Fibromyalgia and Other Functional Pain Syndromes: Pathophysiology, Assessment, and Management

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Disclosures
- Dr. Cheatle receives a grant from Cordant Health Solutions

Learning Objectives
- Describe the common comorbid conditions related to functional pain syndromes
- Examine the neurobiological mechanisms contributing to functional pain syndromes
- Explain 2 pharmacologic and 2 nonpharmacologic strategies to manage pain in this patient population
Neurobiology of Functional Pain

The Problem

- In our current medical system when a patient complains of pain and no physiological ("organic") problem is found despite an in-depth work up, their symptoms are deemed functional and they are labeled as having a functional pain syndrome.

Widespread Pain → Fibromyalgia
Abdominal Pain → IBS

Bladder/Urinary System Pain → Interstitial Cystitis/Bladder Pain Syndrome

- Different diseases with similar neurobiology/pathophysiology?
Goals

Review Article

REVIEW

NEUROBIOLOGY OF FIBROMYALGIA AND CHRONIC WIDESPREAD PAIN

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(10) 100:59/(3) 100:59 (2016-08-03)
Fibromyalgia

- Prevalence about 2% in general population
- Symptoms are diverse
  - Widespread pain
  - Sleep disturbances
  - Mood disturbances
- Seen mostly in women
- Significant overlap with other "functional disorders"
  - TMJ
  - IBS
  - Chronic fatigue
- Originally termed fibrositis but changed to fibromyalgia

Diagnosis of Fibromyalgia

1. Pain and symptoms over the past 3 months, based on the total number of areas with pain or stiffness is reported over a period of time, you have or you think you may have in these symptoms:
   a. Muscle stiffness
   b. Cognitive/memorial or sleep disturbances
   c. Headaches or other pain conditions
   d. Symptoms lasting at least three months at a chronic level
   e. No other health problem that would explain the pain and other symptoms

Fibromyalgia—Genetics

Environment + Genetics → Fibromyalgia
Pathophysiology-Enhanced Pain Processing

- Tenderness is not confined to tender points but it extends throughout the body
- Tender points are influenced by distress
- More sensitive to other stimuli such as heat, cold, electrical stimuli
- Enhanced sensitivity to smell and auditory tone
- Support for amplification of all sensory stimulation on functional imaging studies with the insular cortex consistently hyperactive

So What Lowers The Pain Threshold?

- Reduced Descending Inhibition

  VS

- Hyperactivity of Excitatory Afferent Systems

Reduced Descending Inhibition

- Applying a painful stimulus in healthy volunteers leads to generalized analgesia
- Decreased/absent in fibromyalgia patients
- Thought to be mediated by endogenous opioidergic and serotonergic/noradrenergic pathways
- Fibromyalgia patients endogenous opioid activity may be elevated at baseline (i.e., already working at full levels and thus can't increase with new pain stimuli)
  - High baseline occupancy of opioid receptors
  - Opioids usually ineffective in most patients with FM
- Unlike the opioid system the serotonergic/noradrenergic system is hypofunctional
  - Decreased norepinephrine and serotonin metabolites in CSF
  - Efficacy of compounds that raise serotonin and norepinephrine may be effective
    - Duloxetine, Milnacipran, TCA, Tramadol
Hyperactivity of Excitatory Afferent Systems

- Central sensitization
- Increased levels of Substance P in CSF of Fibromyalgia patients vs controls
- Increased levels of glutamate in CSF of Fibromyalgia patients vs controls
- Exercise, a proven therapy for FM, alters endogenous neurotransmission by increasing antinociceptive neurotransmitters and reducing glutamate

Central Sensitization

- Pain or stress in the periphery bombard the CNS. This initially causes changes in CNS neurotransmitter release and gene expression. Dorsal horn receptive fields increase
- Ultimately can lead to neuroplasticity and a memory of pain (e.g., after nerve decompression surgery, pain may still be present)
- NMDA receptor and glutamate are important

Augmented Pain and Sensory Processing
Studies Using Experimental Pain/QST Methods

- FM patients are more sensitive to pressure everywhere. Tender points are regions where everyone is more tender.
- FM patients were not more expectant or hypervigilant than controls.
- Pressure pain thresholds at any 4 points in the body are highly correlated with the average tenderness at all 18 tender points and control points.
- FM patients display a decreased threshold to other noxious stimuli, heat, cold, and electrical stimuli.
- FM patients are more sensitive to other sensory stimuli such as sound.

