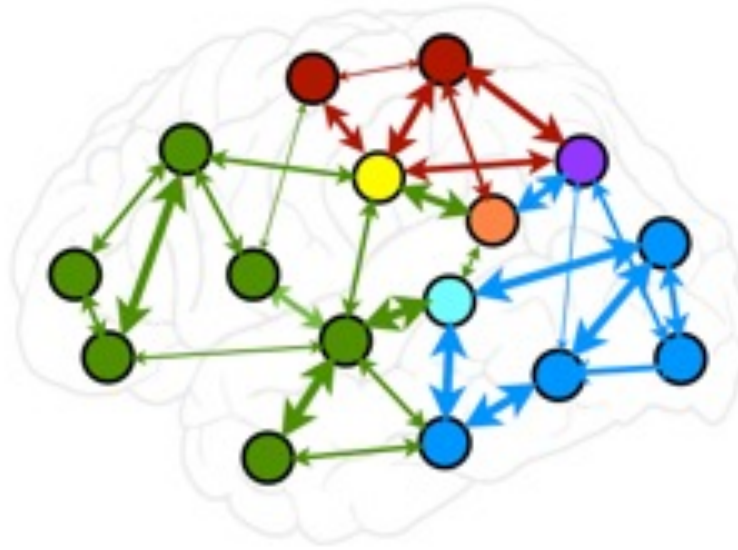


# Acupuncture and Acupressure for Chronic Pain



**Richard E. Harris, PhD**  
**Samueli Endowed Chair and Professor**  
**University of California at Irvine**



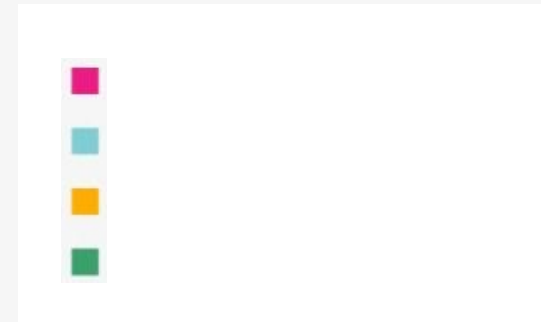
# Conflicts of Interest

- **I have no conflicts of interest to declare for the content of this presentation.**

# Chronic Pain in the United States



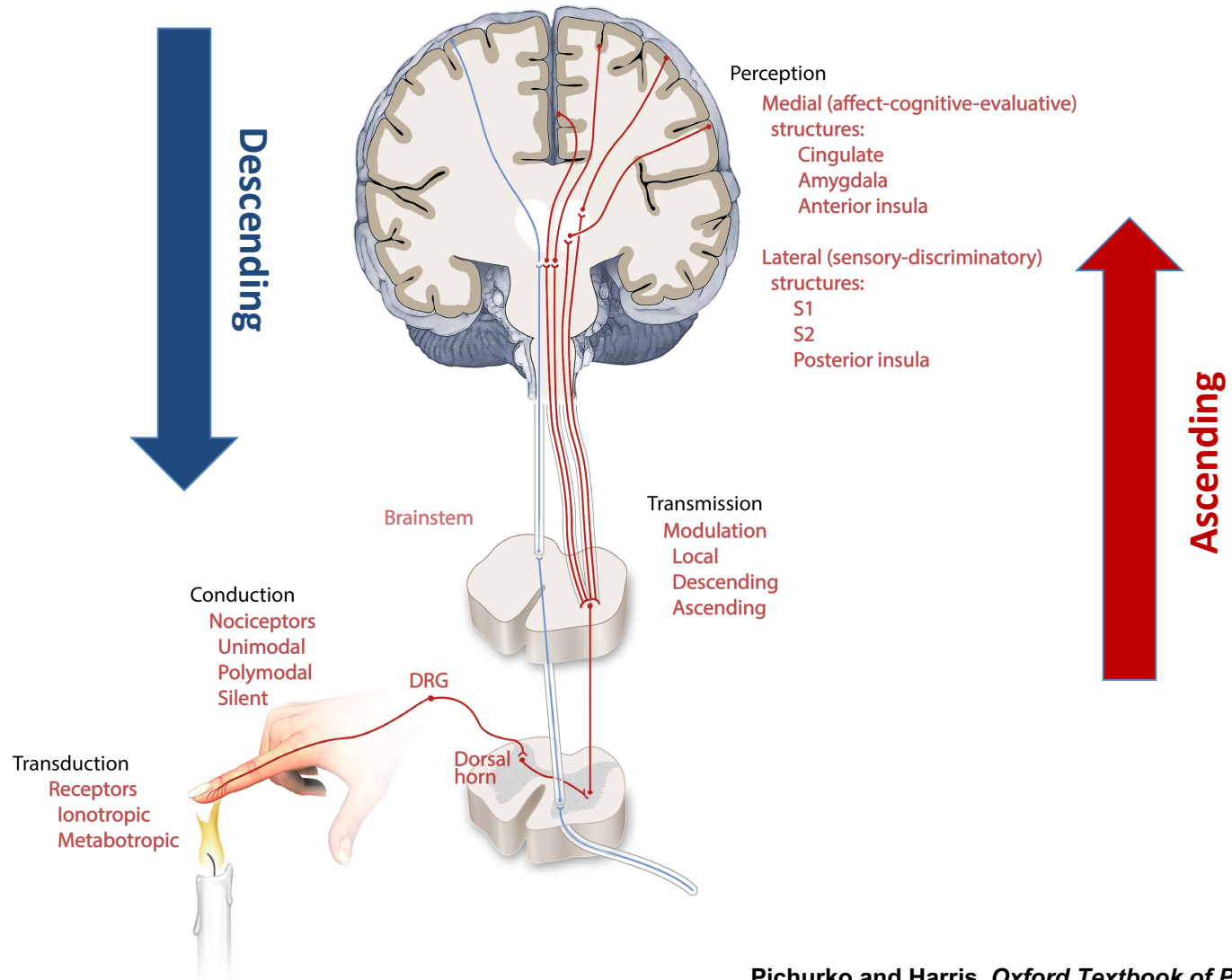
**MORE PEOPLE LIVE WITH CHRONIC PAIN THAN CANCER, HEART DISEASE, AND DIABETES, COMBINED.**



Sources: National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Institute of Medicine

**...by the numbers**

# Pain Pathways...the “simple”



# Mechanistic Characterization of Pain – *The 3 Ns*

Variable degrees of any mechanism can contribute in any pain disorder

Nociceptive	
<b>Cause</b>	Inflammation or tissue damage of nociceptors (normal function)
<b>Clinical features</b>	Pain is well localized, consistent effect of activity on pain
<b>Screening tools</b>	
<b>Treatment</b>	NSAIDs, injections, surgery, opioids (?)
<b>Classic examples</b>	<ul style="list-style-type: none"><li>• Osteoarthritis</li><li>• Autoimmune disorders</li><li>• Cancer pain</li></ul>

Mix

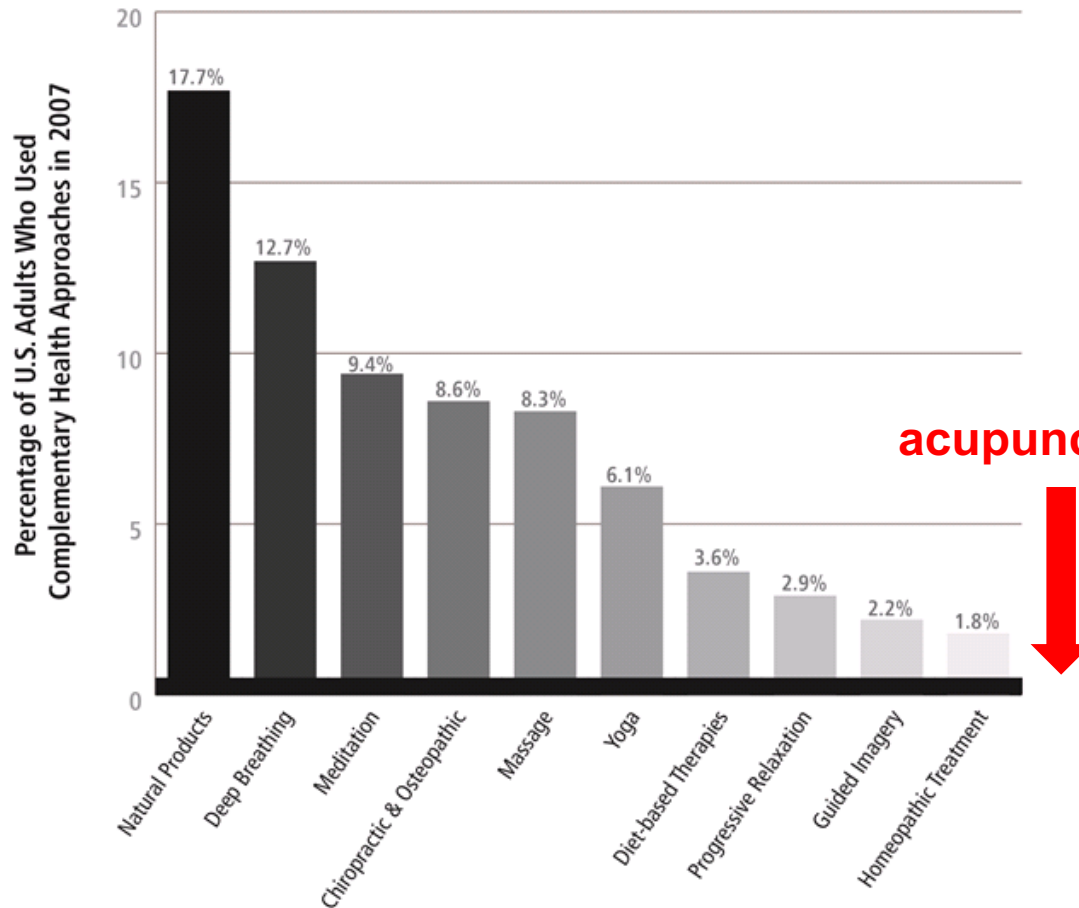
# Integrative Medicine for Pain

- **Pain is one of the major reasons for individuals to seek integrative medicine.**
  - Barnes et al. Adv Data 2004
- **Mind/body interventions are used extensively in integrative and alternative medicine.**
  - Acupuncture/Acupressure
  - Meditation/Chi Kung
  - T'ai Chi



# How much are Integrative Therapies Used in the US?

10 Most Common Complementary Health Approaches Among Adults—2007



In 2007, approximately 38% of adults over 18 years of age used some form of CAM in the US.

This same year over 33.9 billion dollars were spent on “out-of-pocket” visits to CAM practitioners. **~4 billion spent on acupuncture.**

# What is Acupuncture?





# Acupuncture is...

- **A single component of East Asian medical treatment.**
- **Often used in conjunction with herbs, Tai Chi (exercise), Tui Na (massage), cupping, and life style changes.**
- **Acupuncture needles are inserted into specific points on the body (acupoints) and stimulated.**
  - **Mechanical, thermal, electrical, and chemical**

# Acupuncture Meridians and Point Location

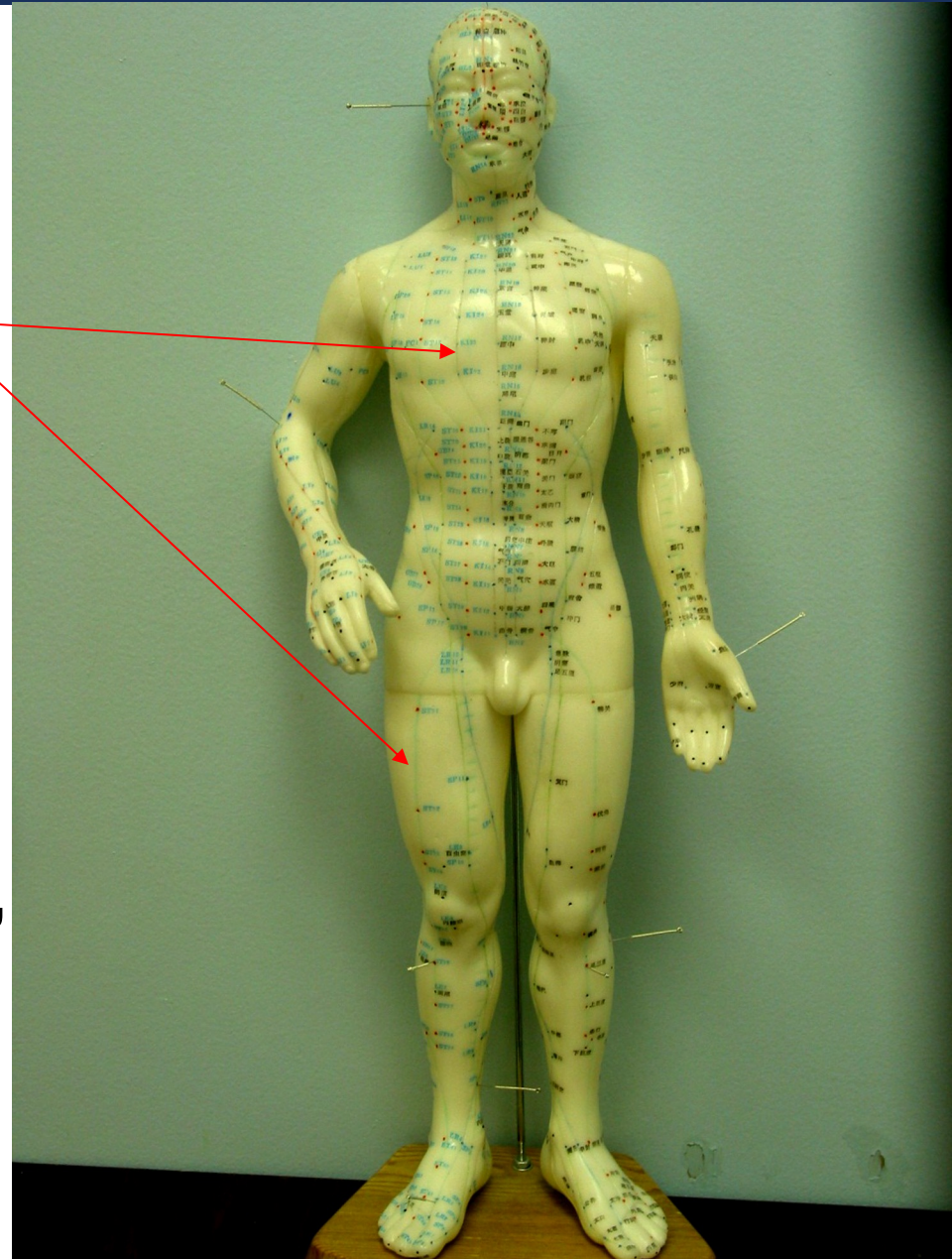
**Meridians are channels through which Qi or energy flows**

**Needles balance Qi**

**Styles: Chinese, Korean, Japanese, French**

Acupuncture theory requires:

