmission (Zubieta 2002)
    - Slightly different in FM (Gursoy 2003)

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"Stressors" capable of triggering these illnesses – supported by case-control studies

- Infections (e.g., parvovirus, EBV, Lyme, Q fever; not common URI)
- Physical trauma (automobile accidents)
- Psychological stress / distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Vaccines
- Certain catastrophic events (war, but not natural disasters)

Clauw, Chrousos; Neuroimmunomodulation, 1997

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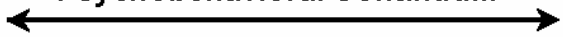
The Physiological / Psychobehavioral Continuum



Population — Primary Care — Tertiary Care

Neurobiological
- Abnormal sensory processing
- Autonomic dysfunction
- HPA dysfunction
- Smooth muscle dysmotility

Psychosocial factors
- General "distress"
- Psychiatric co-morbidities
- Cognitive factors
- Maladaptive illness behavior
- Secondary gain issues

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Sensory Processing in Fibromyalgia
A problem with pain "volume control"

- Patients display a normal "detection threshold" to sensory stimuli, but an decreased "noxious threshold"
- This is not just to pressure, but also other stimuli, e.g. heat, noise, electrical stimulation.
- The general increase in sensory sensitivity could theoretically be due to:
  - psychological (e.g. "expectancy" or hypervigilance) *or*
  - neurobiological changes in nociceptive processing (e.g., sensitization or reduced descending pain inhibition).

Neurobiological Pain Amplification Mechanisms

- Peripheral
  - Sensitization
  - Recruitment of silent nociceptors (e.g. A-beta fibers in inflammation)
  - Alteration in phenotype
  - Hyper-innervation (Ruda, 2001)
- Central
  - Central sensitization (Woolf, 1983)
  - De-afferentation
  - Disinhibition
  - Structural reorganization

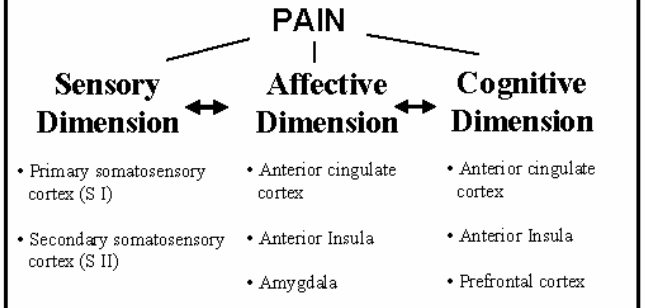
Using Experimental Pain Testing to Examine Pain Processing

- Hyperalgesia / allodynia distant from site of pain
  - FM (Petzke/Clauw/Gracely; Geisser/Casey/Crofford)
  - IBS (Mayer, Naliboff, Chung; Whitehead)
  - TMD (Maixner; Kashima)
  - Tension HA (Langemark)
  - Low back pain (Clauw)
  - Vulvodynia/vulvar vestibulitis (Giesecke/Reed)
- Potential Mechanisms in FM
  - Wind-up in FM (Price, Staud)
  - Absence of DNIC (Kosek; Marchand)

Functional MRI in Chronic Pain
It is "all in your head"

- fMRI takes advantage of magnetic moment of deoxygenated blood, and thus can detect neuronal activations associated with stimuli
- Most imaging sequences take advantage of "on-off" paradigms, where the difference between the blood flow in a "neutral" condition (e.g. touch) and pain is imaged
- PET and fMRI have identified a number of brain regions involved in pain processing

Pain Processing
(Melzack & Wall; Melzack & Casey)



fMRI in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia? (Gracely et. al. Arthritis Rheum 2002)
- Role of depression in pain processing in FM (Giesecke et. al. Arthritis Rheum, in press)
- Role of cognitive factors in pain processing in FM
  - Locus of control
  - Catastrophizing (Gracely et. al. Brain, 2004)
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain? (Giesecke et. al. Arthritis Rheum, 2004)
- Is FM a more global problem with interoception?

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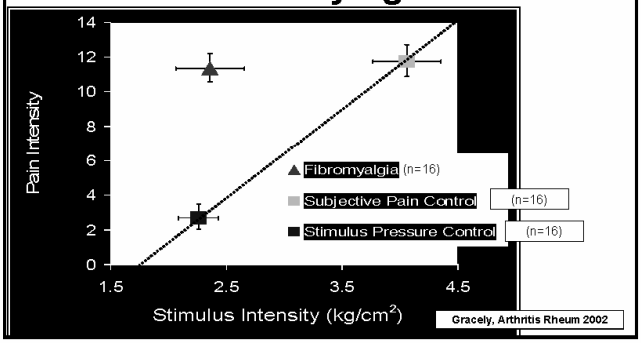
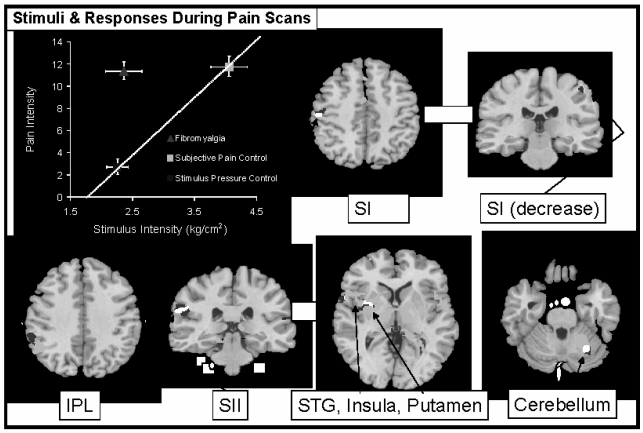
Functional MRI in Fibromyalgia