Biologic Amplification of all Sensory Stimuli Gains

Brain Region Connectivity

- Increased connectivity between the default mode network (resting brain) and the insula (a pronociceptive region).
- The degree of increased connectivity related to intensity of ongoing spontaneous pain.
- There may be hypo-connections between areas associated with antinociception regions in the brainstem in FM patients.
CNS Activation/Excitation

- Wind-up of the CNS is seen in some studies of FM patients
- CNS transmitters seen in wind-up are more prevalent in FM patients
  - Substance P, glutamate are elevated in CNS/brain pronociception regions
    - Pregabalin has been shown to decrease glutamine activity in some of these regions and decrease the functional connectivity between the default mode network and insula.
  - Some subsets of patients may respond to agents that block NMDA receptors (ie, ketamine)
- These excitatory neurotransmitters may also play a role in some of the other symptoms associated with functional pain syndromes such as sleep impairment and anxiety.
  - Patients that have pain improvements with pregabalin/gabapentin usually also report improvements in these other symptoms.

Excitation vs Inhibition

- Diffuse noxious inhibitory control (DNIC)
  - Application of intense painful stimulus leads generalized whole body analgesia
    - Consistently reduced or even absent in FM patients compared to controls (but not seen in all FM patients)
    - Also seen in other “functional pain” – TMJ, IBS
- Endogenous opioids
  - Opioid tone is normal or increased
  - FM patients typically have higher levels of CSF enkephalins
  - FM patients without prior exposure to exogenous opioids had reduced baseline mu opioid receptor binding in multiple pain processing regions
  - Some evidence that blocking endogenous opioid release (ie, low dose naltrexone) may help some pts with FM
  - May explain why mu opioid receptors are typically not effective in FM and other functional pain syndromes
**Excitation vs Inhibition**

- Reduced DNIC may result from reduced serotonergic and adrenergic activity
  - Lower levels of metabolites noted in FM patients CSF
  - Rats given reserpine (depletes biogenic amines) develop widespread muscle and cutaneous hyperalgesia
  - Behavior associated with depression in rats also seen after being given reserpine
- Reasoning behind using agents that raise both serotonin and norepinephrine-SNRI (duloxetine, milnacipran), TCA, tramadol
- TENS unit, sleep, exercise potentiate descending inhibition

**Psychological Factors and Fibromyalgia**

**Psychological Factors**

- Various stressors are correlated with severity of functional pain
- Better correlated with personal stressors rather than generalized stressors
- Changes in stress response early in life can predict which symptom free individuals are more prone to develop chronic pain issues
- Studies show hyper/hypo activity in the hypothalamic-pituitary axis in functional pain syndromes
  - Not consistent: did HPA changes come before or after pain?
Some studies note increased circulating inflammatory mediators and enhanced release of cytokines.

- But some also show a decrease and others no differences compared to controls.
- Studies also vary due to low sample sizes and different analysis methods.
- Some interleukins, cytokines, and tumor necrosis factor alpha may sensitize nerve endings/nociceptors and produce pain in humans. They are also known to produce hyperalgesia in animals.
- NSAIDs and other anti-inflammatories have not been shown to be beneficial in fibromyalgia or other functional pain syndromes.

Central nervous system is thought to be the key player.