- 1) Correct needle placement
- 2) Correct needle stimulation



# Acupuncture Origins

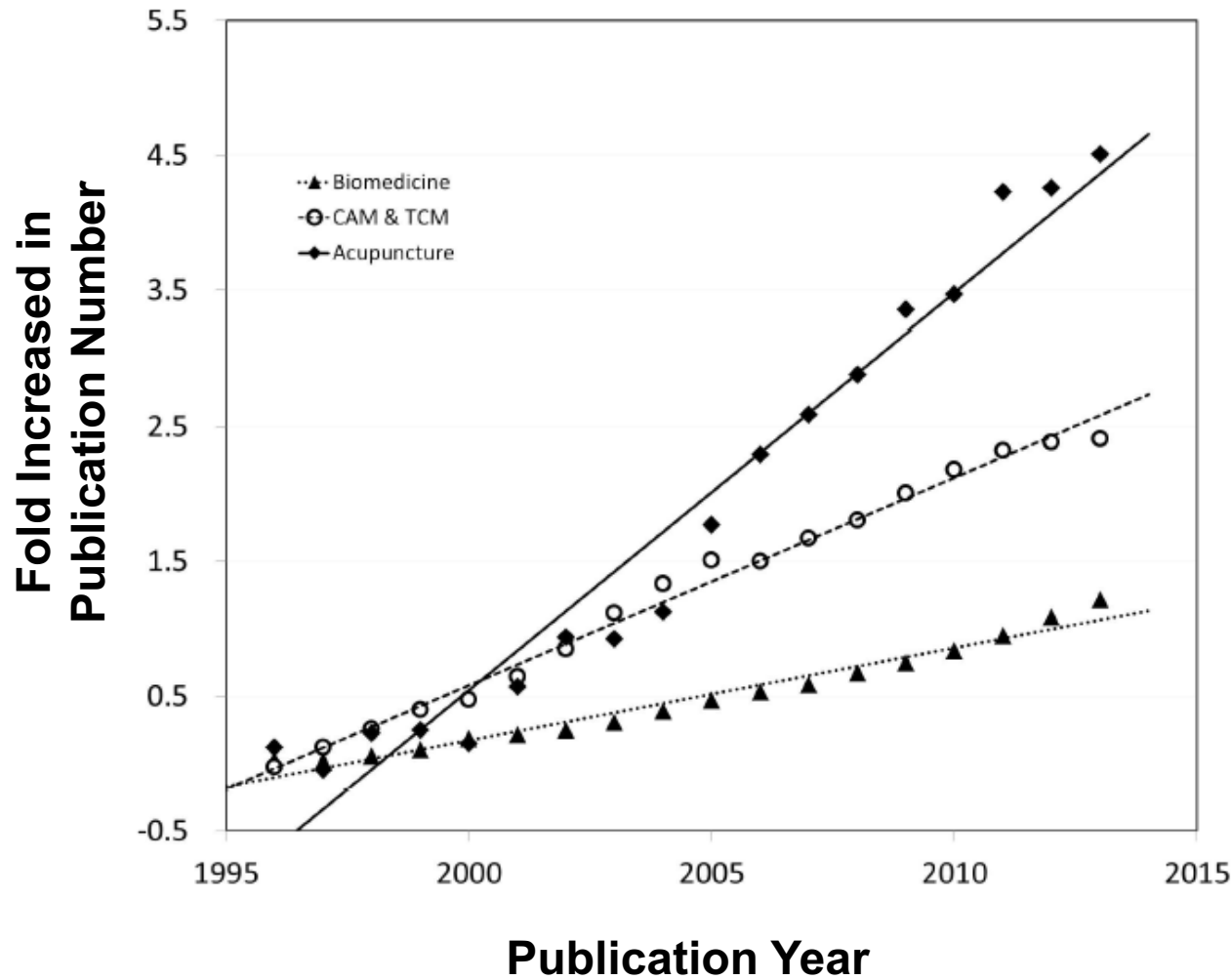
- **Bones and stones at burial mounds in China suggest over 3,000 year old tradition in Asia.**

**But...Otzi the iceman.**

- **Discovered in Alps in 1991.**
- **Over 5,000 yrs. old.**
- **Over 50 tattoos along acupuncture meridians.**

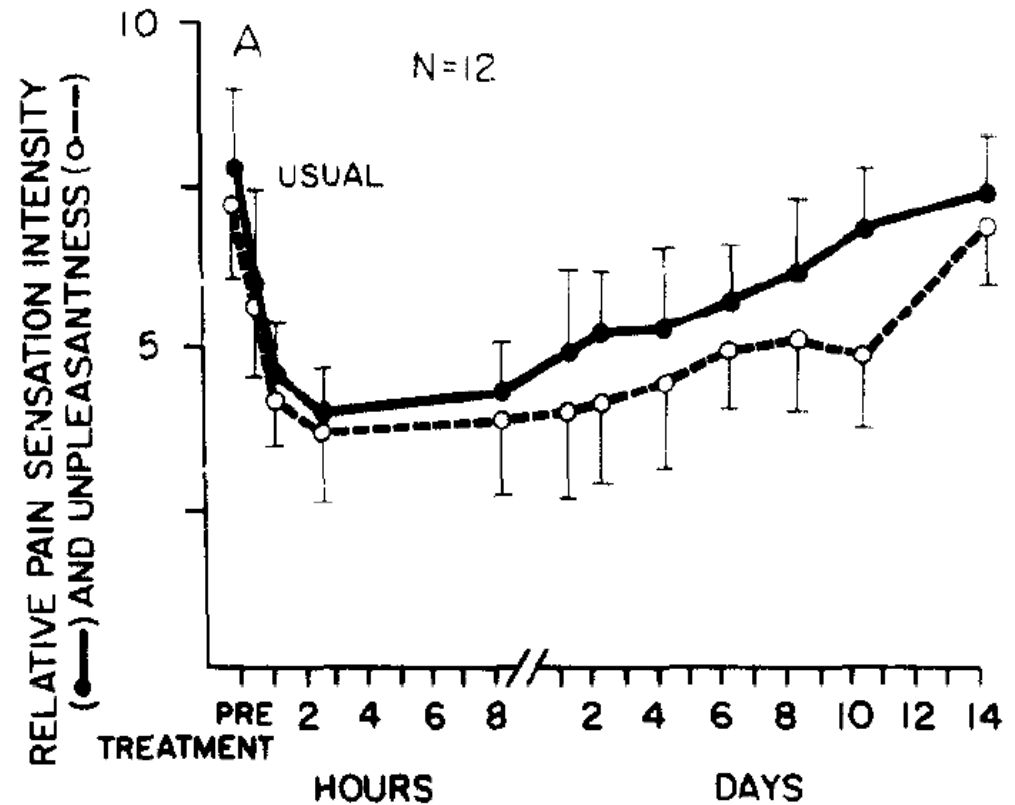


# Rise of Acupuncture Research



# Temporal Dynamics of Acupuncture

- Acupuncture analgesic effect (VAS of chronic low back pain) is maximal *several hours* to 2 days after treatment
- What are the dynamic mechanisms involved in acupuncture effects?



# Key Research Questions to ask About Acupuncture

**Question 1: is acupuncture better than standard care, usual care, waitlist, etc for chronic pain?**



**Question 2: is acupuncture better than sham acupuncture for chronic pain?**

[www.acupuncturetrialistscollaboration.org](http://www.acupuncturetrialistscollaboration.org)

# Results

**Raw data obtained from 29 trials with  
17,922 patients:**

**20 trials with sham controls  
(5,230 patients)**

**18 trials with non-acupuncture controls  
(14,597 patients)**

# Individual Patient Data Meta-Analysis

## Acupuncture vs. Non-acupuncture Controls (n= 14,597) and vs. Sham Controls (n= 5,230)

Indication	Effect size (Fixed effects)	All P-Value
<b>Acupuncture vs. Non-acupuncture controls OR vs. Sham controls</b>		
Migraine/headache	0.42 (0.46, 0.37)	<b>0.15 (0.24,0.07)</b> P<0.001
Osteoarthritis	0.57 (0.64, 0.50)	<b>0.16 (0.25,0.07)</b> P<0.001
LBP & Neck Pain	0.55 (0.58, 0.51)	<b>0.23 (0.33,0.13)</b> P<0.001

### Effect sizes:

0.8 = LARGE

0.5 = MODERATE

0.3 = SMALL

NSAIDS for KOA = 0.15-0.20

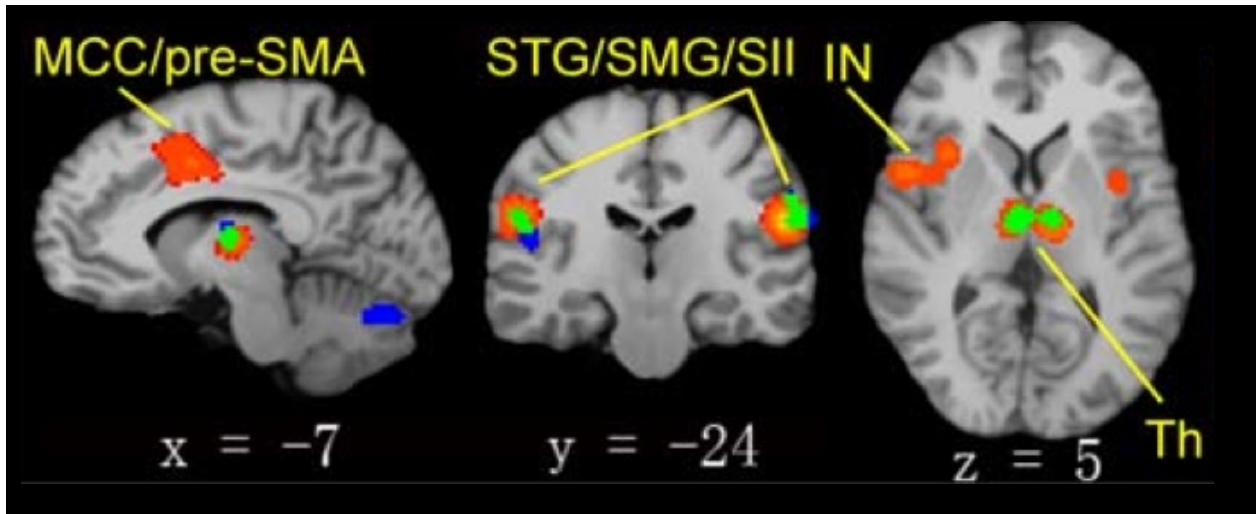
Zhang et al. *Arth Rheum Dis* 2004

Pregabalin for FM = 0.25-0.30

Hauser et al. *Pain* 2009



# Acupuncture and Sham Acupuncture can both Evoke Sensory Afference

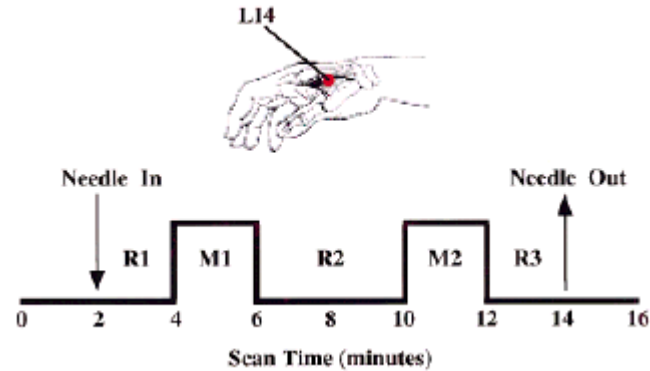
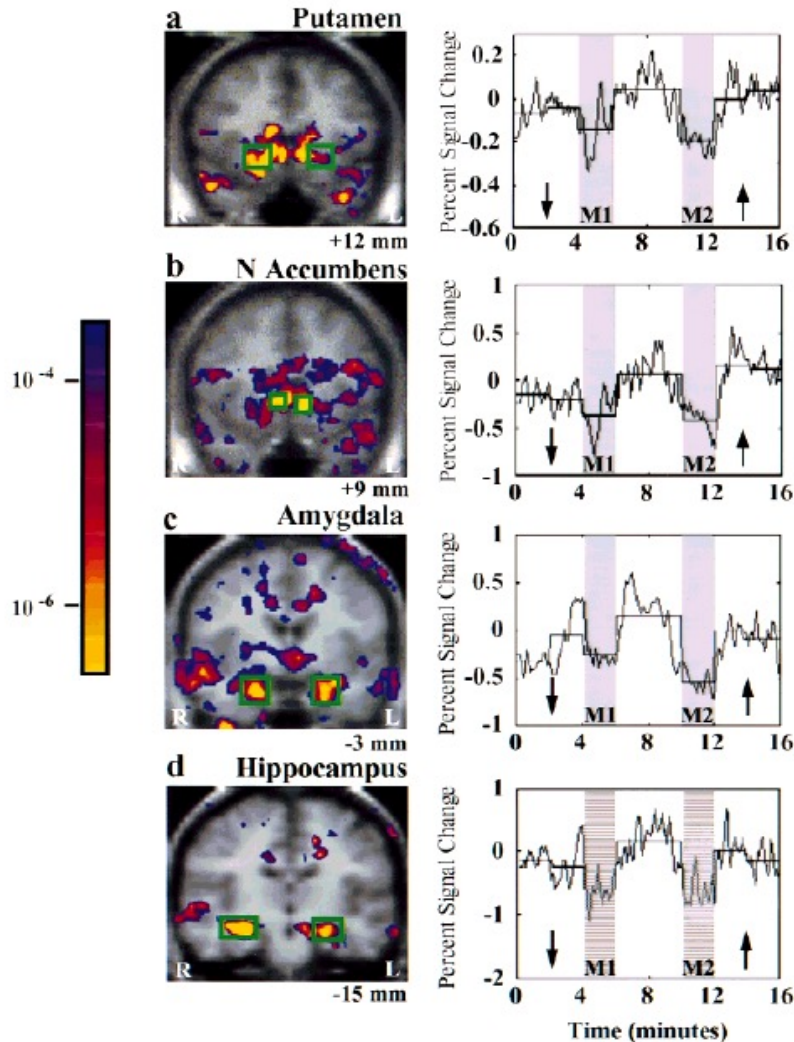


- verum acupuncture stimulation > rest
- sham acupuncture stimulation > rest
- overlap

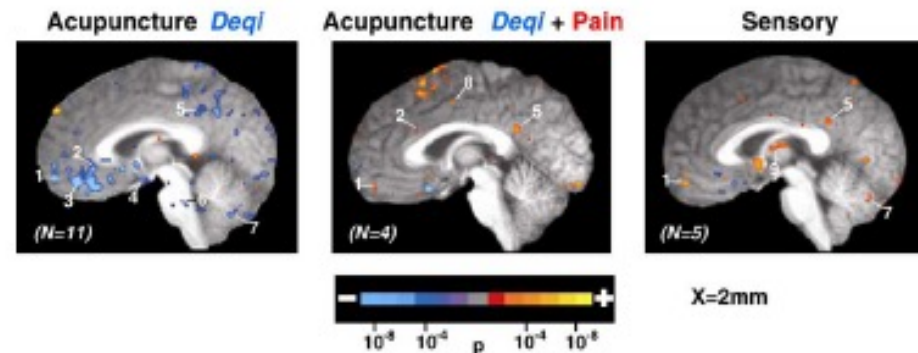
**Meta Analysis of 34 fMRI studies of acupuncture needle stimulation finds overlapping yet distinct regions of brain activation between acupuncture and sham acupuncture.**

**Somatosensory areas (as well as affective and cognitive regions) are altered.**

# Acupuncture Needle Manipulation Deactivates the Limbic System



Subsequent work then shows that this deactivation is during *De Qi* only and is not seen during pain.