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Influence of Depression on Pain Processing

- **30 subjects with FM and various levels of depressive symptomatology**
- **Received painful stimuli to left thumb**
- **Neuronal activations in pain processing areas**
  - **Correlated with depressive symptoms as measured by CES-D**
  - **Group comparisons performed comparing FM with major depression, FM without major depression, and controls**

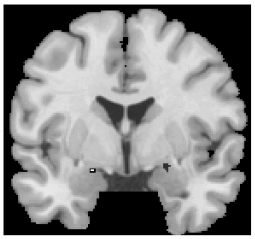
Correlational Results

PAIN

Sensory Dimension	Affective Dimension	Cognitive Dimension
•Primary somatosensory cortex (S I) r = .28	•Anterior cingulate cortex r = .10	•Anterior cingulate cortex r = .10
•Secondary somatosensory cortex (S II) r = .10	•Anterior Insula **r = .51**	•Anterior Insula **r = .51**
	•Amygdala **r = .4 / .5**	•Prefrontal cortex r = .06

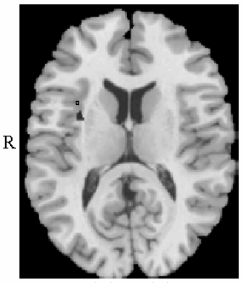
fMRI correlations with CES-D

Amygdala



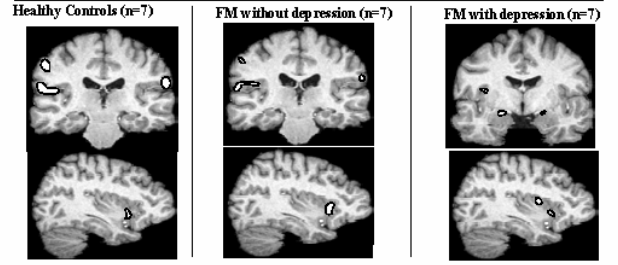
x/y/z –20/0/-12
18/0/-10

Insula



x/y/z 32/2/14

Graphical presentation of fMRI findings with equal pain



Healthy controls and FM without depression show activations in primary somatosensory cortex, secondary somatosensory cortex, and anterior insula

FM with depression have additional activations in amygdale and anterior insula

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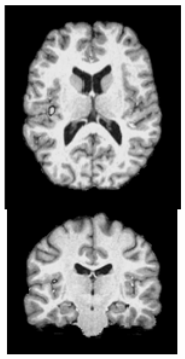
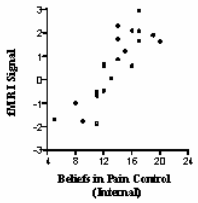
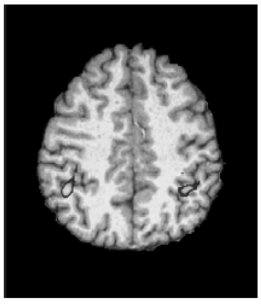
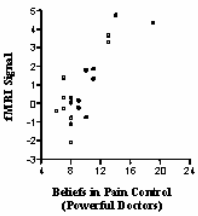
Internal Locus of Control & SII





Powerful Doctors & IPL BA 40





Influence of Catastrophizing on Pain Processing

- Refers to the fact that individual characterizes pain as awful, horrible, unbearable
- Predicts poor response to therapy
- 29 fibromyalgia subjects had fMRI performed with pressure on left thumbnail and correlations between neuronal activations and residual catastrophizing were calculated, after controlling for depression

Gracely et. al., Brain, 2003

Correlational Results

PAIN

Sensory Dimension	Affective Dimension	Cognitive Dimension
•Primary somatosensory cortex (S I) r = NS	•Anterior cingulate cortex r = .42	•Anterior cingulate cortex r = .42
•Secondary somatosensory cortex (S II) r = .41	•Anterior Insula r = NS •Amygdala r = NS	•Anterior Insula **r = NS** •Prefrontal cortex r = .47

fMRI in Fibromyalgia and Related Conditions

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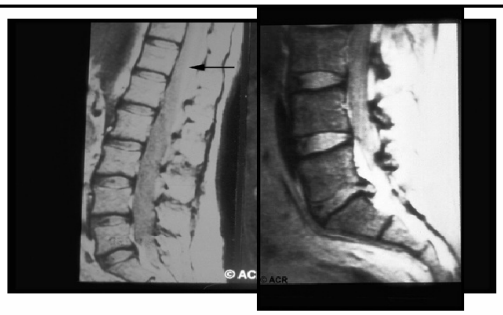
- **Is there objective evidence of augmented pain processing in idiopathic chronic low back pain?**
- Is FM a more global problem with interoception?