- Some patients may have a peripheral component.
- Mood and sleep disorders contribute to the patient's pain experience.
- The immune system may also play a role.
Functional Pain Syndromes:
Pharmacology/Medication Management

- Irritable bowel syndrome (IBS)
- Fibromyalgia
- Interstitial cystitis
- Vulvodynia

Key observations:
- Outcomes are best with integrated care
- Data supporting use of specific medications may be weak
- Opioid use is subject to adverse selection in these patient populations

Irritable Bowel Syndrome

- Functional bowel disorder characterized by:
  - Symptoms of abdominal pain or discomfort and changes in bowel function for at least 3 days/month for at least 3 months
- Spectrum of severity
  - Mild IBS patients have few symptoms, report good health-related QOL, seek medical care on average once a year
  - Severe IBS have high number of symptoms (abdominal pain, bloating, dietary restrictions), report fair to poor HRQOL, seek medical care 2-7 times a year
- Classification based on stool consistency
  - Constipation-predominant IBS-C
  - Diarrhea-predominant IBS-D
  - Alternating between constipation and diarrhea IBS-M
  - Unsubtyped IBS

Irritable Bowel Syndrome (cont’d)

- Patients with IBS often have significant symptom burden
  - Fatigue (69.3%)
  - Sleep disturbance (67.3%)
  - Back pain (37.3%)

- Patients with IBS are more likely than the general population to have depression and anxiety
  - 30% of patients with IBS have reported thoughts of suicide
  - Psychosocial factors (physical, sexual, psychological abuse, and psychiatric conditions) are reported more commonly in patients with severe IBS

Pharmacology Is NOT First-line Treatment

- Lifestyle changes
- Dietary modification
- Proper integrated treatment for anxiety and depression
  - Psychological therapies are at least as effective as most medication options

- Of the medications with demonstrated improvements in IBS symptoms:
  - Lubiprostone
  - Linaclotide
  - Rifaximin
  - Fiber supplementation, and
  - Peppermint oil

  Have the most reliable evidence supporting their use

Medications to Improve Colonic Transit Time (IBC-C)

- Lubiprostone
  - Selective chloride channel activator
  - Studied for treatment of IBC-C
    - Labeled dose is 8 mcg twice daily
    - Studies evaluated response up to 48 mcg twice daily
  - Moderate to significant relief compared with placebo
  - Onset of efficacy starts at 1 month of treatment
    - Some symptoms were not improved until 2 months

  - Adverse events include
    - Nausea, vomiting, diarrhea, abdominal pain and distension
    - Taking with food and water may help

  - Pharmacology Is NOT First-line Treatment
  - Of the medications with demonstrated improvements in IBS symptoms:
    - Lubiprostone
    - Linaclotide
    - Rifaximin
    - Fiber supplementation, and
    - Peppermint oil
  - Digestion (2014) 89:2534-267
Targeting Gut Microbiota

- **Rifaximin**
  - Nonsystemic antibiotic approved for treatment of IBS-D in May 2015
  - Originally approved for travelers' diarrhea and hepatic encephalopathy
  - 40% patients report global improvement in symptom burden
  - Treatment duration is 2 weeks, and effect can last 3 months
  - Adverse effects were no different than placebo

Medications to Improve Colonic Transit Time (IBC-C)

- **Linaclotide**
  - Guanylate cyclase-C agonist
  - Drug leads to an increase of intestinal fluid in the GI lumen, thus increasing GI transit time
  - Almost 50% of patients report more than 30% reduction in pain
  - Approved dose is 290 mcg daily
  - Best taken on an empty stomach 30 min before breakfast
  - Onset of symptom relief may be within first week

  - Common adverse events are dose related and commonly occurred within first 4 weeks or treatment
    - Diarrhea
    - Flatulence
    - Abdominal pain

Antispasmodics and Peppermint Oil

- Several antispasmodics improve symptom burden over placebo
  - Otilonium
  - Hyoscyamine bromide
  - Clidinium bromide
  - Pinaverium bromide
  - Dicyclomine hydrochloride

- Multiple trials support the use of peppermint oil for improving IBS symptoms
  - 9 trials, 726 patients
  - Product is NOT FDA approved
  - Batch-to-batch consistency may be a problem
Medication Treatment Options for IBS

- **SSRIs**
  - Pooled data from 7 RCTs documented decreased symptom burden with treatment

- **TCA**
  - Pooled data from 11 RCTs documented decreased symptom burden

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Gabapentin and Pregabalin

- Small studies have demonstrated benefit in patients with all types of IBS
  - Gabapentin dose 200 mg every 8 hours
  - Pregabalin starting dose was 50 mg every 8 hours

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Fibromyalgia Medications
Fibromyalgia: Key Points
- Medications are NOT mandatory for the management of fibromyalgia
- Available medications have a modest effect, and patients often discontinue medications due to adverse effects
- Expectations for value (both patient and physician) are often too high, leading to poor decision making (again, but on the part of the patient and the physician)

Fibromyalgia: First Line Medications
- Amitriptyline (TCAs)
- Duloxetine
- Pregabalin
- Milnacipran

How modest is the effect?