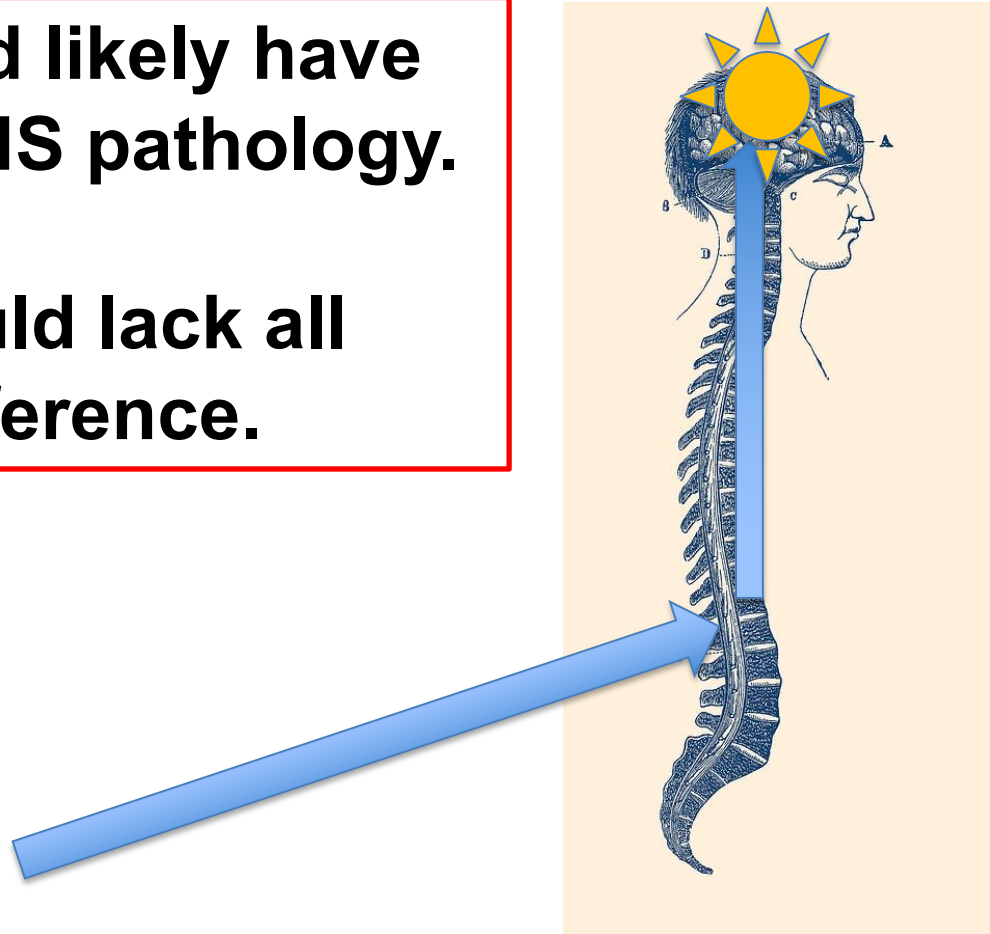
Hui et al *HumBrainMapping* 2000  
 Hui et al *Neuroimage* 2005

# Research Question

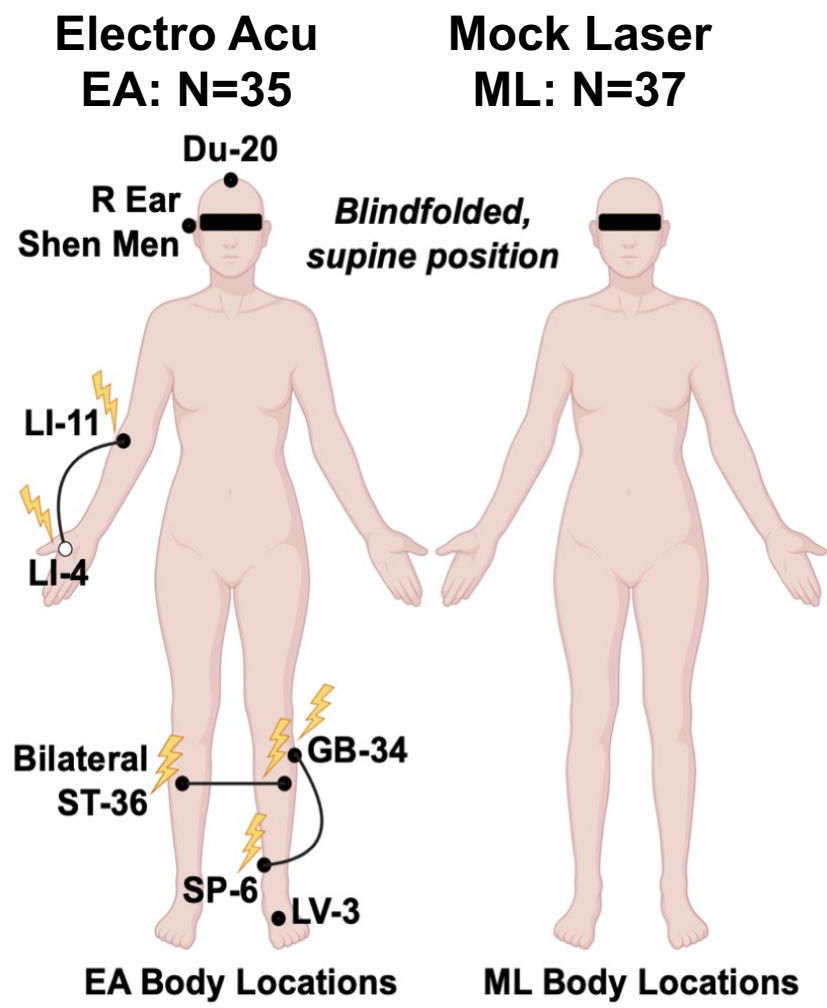
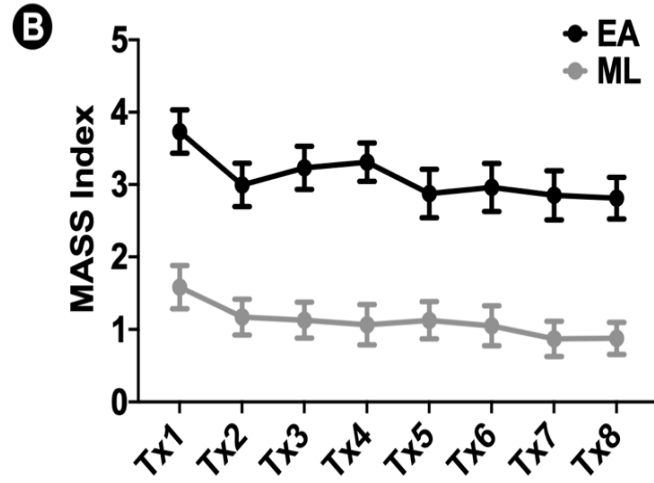
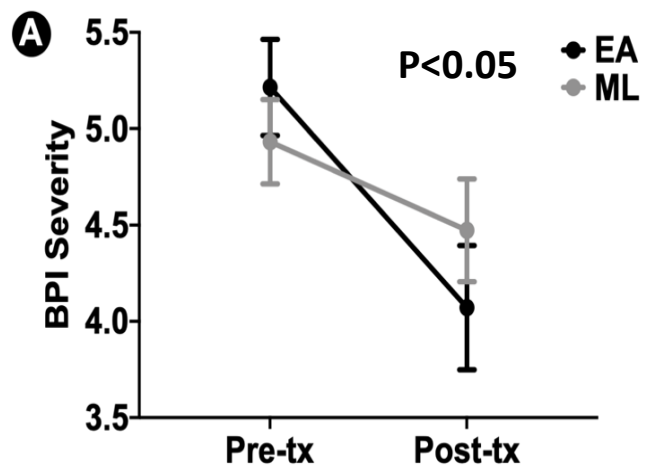
**What is the contributing factor of somatosensory afference toward acupuncture analgesia?**

**Pain patient should likely have some degree of CNS pathology.**

**Sham control should lack all somatosensory afference.**



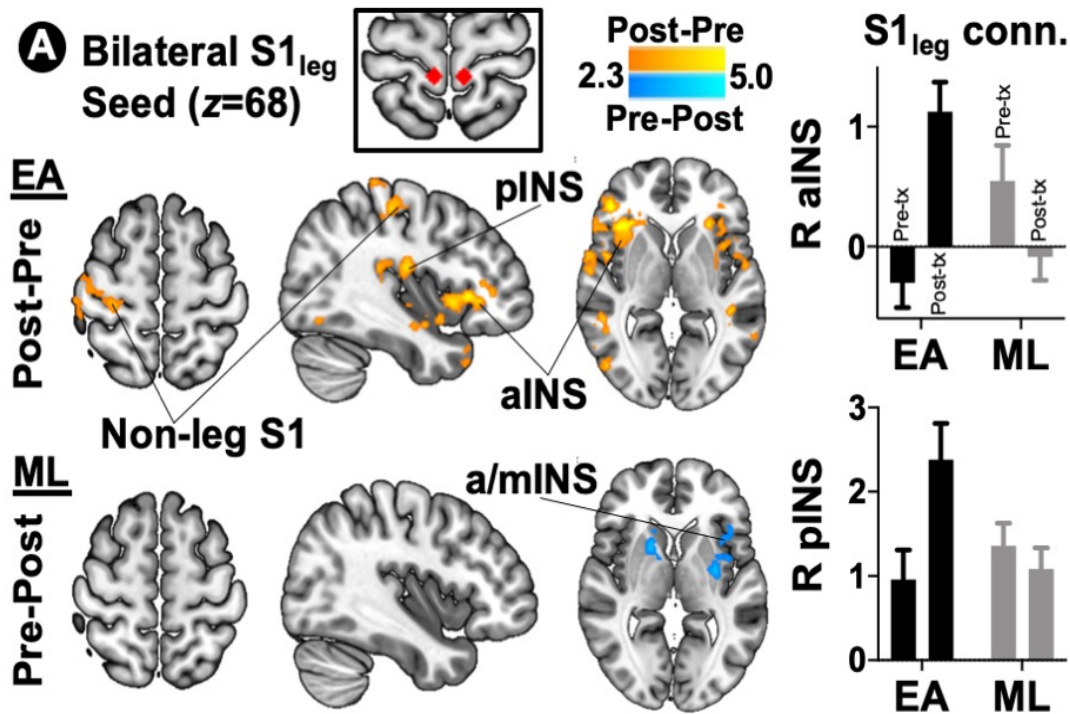
# Acupuncture Somatosensory Afference in Fibromyalgia: Study Design and Analgesia



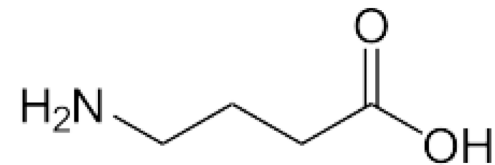
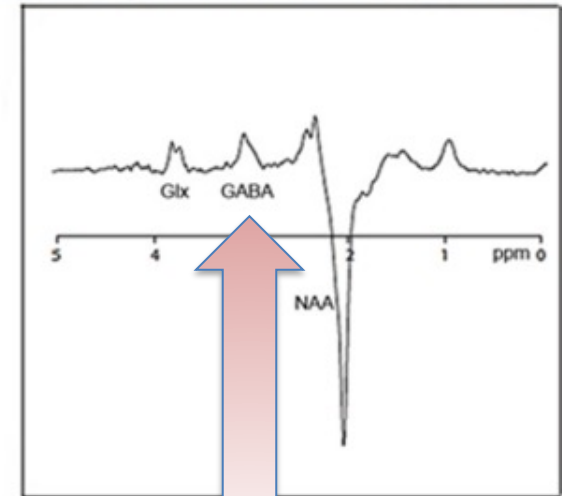
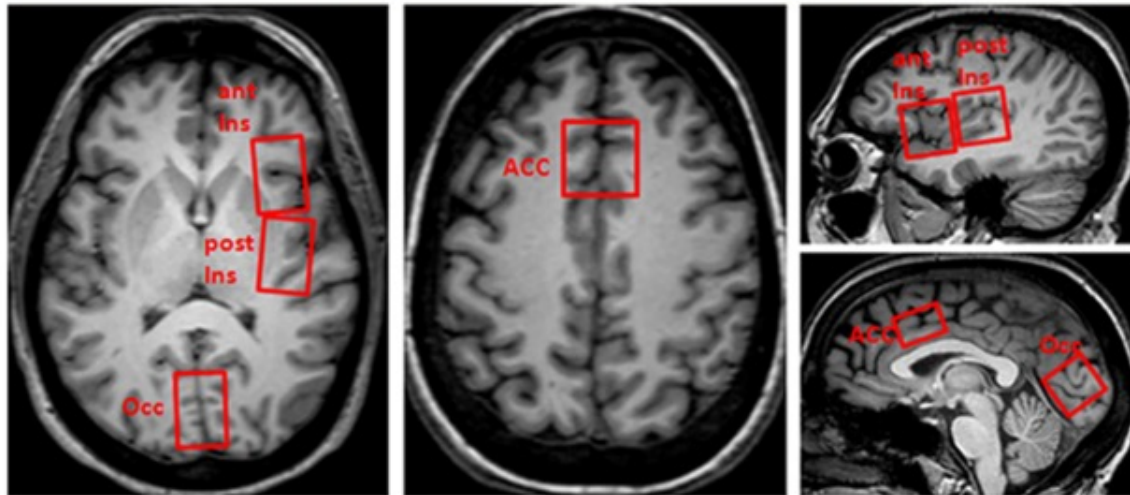
Ishtiaq Mawla