Patient A - Low pain threshold threshold

Normal MRI of spine

Severe back pain

Patient B - High pain

Prominent bulging disc

No pain or symptoms

Clauw et. al. Spine 1999

fMRI in Fibromyalgia and Related Conditions

- **Is there objective evidence of augmented pain processing in fibromyalgia?**
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  - **Catastrophizing**
  - **Locus of control**
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain?
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Functional Imaging in Other "Central" Pain Syndromes

- Innumerable studies showing abnormalities in PET, SPECT in a number of chronic pain states
- Proton spectroscopy (Apkarian)
  - Proton spectroscopy abnormal in chronic low back pain (Grachev, Pain, 2000)
  - The degree of abnormality is influenced by co-morbid anxiety (J Neural Transm 2002)
  - May be atrophy of brain regions in low back pain (J Neuroscience 2004)

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- Genetics
- "Triggers"
- Mechanisms
  - Relationship between physiologic and psychologic factors
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HPA axis and autonomic nervous system in chronic pain syndromes

- HPA abnormalities have been consistently identified in fibromyalgia, TMD syndrome, LBP
- Autonomic abnormalities have been consistently identified in FM, IBS, tension and migraine H/A
- The precise nature, and even direction, of these abnormalities is dependent on
  - the methodologies used,
  - the population studied, and
  - whether these axes are studied at baseline (where there is sometimes increased activity) or in response to stressors (where there is usually an attenuated response)

Why Should the RAC on Gulf War Veteran's Illnesses Care?

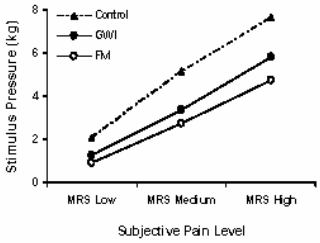
Studies of Physiology of Gulf War Veterans vs. Healthy Controls, with FM as "Positive Control" Group

- Sensory processing
- Autonomic function

Sensory Processing in Gulf War Veterans

- **Quantitative sensory testing for pressure pain threshold**
  - 20 GWI participants with chronic multisymptom illnesses
  - 36 age- and gender-matched controls
  - 27 individuals with fibromyalgia
- **fMRI in a representative cohort from above**

Pressure Pain Threshold



Gulf War Veterans

Brain Region	X coord.	Y coord.	Z coord.	t score
Anterior Cingulate	-2	-32	34	3.85
S1	44	-26	55	4.88
S2	65	-24	21	5.17
Ipsilateral S2	-61	-17	19	3.35
Inferior Parietal Lobule	-51	-34	53	4.74
Cerebellum	-30	-52	-21	5.01
Inferior Frontal Gyrus	40	62	6	4.90

Fibromyalgia

Brain Region	X coord.	Y coord.	Z coord.	t score
Putamen	-24	4	7	3.83
S1	55	-18	32	4.27
S2	59	-34	18	3.33
Ipsilateral S2	-59	-21	12	3.72
Inferior Parietal Lobule	53	-38	57	4.13
Cerebellum	-30	-54	-23	3.21
Inferior Frontal Gyrus	38	61	-10	3.45

Fibromyalgia Patients

Healthy Controls

Brain Region	X coord.	Y coord.	Z coord.	t score
S2	63	-30	21	3.53

Studies of Physiology of Gulf War Veterans vs. Healthy Controls, with FM as "Positive Control" Group

- Sensory processing
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Heart Rate Variability as a Surrogate Measure of Autonomic Function

- Subjects included 26 (19F,7M) with FM, 11 (6M,5F) with GWI and 36 (18M,18F) normal controls. HRV was determined from Holter recordings obtained in the Clinical Research Center.
- In FM and in GWI females, HRV was significantly lower than in FM and GWI males. HRV was similar in male and female controls. When HRV was compared by group within gender, HRV was significantly decreased in female FM and GWI and no significant differences were seen for males with these conditions.
- Decreased HRV in FM and GWI appears to be gender-dependent. Results suggest that different mechanisms may be operative in symptom expression in males and females with this spectrum of illness.

Summary

- **Recent research is giving significant insights into the underlying mechanisms of Chronic Multisymptom Illnesses**
  - **CNS disorder**
  - **Triggered by a variety of "stressors"**
  - **Abnormalities in brain function, especially in**
    - **Sensory processing**
    - **Autonomic nervous system**
    - **Hypothalamic pituitary adrenal axes**
- **Very few mechanistic studies have compared GWV to those with CMI that are in general population, but this is an essential "control" group to interpret findings of physiological studies in GWV**