<table>
<thead>
<tr>
<th>Drug</th>
<th>N/C participants</th>
<th>Pain reduction (drug vs placebo, %)</th>
<th>Drop out rate due to adverse events, (drug vs placebo, %)</th>
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<tbody>
<tr>
<td>Duloxetine</td>
<td>5 / 1,894</td>
<td>46.8 vs 29.0</td>
<td>31.1 vs 15.2</td>
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<td>Duloxetine</td>
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<td>36.4 vs 28.0</td>
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<td>36.4 vs 23.6</td>
<td>13.1 vs 11.0</td>
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<td>TCAs</td>
<td>9 / 357</td>
<td>46.3 vs 21.0</td>
<td>13.0 in 6.4</td>
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<tr>
<td>Pregabalin</td>
<td>5 / 3,329</td>
<td>40.8 vs 19.9</td>
<td>11.0 vs 11.0</td>
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</tbody>
</table>
Impact of Medications on Outcomes Is Limited

- Review of large data sets document that patients often stop medications prescribed for fibromyalgia
  - 150 days with TCAs
  - 25% stop in 1 year and 50% stop in 2.5 years for pregabalin, duloxetine, and milnacipran
- This is likely driven by global impression or change
  - Modest improvement in pain intensity report
  - No significant long-term improvement in fatigue or physical functioning
  - Medications perceived as causing harms

Other Medication Options

- Tramadol
  - 1 study with 313 patients reported lower pain and improved QOL at 12 weeks
  - Open-label safety study demonstrated continued pain relief, no change in HRQOL
- Cyclobenzaprine
  - Meta-analysis of 5 RCTs with 392 patients demonstrated improved pain and sleep at 4 and 24 weeks
  - A recent RCT with 36 patients demonstrated improved outcomes at 8 weeks

Potent Opioids for Fibromyalgia

- There are NO large RCTs evaluating role of opioids in fibromyalgia
  - Small studies report no value
  - A large dataset of 295,758 patients with fibromyalgia documented that 1.3% received chronic opioids
  - Opioid use appears to be associated with negative HRQOL
- Canada and Germany guidelines strongly discourage opioid use
  - Lack of supporting evidence
  - High risk of poor outcomes

International J Rheumatic Dis (2011) 14:6-11
Schmerz (2011) 25:402-404
### Drugs That Have FAILED Fibromyalgia Clinical Trials

- Valacyclovir
- Antidepressants
  - Amoxapine
- Bromazepam
- Dopamine agonists
  - Pramipexole
  - Ropinirole
- Tramadol
- Opioids
- Calcium
- Dehydroepiandrosterone
- Prednisone
- Hypnotics
- Zolpidem
- Interferon
- Ketamine (IV)
- Local anesthetics (IV)
- Ribose

### Drugs That Might Work

- Cannabinoids
  - Weak evidence to support efficacy
- Growth hormone
  - 3 RCTs of 157 total patients demonstrated benefits on pain and fatigue at 9 and 18 months
- Quetiapine
  - 4 RCTs (1 published) suggests possible benefit
- Naltrexone
  - Low dose (4.5 mg daily)
  - 2 RCTs with 31 patients demonstrated improvement in pain and mood with low-dose naltrexone (no benefit for fatigue and sleep)