# EA Increases $S1_{leg}$ -Insula Connectivity which is Associated with Less Pain



# Proton Magnetic Resonance Spectroscopy (<sup>1</sup>H-MRS)



- **Metabolites**

  - GABA**

  - Glx (glutamate + glutamine)**

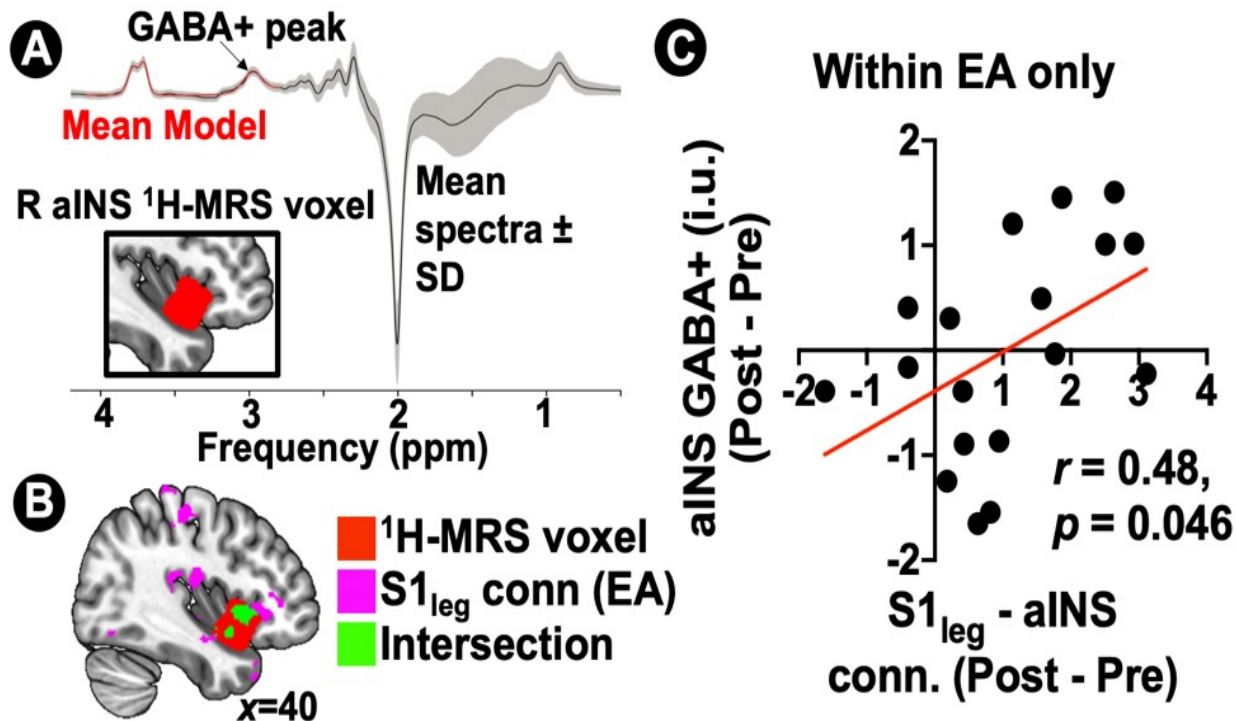
  - N-acetyl aspartate (NAA)**

  - Creatine (Cr)**

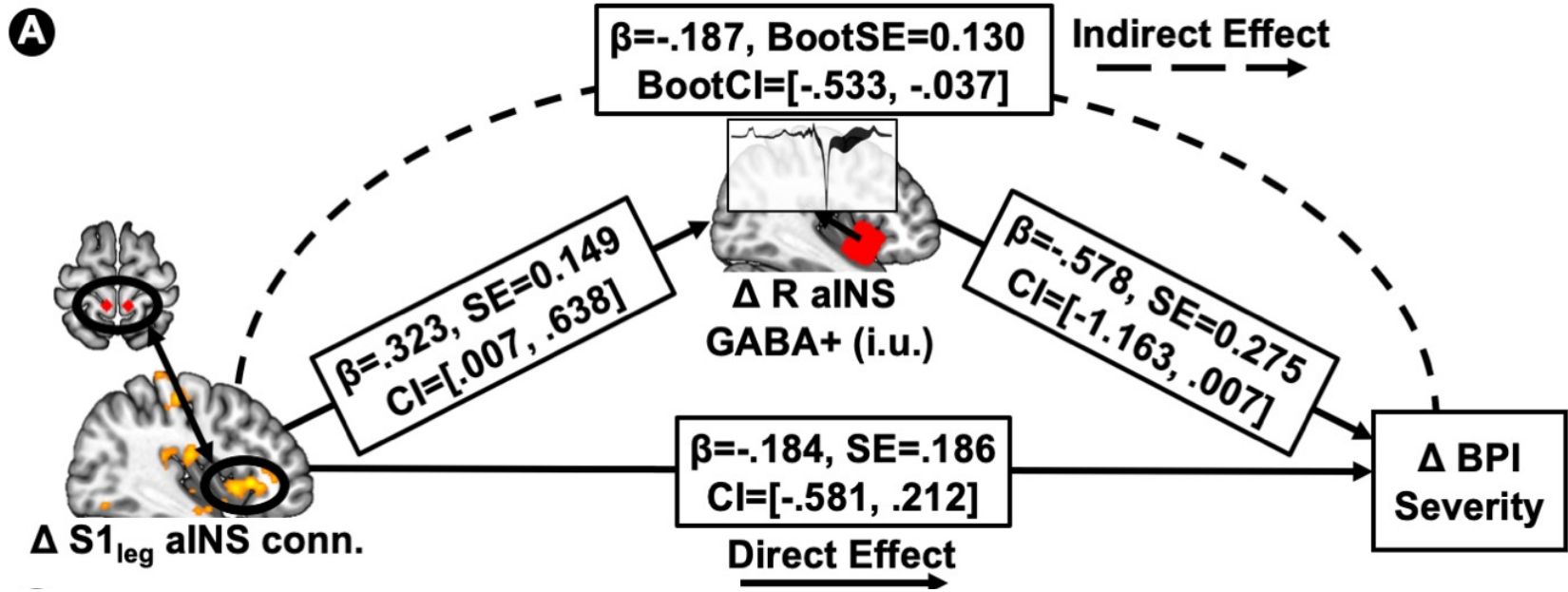
  - Choline containing compounds (Cho)**

- **Absolute concentrations in tissue are estimated in arbitrary units (AIU) or ratios are taken to other metabolites (Cr).**

# Increased Anterior Insula GABA is Associated with Greater S1<sub>leg</sub> Connectivity and Less Pain



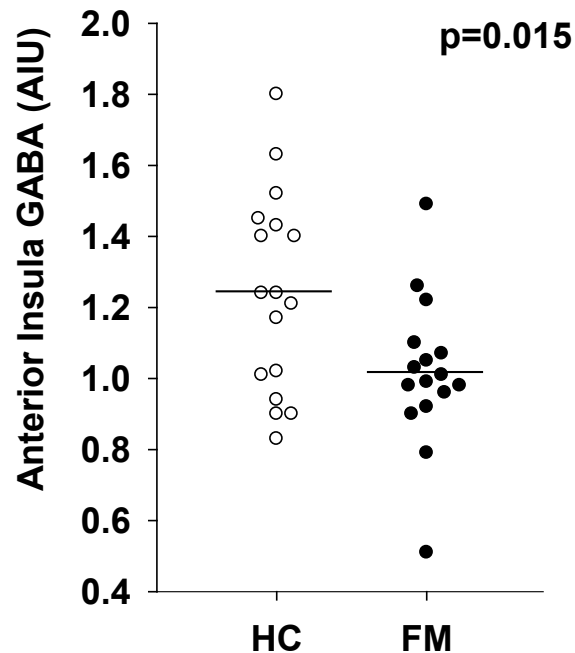
# Anterior Insula GABA Mediates $S1_{leg}$ Connectivity Action to Reduce Clinical Pain





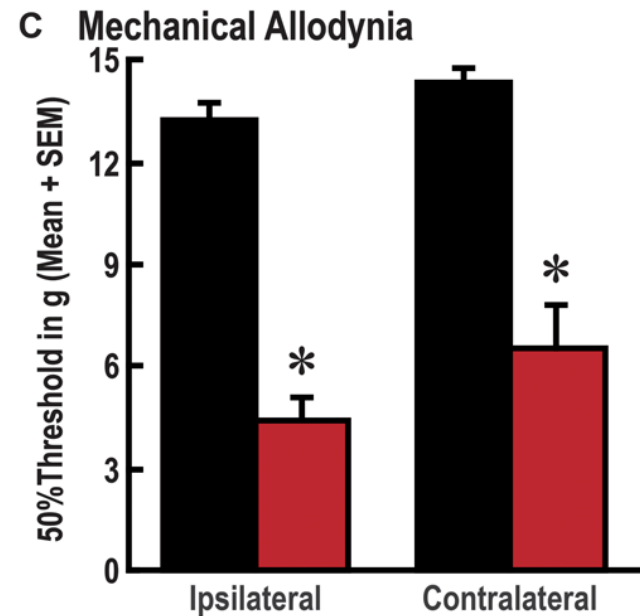
# Reduced GABA in Insula is Associated with Elevated Pain in Humans with FM and Rodents

## Reduced GABA in FM in Anterior Insula



Foerster et al. *AnR* 2011

## Block GABA Synthesis in Insula Reduces Pain Threshold



Watson *Pain* 2016

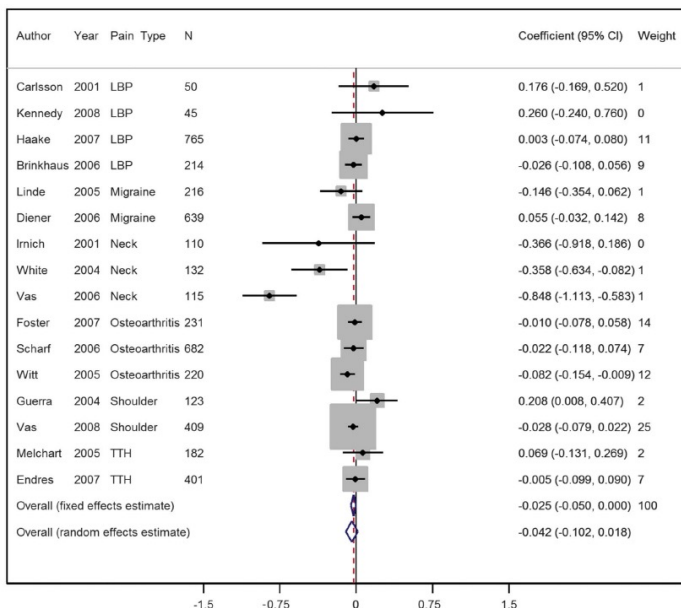
# Persistence of Acupuncture Analgesia in Chronic Pain

**PAIN**

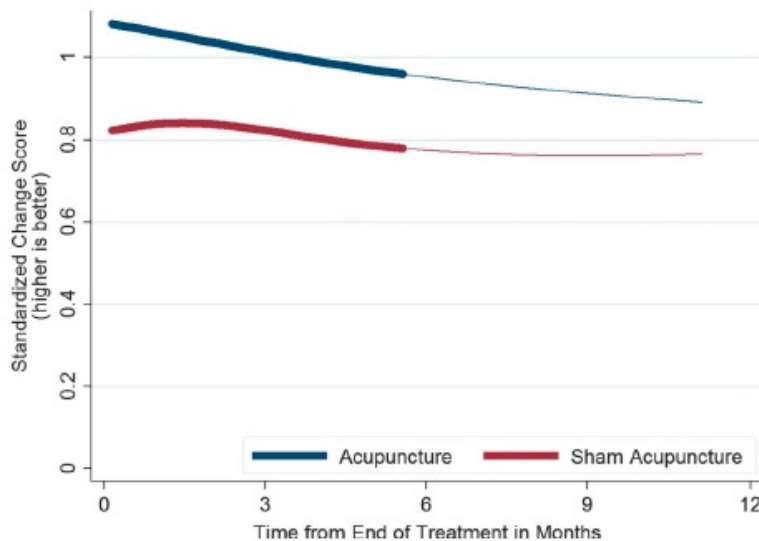
## The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain

H. MacPherson<sup>a,\*</sup>, E.A. Vertosick<sup>b</sup>, N.E. Foster<sup>c</sup>, G. Lewith<sup>d</sup>, K. Linde<sup>e</sup>, K.J. Sherman<sup>f</sup>, C.M. Witt<sup>g,h,i</sup>, A.J. Vickers<sup>b</sup>,  
On behalf of the Acupuncture Trialists' Collaboration

Hugh MacPherson



Decrease w/Time      Strengthen w/Time



# Long Term Potentiation at Neuronal Synapses

## LONG-LASTING POTENTIATION OF SYNAPTIC TRANSMISSION IN THE DENTATE AREA OF THE ANAESTHETIZED RABBIT FOLLOWING STIMULATION OF THE PERFORANT PATH

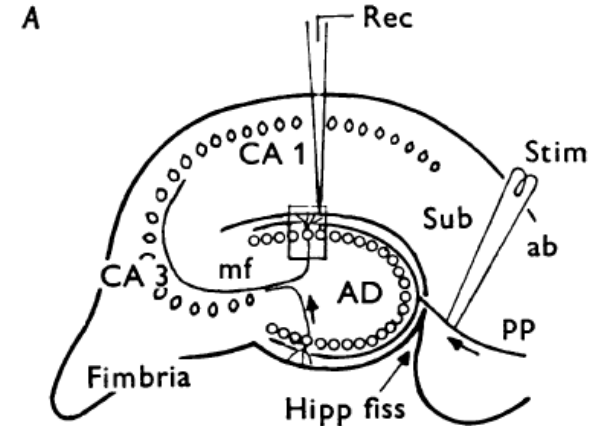
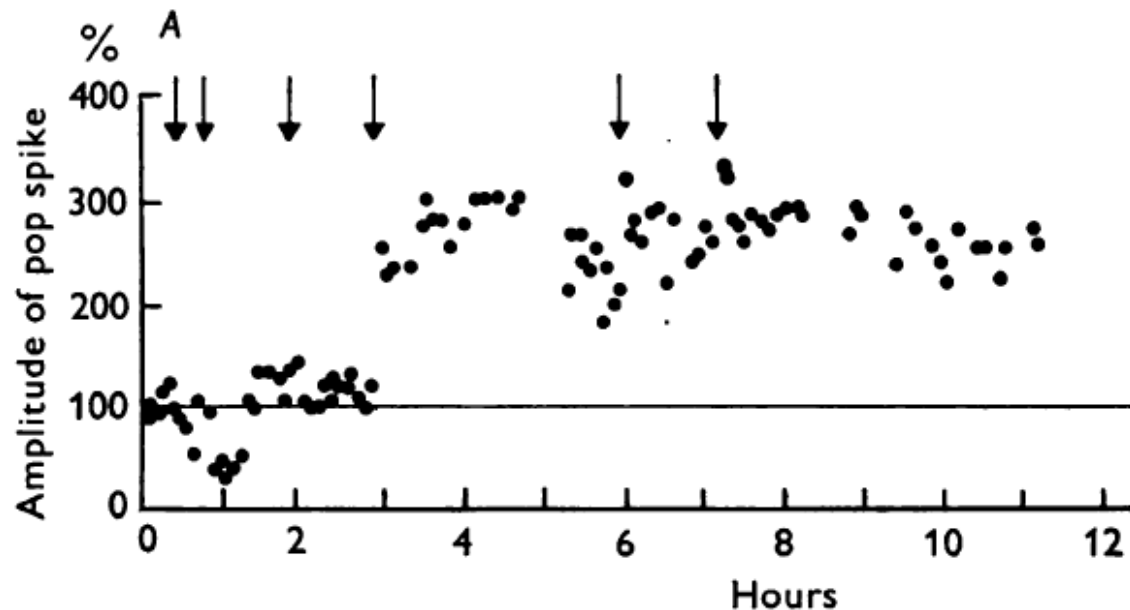
BY T. V. P. BLISS AND T. LØMO