### Interstitial Cystitis
Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)

- New nomenclature and classification system developed by the European Society for the Study of IC/BPS
- Diagnostic criteria:
  - Chronic pelvic pain lasting more than 6 months
  - Pressure/discomfort perceived to be related to the urinary bladder
  - One or more urinary symptoms such as urgency or frequency
- Since pain is the fundamental character, they suggested changing the name to BPS
- American Urological Association requires exclusion of other identifiable causes

Diagnosis and Classification

1. Patient selection
   - Chronic pelvic pain perceived to be related to the urinary bladder
2. Exclusion of similar diseases
   - Cancer, infection, diverticulum, prolapse, endometriosis, among others
3. Classification
   - Cystoscopic findings
   - Biopsy findings*
   - Utility unvalidated

IC/BPS May Be a Visceral Neuropathic Pain Condition

- TCAs
  - Have been demonstrated to have an effect in small clinical trials
  - About 40% of patients on amitriptyline 25-75 mg daily reports 30% or better pain relief at 4 months
- Gabapentin/pregabalin
  - Supported via case series reports only
  - About 50% patients report clinical meaningful relief
Interstitial Cystitis

- Anticholinergics
  - Can be used to treat the urinary frequency component of IC
  - Most commonly used agent is hydroxyzine

Vulvodynia

- Persistent vulvar pain in the absence of any obvious disease pathology

- No consensus on the underlying cause of the disorder

- Commonly thought of as a "multifactorial disorder." Others have advocated that vulvodynia and BPS should be considered as functional pain disorders
Vulvodynia Treatment Options

- Topical therapies
  - Often compounded combination therapies
  - Decisions guided by opinion and not data

Expert Committee Treatment Options

- Committee formed as part of the 4th Annual Consultation on Sexual Medicine
  - Reviewed available data on treatment options
- They basically advised against medications:
  - Topical lidocaine
  - Topical capsaicin
  - Botulinum toxin A
  - Corticosteroids
  - Interferons
  - NSAIDs
  - Hormonal therapy
  - TCAs
  - Anticonvulsants

They advocated for vestibulectomy as the treatment option of choice

(J Sex Med 2016; 13:243-300)

Vulvodynia: a Visceral Neuropathic Pain Condition

- TCAs
  - Have been demonstrated to have an effect in small clinical trials
  - Outcome measures were not precise and the true drug effect is not clear

- Gabapentin/pregabalin
  - Small trials and case series report benefit with gabapentin
  - Again, limited data on outcomes and the supportive data are weak

Biopsychosocial Approach to Assessing and Managing Patients With Functional Pain Syndromes

Mind-Body Medicine

- Persistent Pain
- Secondary medical problems
- Sleep disturbance
- Cognitive distortions
- Substance misuse, abuse
- Depression
- Anxiety

Mind-Body Medicine

Health
Mind
Body
Spirit
Fitness
Relieving Pain in America: Institute of Medicine June 2011

- We believe pain arises in the nervous system but represents a complex and evolving interplay of biological, behavioral, environmental, and societal factors.

http://www.nap.edu/catalog.php?record_id=13172

Biopsychosocial Approach to CPS

Comprehensive pain management programs based on the biopsychosocial model of pain, typically emphasizing cognitive behavioral therapy, a graded exercise program and appropriate medication management have been shown to significantly improve treatment outcomes (return to work, pain reduction and increase in activity).

Gallagher, 1999
Loeser & Turk, 2000
McCaree & Turk, 2003
Ondra & Gallagher, 2006
Biopsychosocial Treatment Program for FPS

- CBT
- Functional restoration
- Evidence-based rational pharmacotherapy
- Social support
- Graded motor imagery

CBT/ACT

Cognitive Behavioral Therapy

- CBT focuses on maladaptive thought patterns (catastrophizing) and behaviors (kinesiophobia) that occur frequently in patients with CNCP
- The objective of CBT is to guide the patient in recognizing and reconceptualizing his/her personal view of pain, identifying their role in the process of healing and promoting the patient being proactive rather than passive, and competent rather than incompetent
- CBT include specific skill acquisition (relaxation therapy, stress management, cognitive restructuring) followed by skill consolidation and rehearsal, and relapse training (Turk, Flor, 2006)
Efficacy/Effectiveness