*From the National Institute for Medical Research, Mill Hill,  
London NW7 1AA and the Institute of Neurophysiology,*

*University of Oslo, Norway*

*Journal of Neurophysiology*

*(Received 12 February 1973)*

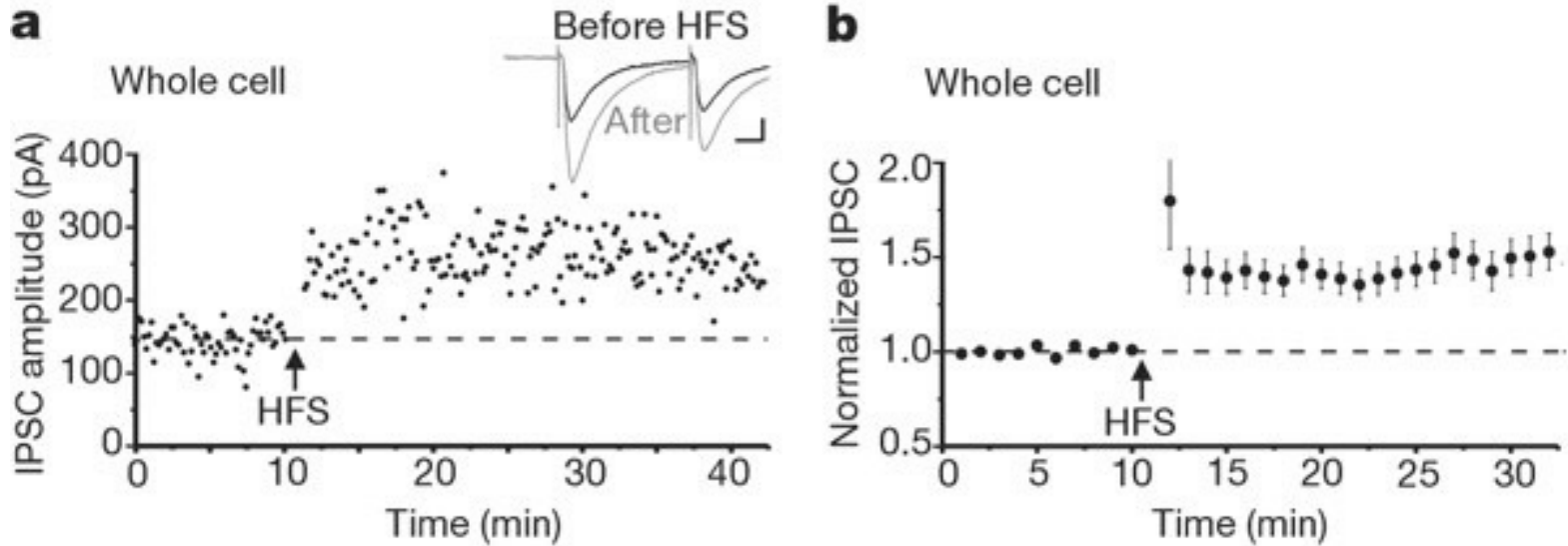


Timothy Bliss



Terje Lomo

# Long Term Potentiation of Inhibitory GABAergic Synapses in the Mammalian Brain



## Opioids block long-term potentiation of inhibitory synapses

Fereshteh S. Nugent<sup>1\*</sup>, Esther C. Penick<sup>1\*†</sup> & Julie A. Kauer<sup>1</sup>

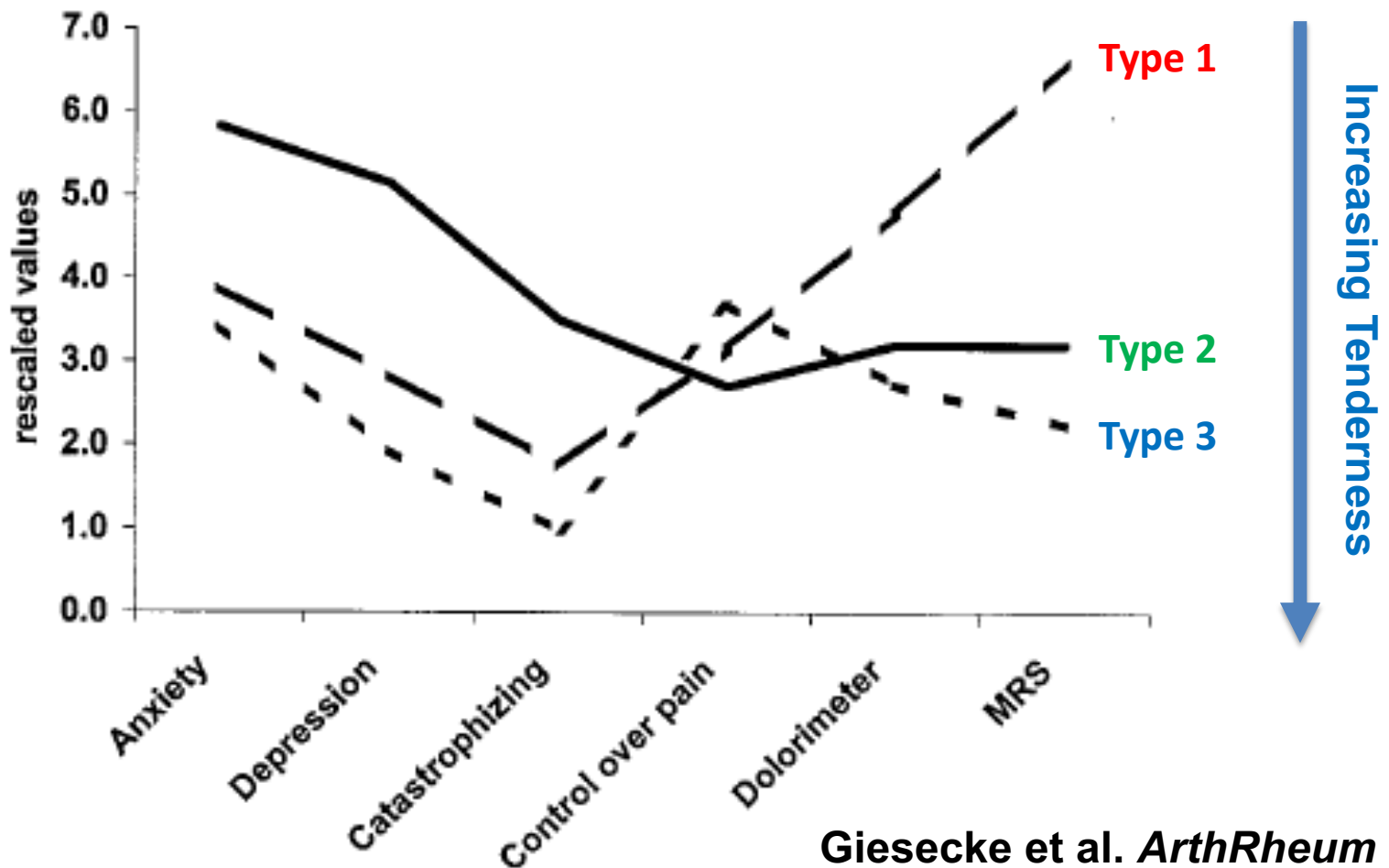
*Nature* 2007

# Same Pain Diagnosis...but not Identical

**Type 1** - moderate anxiety/dep with lowest tenderness

**Type 2** - highest anxiety/dep with high tenderness

**Type 3** - lowest anxiety/dep with highest tenderness



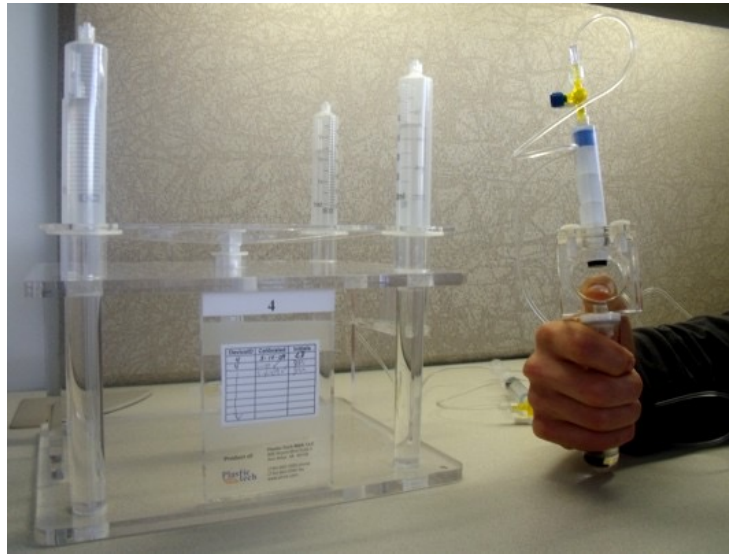
# Personalized Pain Medicine

- **Mechanistic pain outcomes can be used for pain diagnosis and treatment.**

*Woolf and Max Anesthesiology 2001*

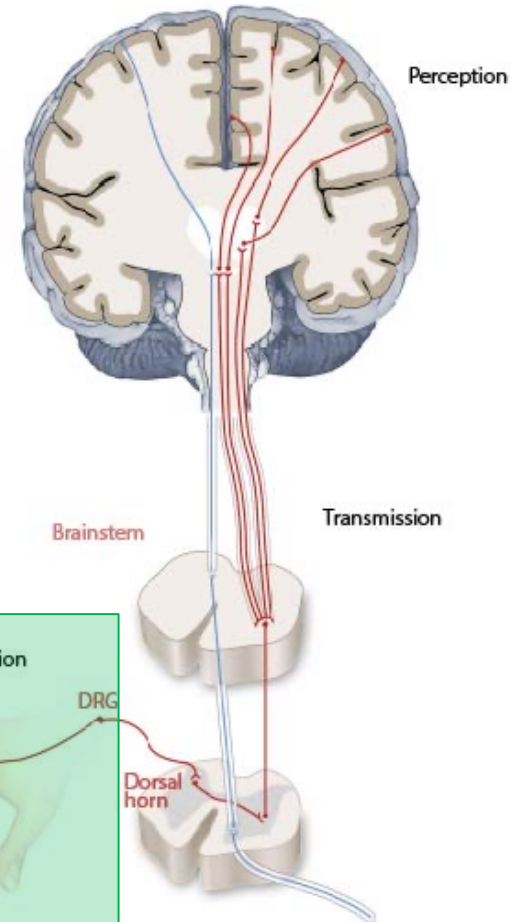
- “Pain can be generated in multiple ways at a number of different sites that may coexist between and across diverse disease states...The discovery of targets specific to particular pain mechanisms will soon enable therapy to be targeted specifically at those mechanisms.”

# Evoked Pressure Pain



"Old School"  
Device

Pain Rating



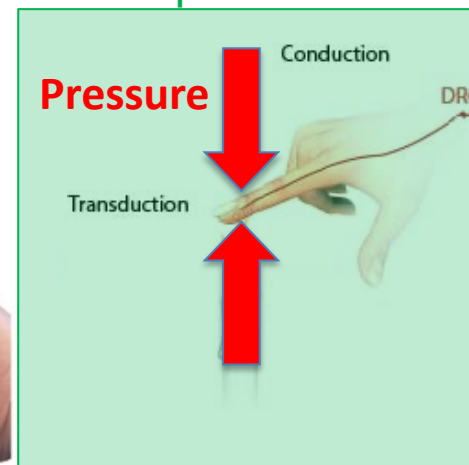
Steve Harte, PhD



MAST  
Multimodal  
Automated  
Sensory  
Testing



Nociceptive

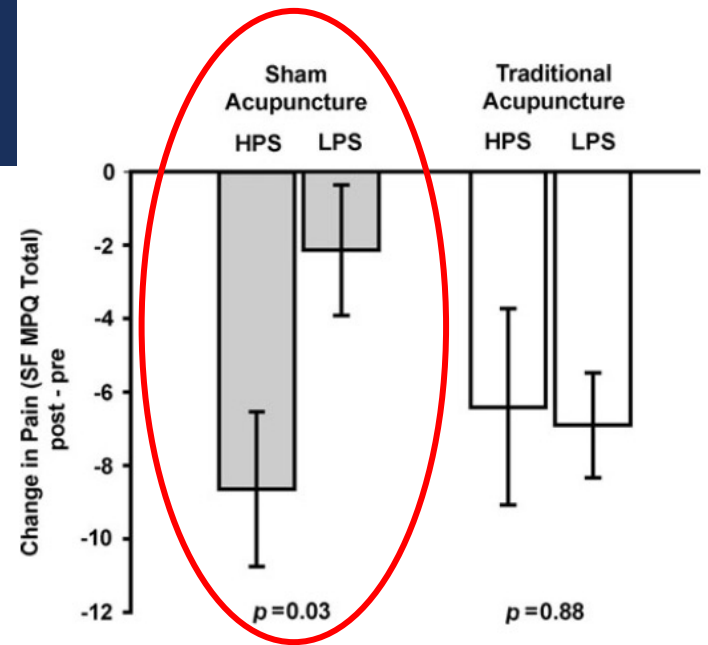


# Evoked Pressure Pain Predicts Acupuncture Response

MEDICAL ACUPUNCTURE  
Volume 25, Number 2, 2013  
© Mary Ann Liebert, Inc.  
DOI: 10.1089/acu.2013.0965