- Objective: evaluate the effectiveness of CBT for FM

- Main results: 23 studies met inclusion criteria with a total of 2031 patients included. CBT was superior to controls in pain reduction, reducing negative mood and reducing disability both at end of treatment and at 6 month follow up

Acceptance and Commitment Therapy

- Acceptance and commitment therapy (ACT) is a form of CBT that is a directive and experiential type of therapy based on rational frame theory. The goal of ACT is to experience life mindfully and reinforce psychological flexibility

- The core processes of ACT include:
  - Contact with the present moment
  - Self as context
  - Diffusion
  - Acceptance
  - Values
  - Committed action

- There are 5 randomized control trials on the use of ACT in chronic pain demonstrating efficacy in improving mood and function
171 subjects with chronic MSK completed a course of ACT.
At a 3 year follow up 68% of the cohort noted improvement in key outcomes including pain related anxiety, physical and psychosocial disability, and depression.
Functional Restoration

- Focus on improvement of functional restoration
  - Occupational and physical therapy
    - The most effective treatment option
    - Desensitization and resetting altered central processes of the brain
  - Aquatic therapy
    - Hydrostatic principle and buoyancy component
    - Mild compression force around affected extremities
      - Decrease edema
      - Assist in weight bearing of the extremity

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<th>OS</th>
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<th>P-value</th>
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<td>Low-back pain</td>
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<td>Risk of suicide</td>
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<tr>
<td>Fibromyalgia</td>
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<tr>
<td>Low-back pain</td>
<td>4.723</td>
<td>0.019</td>
</tr>
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</table>
Social Support

Graded Motor Imagery (GMI)

Pain Is a Disease of the Brain
- Theory of pain modulation based on nociception
- Pain perception involves all areas of the brain
Factors That Influence Nociceptive Inputs to Pain Perception

Tracey, I. Neuron 55, August 2, 2007

CNS Plasticity in Pain
CNS reorganization in a variety of chronic pain states: review.
Henry, Chiodo, Yang. PM&R Vol 3 Dec 2011

- CNS reorganization in response to sensory and emotional experiences
- Both structural and functional intrinsic changes are demonstrated
- Changes occur in number/location of synapses

Neuroplasticity Changes in PLP
- Phantom limb pain
  - Remapping of somatosensory cortex
  - Brain activity changes in ipsilateral motor cortex, thalamus, insula, fundobul, ACC
Pain catastrophizing and neural responses to pain among persons with fibromyalgia. 

Increased activity in brain areas related to: anticipation of pain (FC), attention to pain (ACC, PFC) emotional aspects of pain (amygdala)

What Is Graded Motor Imagery (GMI)?

- Therapeutic technique
- Began approximately 28 years ago
- Developed by a group of professional staff at the Neuro Orthopaedic Institute (NOI) group in Australia
- Lorimer Moseley credited with researching and progressing techniques
- Is progressively expanding and is taught internationally
- Research is ongoing

GMI Continued...

- Based on research, the brain is adaptable and changes over the course of our lives
- The brain can be "retrained" to help reduce pain
- GMI uses "brain exercises" to retrain how the brain processes pain

"Graded Motor Imagery is the most up to date rehabilitation program – based on the latest science and clinical trials to treat many complex pain, and movement problems" (noigroup.com)
How is GMI used in therapy?

Three phases:
1. Laterality training
2. Explicit motor imagery
3. Mirror therapy

Who is GMI used with?
- People with:
  - Chronic pain
  - Chronic regional pain syndrome (CRPS)
  - Brachial plexus injuries
  - Amputations
  - Stroke/CVA
  - Arthritis
  - Fibromyalgia

*GMI techniques can be individualized for any diagnosis, depending on the person’s needs*

View Video:
http://vimeo.com/2014/18/32/what-is-graded-motor-imagery/
References/Further Information on GMI

- http://www.bodyinmind.org/
- Lorimer Moseley’s TedX Lecture: "Why Things Hurt?"
  https://www.youtube.com/watch?v=gwd-wLdHJs

New Frontiers

Multimodal Approach
Thank you !!!

Q and A ?