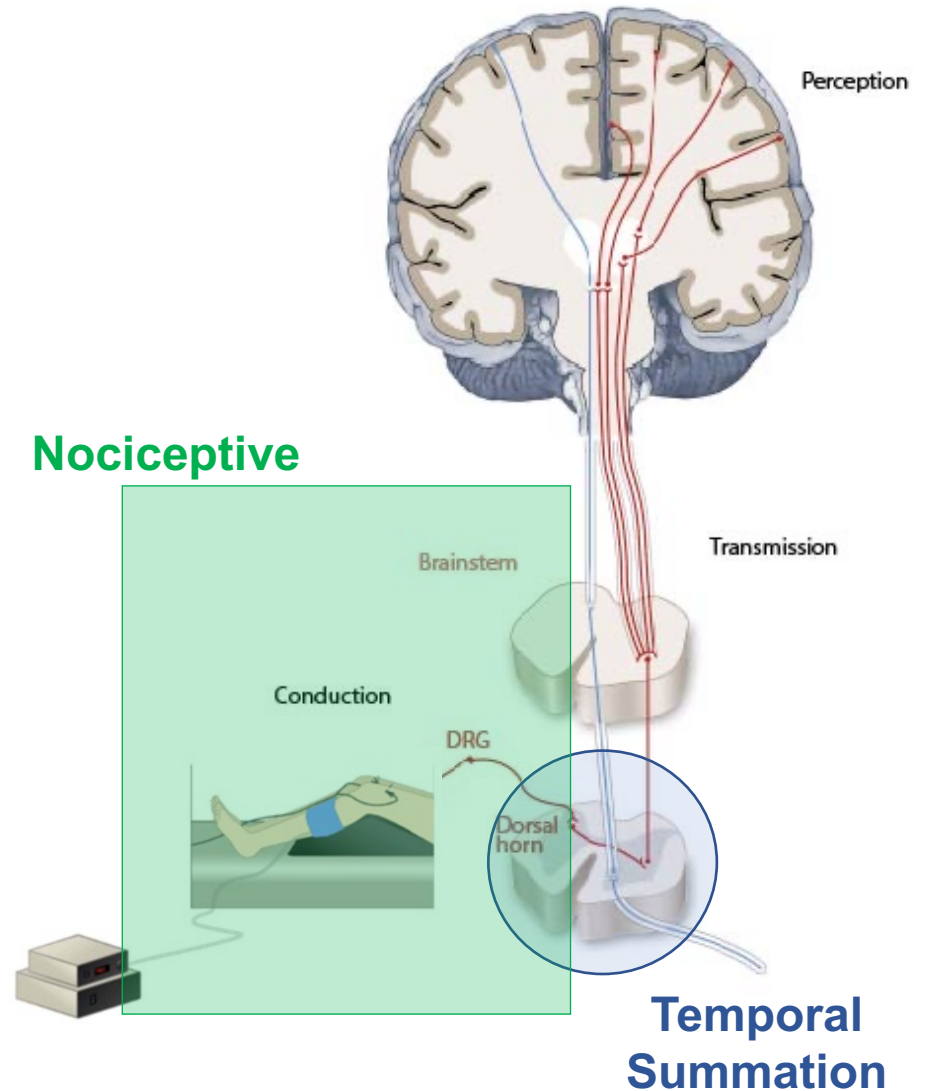
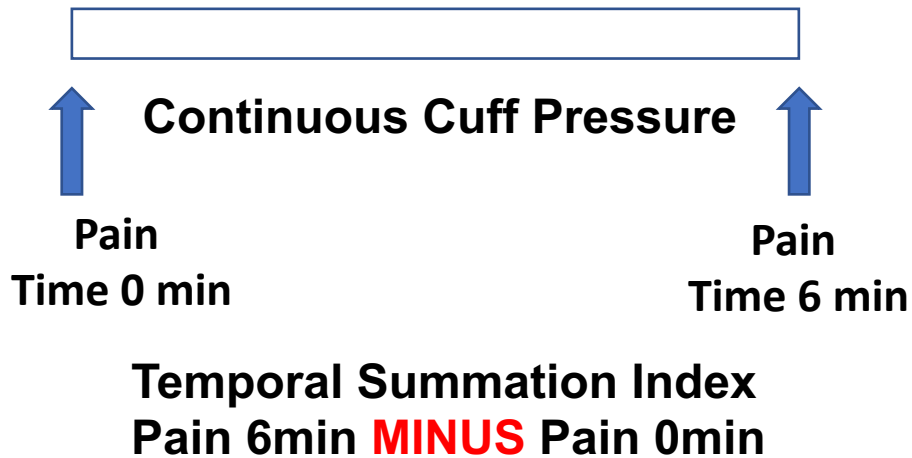
Pressure Pain Sensitivity and Insular Combined Glutamate and Glutamine (Glx) Are Associated with Subsequent Clinical Response to Sham But Not Traditional Acupuncture in Patients Who Have Chronic Pain

Steven E. Harte, PhD<sup>1</sup>, Daniel J. Clauw, MD<sup>1</sup>, Vitaly Napadow, PhD,<sup>2</sup> and Richard E. Harris, PhD<sup>1</sup>





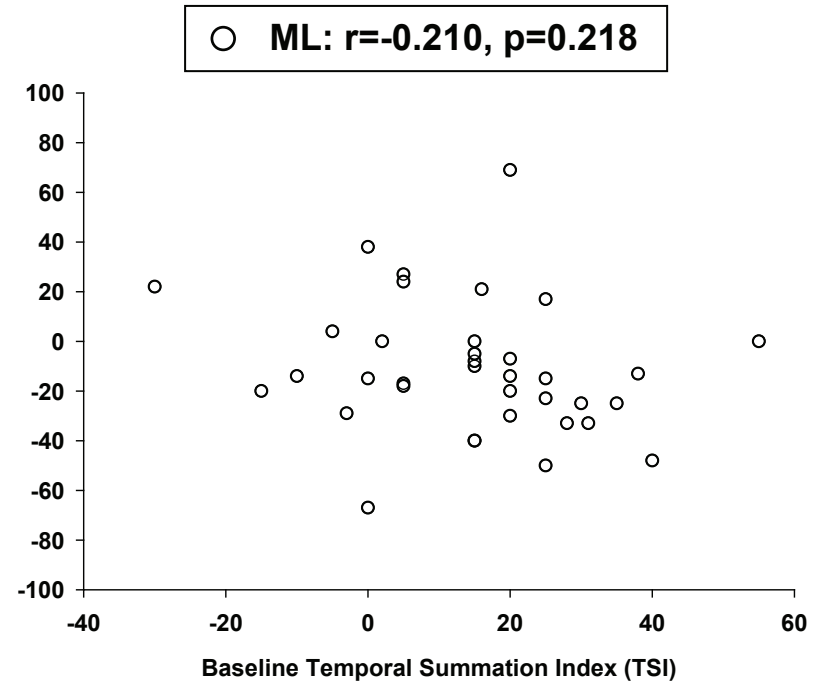
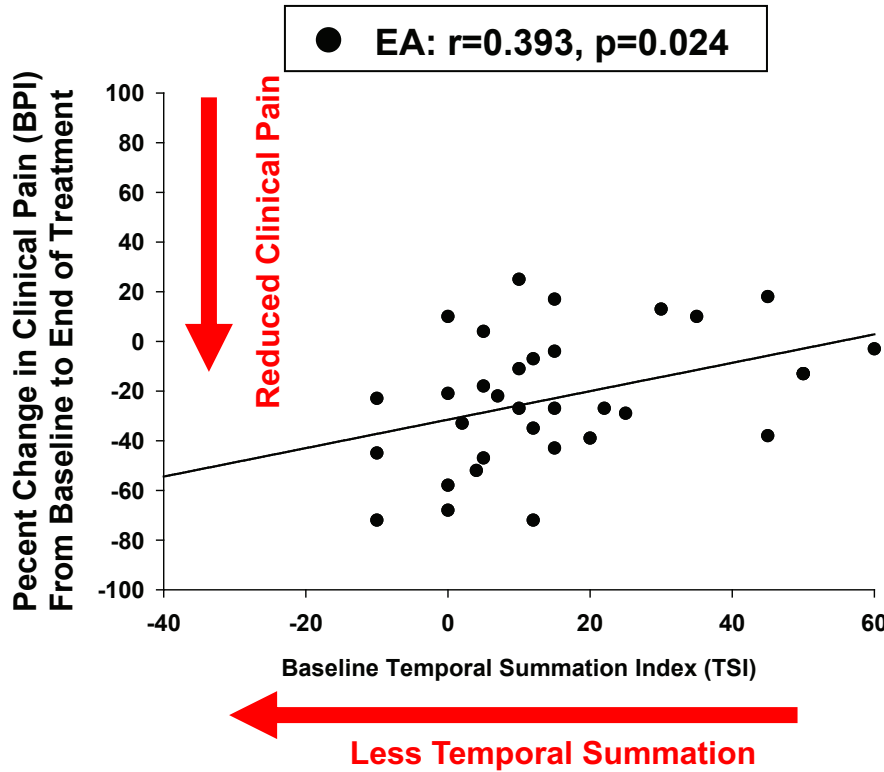
# Cuff Pain Threshold and Temporal Summation Index



# Better Clinical Pain Reduction with Lower TSI of Pain at Baseline



Anne Murphy, MD



**Less Temporal Summation is Associated with Improved Electro Acupuncture Response for Clinical Nociceptive Pain**

# Self-Acupressure...an Alternative

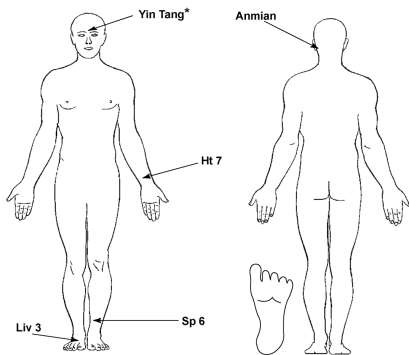
- **Stimulation of acupuncture points with pressure from fingers or device**
  - **Advantages**
    - **Low cost**
    - **Requires minimal instruction (15mins)**
    - **Patient controls dose and timing**
    - **Empowers patient**
    - **Reduces practitioner burden**
    - **Applicable in areas with few or no practitioners (AcuApp)**
    - **Vulnerable groups elderly and children**



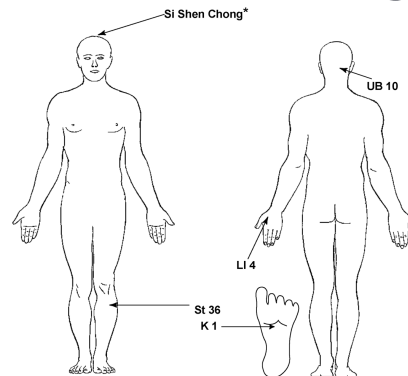
# Phase III Study of Self-Acupressure for Persistent Fatigue in Breast Cancer Survivors

- NIH/NCI funded R01
  - Breast cancer survivors >12 months post treatment.
  - Recruited from county extension offices throughout southeastern Michigan.
  - Sample size N=288 completers randomized to relaxing acupressure (n=98), stimulating acupressure (n=94) and usual care (n=96).

## Relaxing

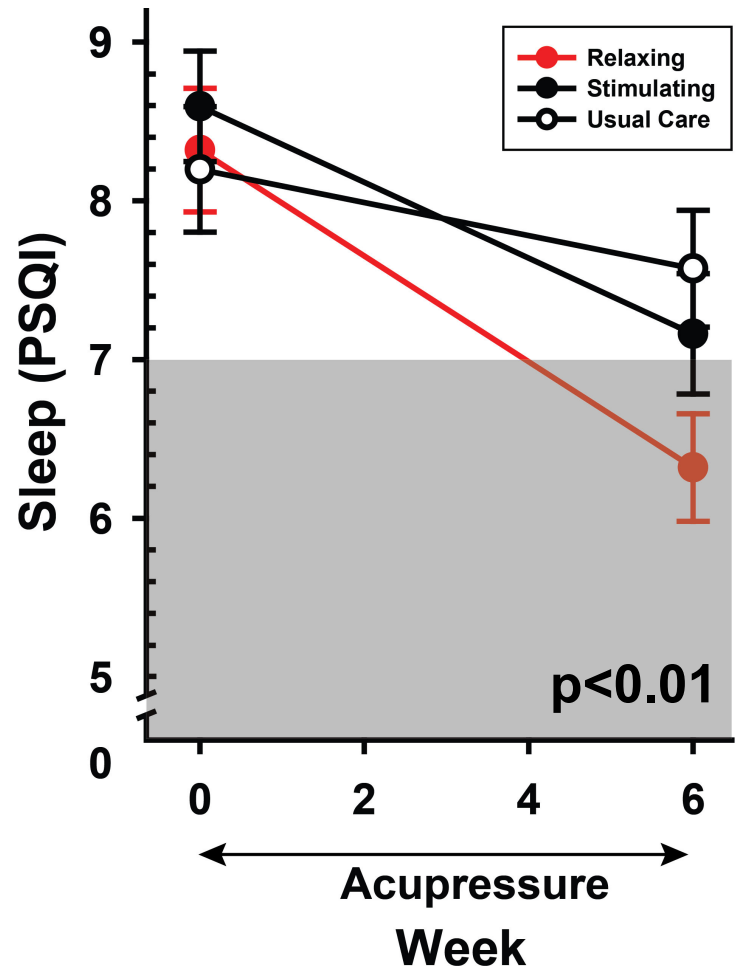
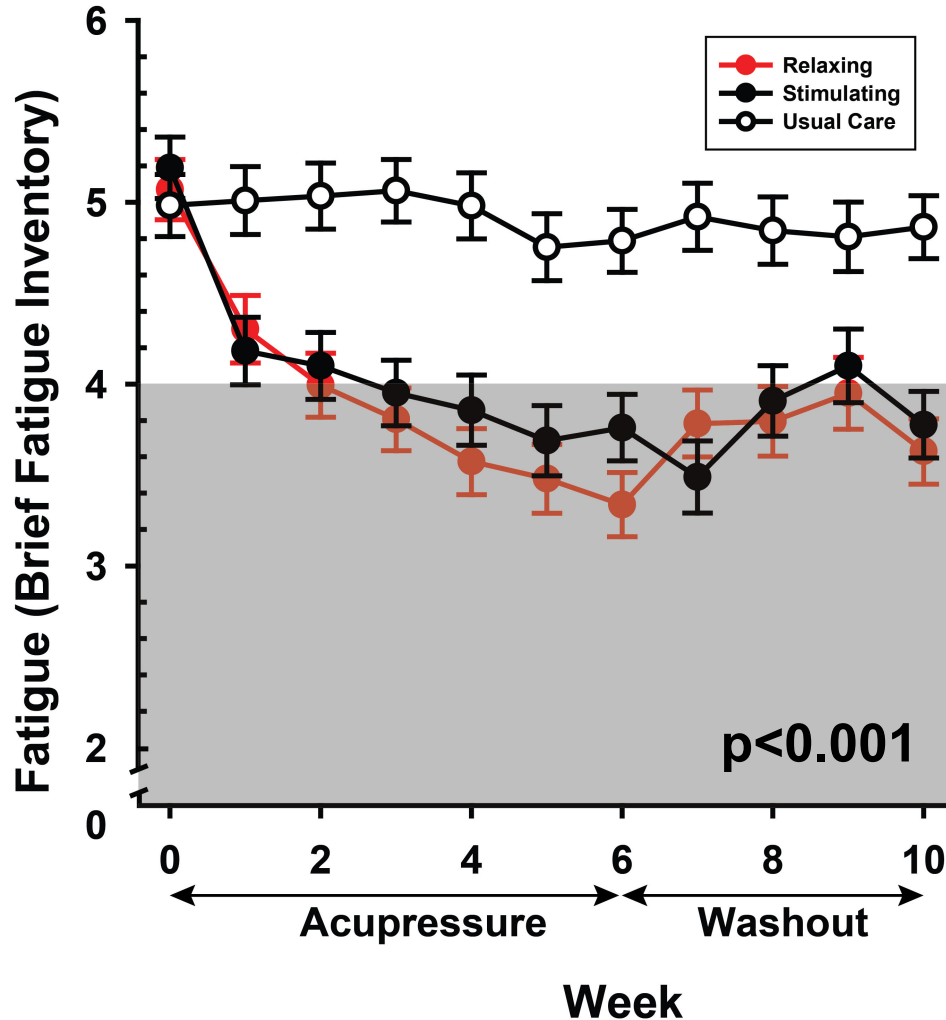


## Stimulating

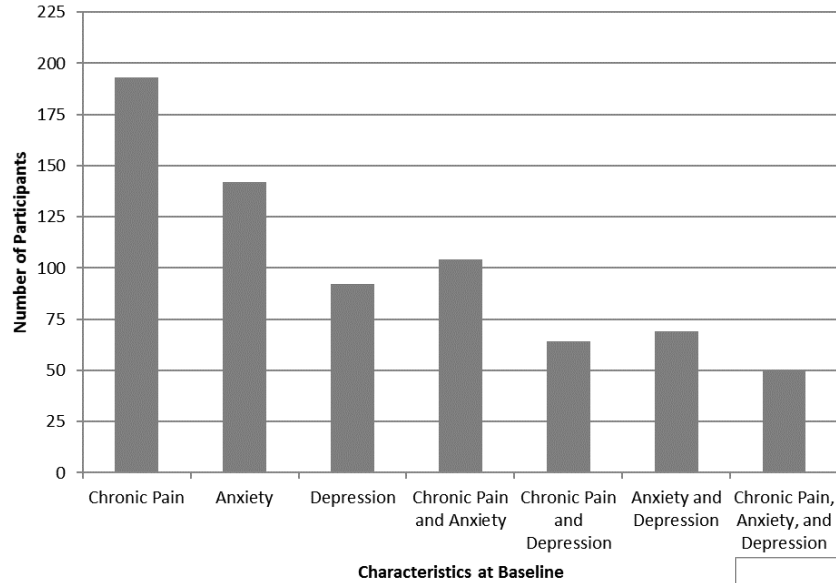


Acupressure performed daily for 30 minutes over 6 weeks followed by 4 week washout

# Acupressure Reduces Fatigue and Improves Sleep



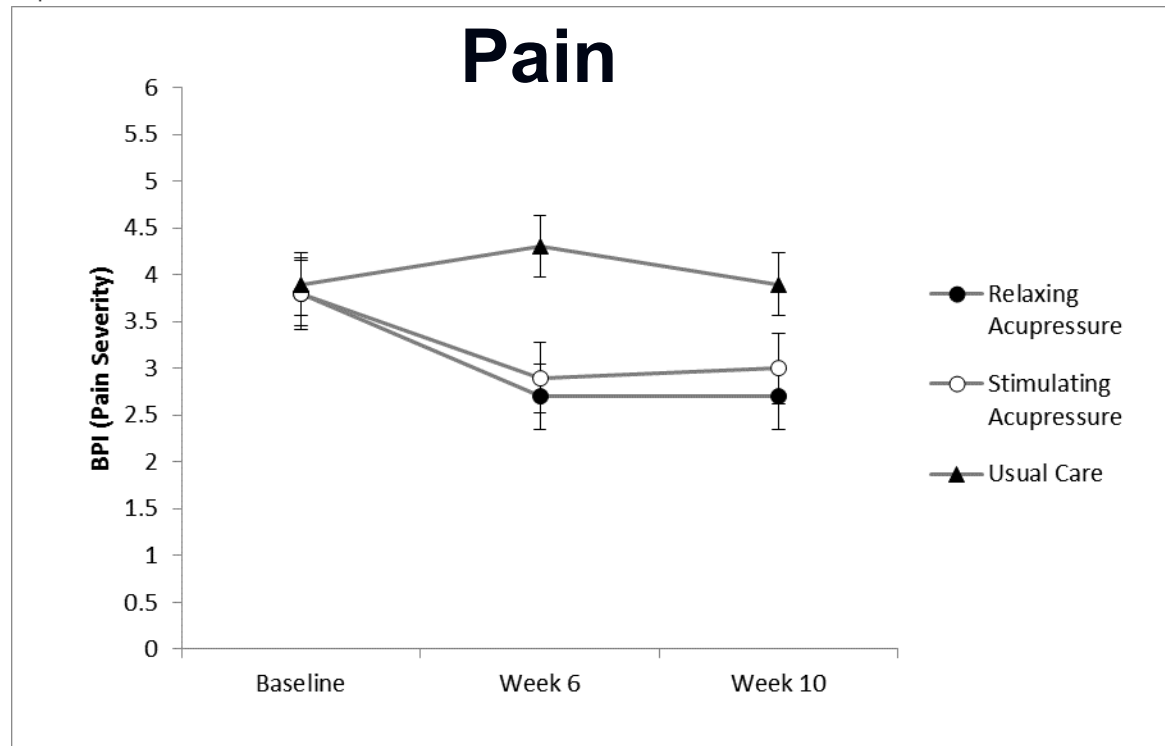
# Acupressure Improved Pain



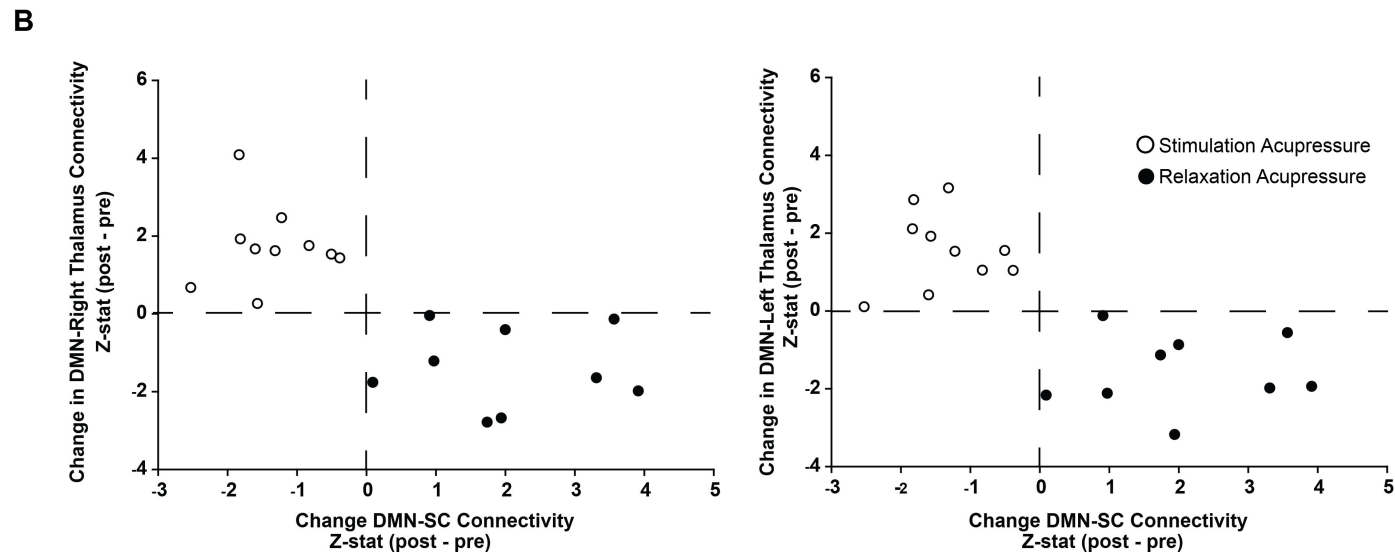
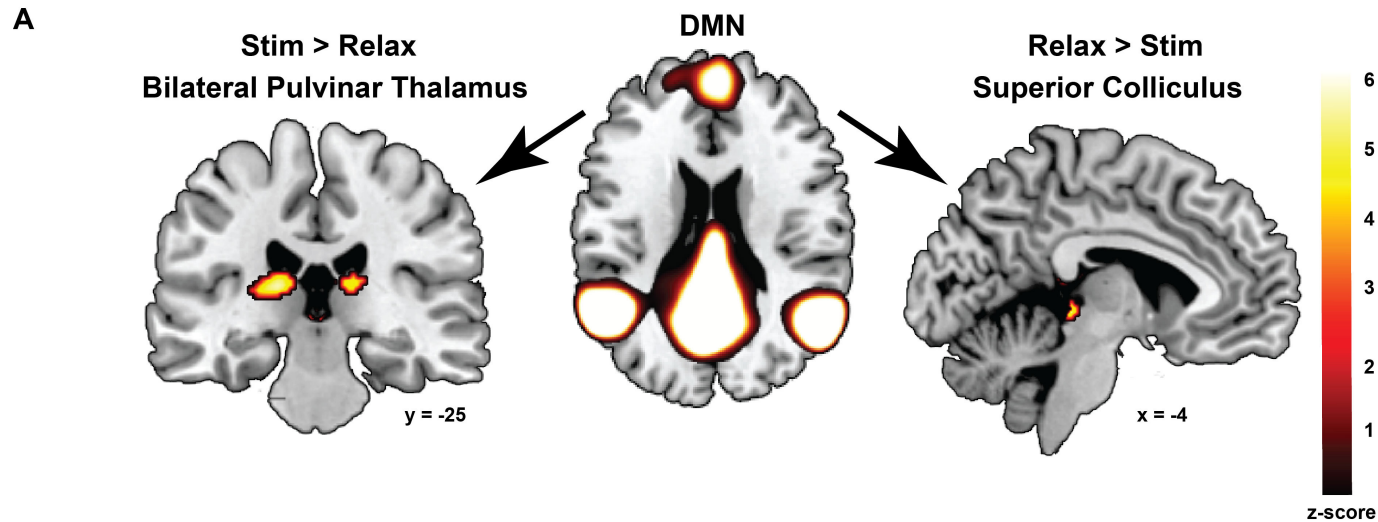
**N=288 w/fatigue**

**p<0.05 RA and SA vs UC**

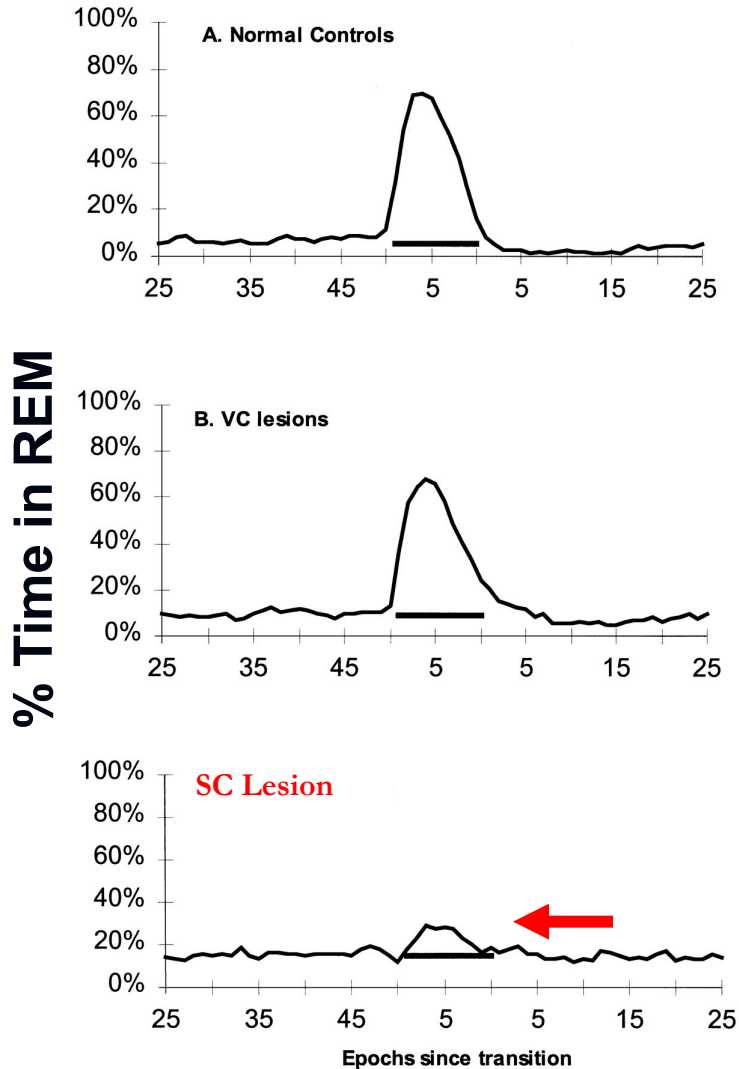
**Zick et al *JNCI Spectr* 2018**



# Differential Acupressure Formula Effects on Brain Network Connectivity

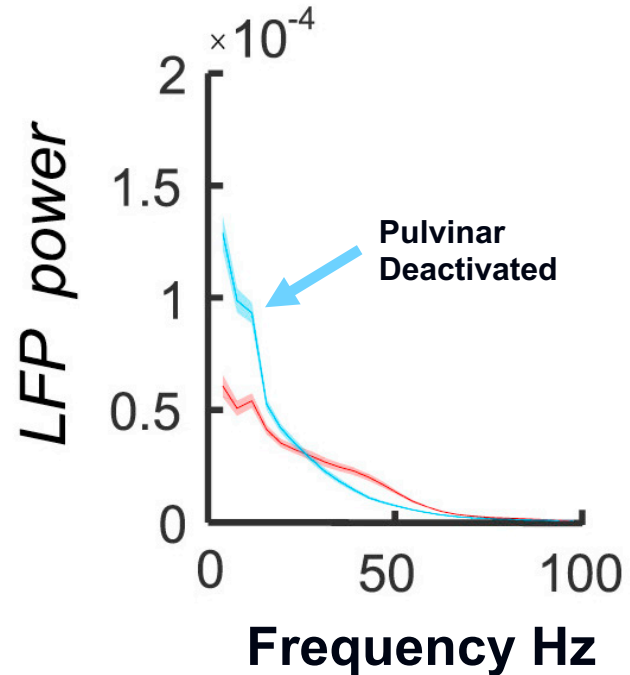


# Superior Colliculus Promotes Sleep



Miller et al. *PNAS* 1998

# Pharmacologic Deactivation of Pulvina, by Muscimol, Leads to Brain Slow Wave "Sleep" Activity



Zhou et al. *Neuron* 2016

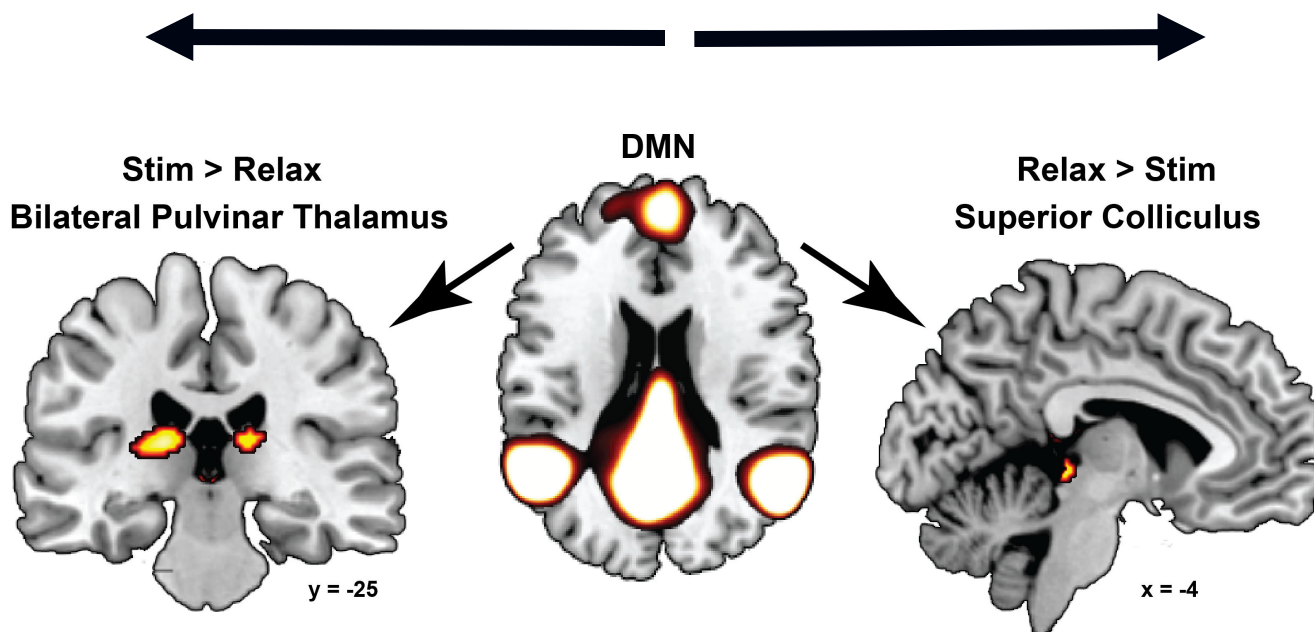
SC is needed for sleep whereas pulvina is needed for wakefulness. (Yin - Yang)



# Acupressure Differentially Modulates Sleep and Alertness

**Stimulating Acupressure  
Promotes Alertness**

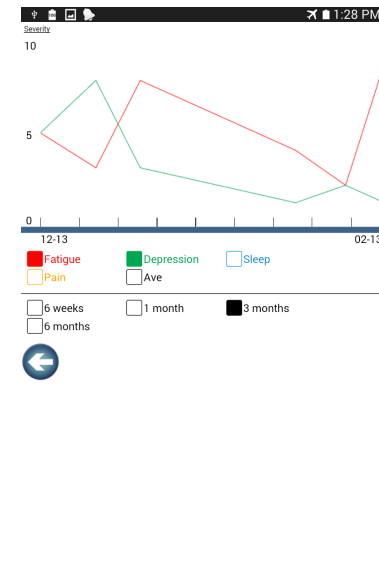
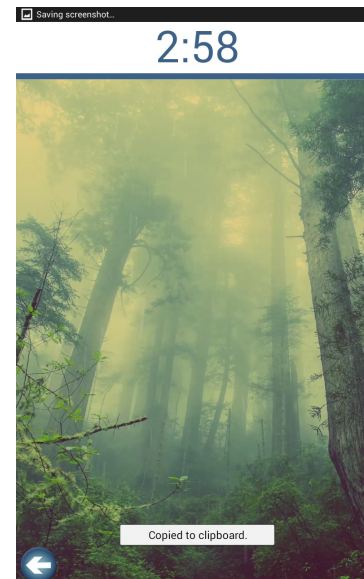
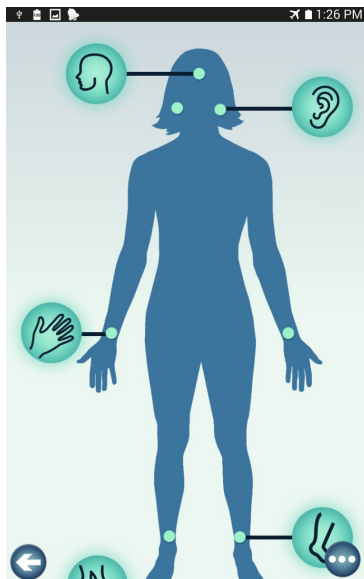
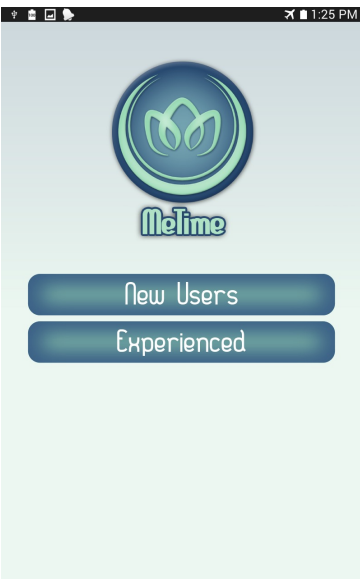
**Relaxing Acupressure  
Promotes Sleep**



**Might a personalized treatment approach make sense?**

# Acupressure Smartphone App

- Many individuals with pain and fatigue have little access to medical care.
- To reach more patients, we developed a smartphone app that is widely accessible.
- 6 Focus group meetings with 8 breast cancer survivors.
- Available now in Apple and Android app stores.



# AcuEase Device for Applying Pressure



## Study Log Book

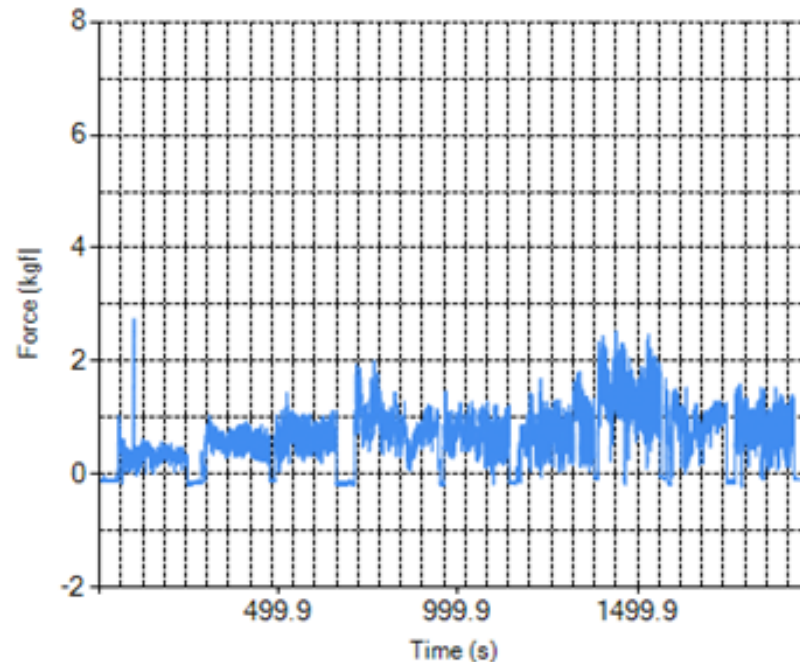
Did you complete your acupressure today?  Yes  
 No

Start time of acupressure: 20:58

End time of acupressure: 21:30

Did you take a break between acupressure points?  Yes  
 No

### Time X Pressure



**AcuEase**

**1730 seconds = 28.8 minutes**

**Log Book = 32 minutes**

**In Association with Arbor Medical Innovations (AMI)**

# Acupuncture Barriers

- **Increased access to acupuncture is needed.**
- **Implementation science on the rise at NIH.**
- **Physicians need to know how to refer patients for acupuncture.**

**National Certification Commission for  
Acupuncture and Oriental Medicine**

- [www.nccaom.org](http://www.nccaom.org)

# Summary

- **Three types of pain mechanisms: Nociceptive, Neuropathic, and Nociplastic.**
- **Acupuncture can reduce pain but most studies don't focus on what type of pain mechanism is being treated.**
- **Acupuncture and acupressure change the central nervous system.**
- **Experimental pain sensitivity differentially predicts response to verum and sham acupuncture.**
- **Can these results be applied in the clinic?**

# The Team, The Team, The Team

## ■ The Team

- Daniel Clauw, MD
- Vitaly Napadow PhD (Harvard); Suzie Zick ND (UMich)
- Richard Edden PhD, Helge Zollner PhD (Johns Hopkins)
- Eric Ichesco, Scott Peltier, Tom Chenevert: fMRI
- Anne Murphy MD, Steve Harte PhD
- Ishtiaq Mawla, PhD, Tony Larkin, PhD
- Noah Waller: graduate student

Anne Murphy Ishtiaq Mawla



Vitaly Napadow Suzie Zick



## ■ The Funding

- Department of Army grant W81XWH-07-2-0050
- NIH grants
  - R01 AT007550; R01CA151445
  - NCCIH K01 AT01111
- Dana Foundation award in brain and immunoimaging

Dan Clauw

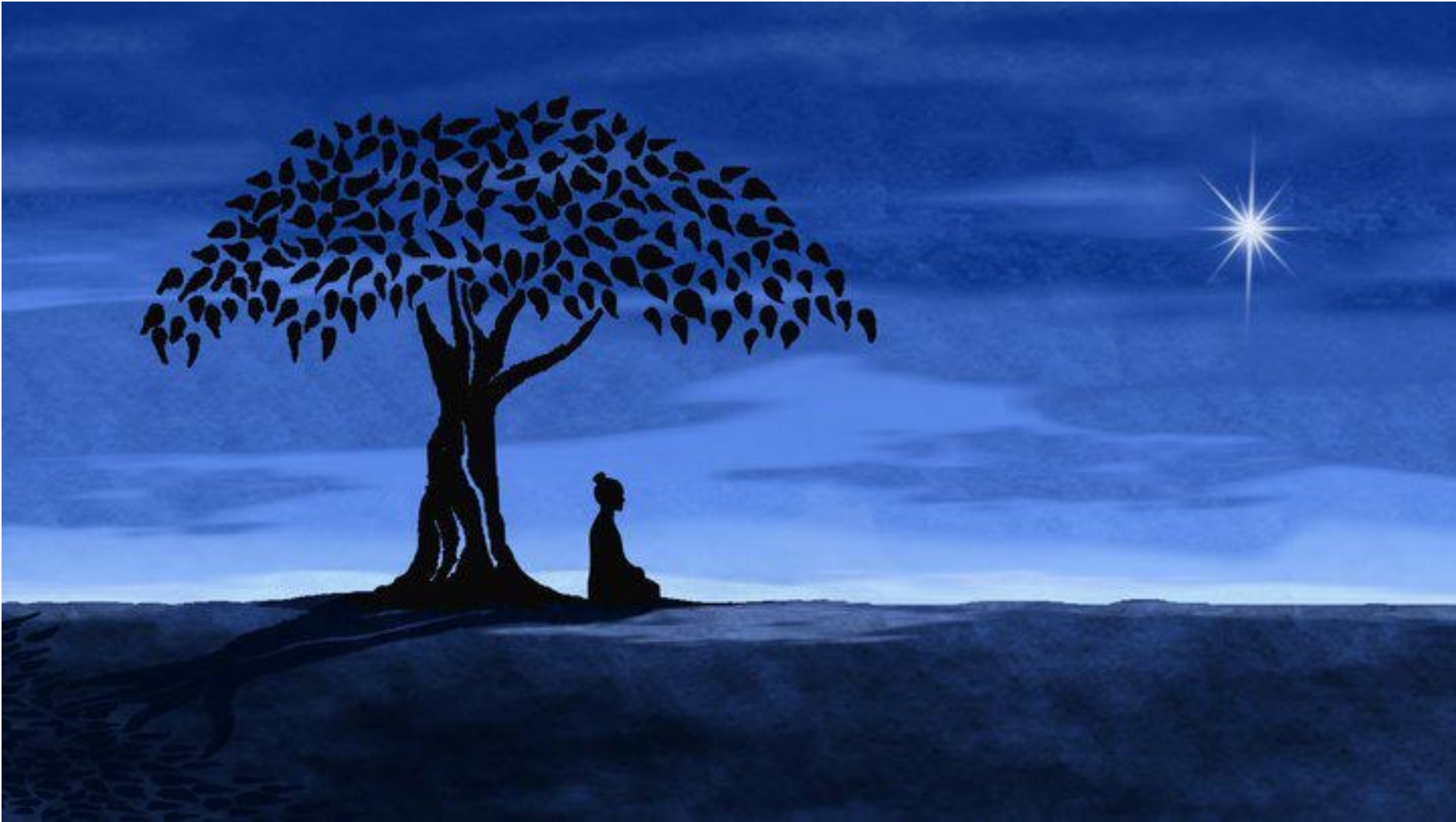


# TEAM 2...Susan Samueli Integrative Health Institute at UC Irvine



- Institute started by gifts from Samueli family in 2005, 2018.
- Creation of new building on UC Irvine campus, a home for integrative health research, education, and clinical care.
- Hiring new faculty, postdocs, clinicians, and students.
- Endowed chair positions.
- Future hub for integrative care and research: SAR 2025!

# Thank You For Listening



**Tongva** and **Acjachemen** tribes that lived on the land of Orange County for many years before the present day.



**Self-Administered Acupressure for Veterans with Chronic Back Pain: A Multisite Evaluation of Effectiveness and Implementation**

**VA HSR&D funded IIR 20-242**

**June 1, 2022 – May 31, 2026**

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## **Principal Investigator/Study Chair:**

- Sarah Krein, PhD, RN. VA HSR&D Research Career Scientist, Rensis Likert Collegiate Research Professor and Research Professor of Internal Medicine, University of Michigan (UM)

## **Co-Investigators:**

- Susan Murphy, ScD, OTR. Professor, Department of Physical Medicine and Rehabilitation, UM
- Suzanna Zick, ND, MPH. Research Professor, Family Medicine, UM
- Richard Harris, PhD. Professor of Anesthesiology and Internal Medicine, UM/ Susan Samueli Endowed Chair and Professor in the Department of Anesthesiology and Perioperative Care in the School of Medicine at the University of California at Irvine
- Shawna Smith, PhD. Assistant Professor of Health Management and Policy, School of Public Health and Research Assistant Professor, Psychiatry, UM
- Ananda Sen, PhD. Research Professor of Family Medicine with a joint appointment in the Department of Biostatistics, UM
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## **VA Collaborators:**

- Allison Mitchinson, MPH
- Rachael Maciasz, MD
- Juliette Perzhinsky, MD

## **Research Staff:**

Jen Caldararo, Project Manager  
Pia Roman, Research Assistant  
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# Background

- >60% of U.S. military veterans report having pain in the prior three months
- Veterans report higher rates of severe pain and chronic pain compared with nonveterans, with back pain being one of the most commonly reported and diagnosed pain conditions
- Chronic low back pain is a leading cause of disability, and often accompanied by fatigue, sleep disturbance, and depression
- Need for effective non-pharmacologic, self-management strategies for chronic pain including complementary and integrative health treatments

# Study Aims

1. Determine effectiveness of a 6-week self-administered acupressure protocol on pain interference, disability, fatigue, and sleep post intervention.
2. Evaluate facilitators and barriers to implementing a program in VHA of self-administered acupressure to Veterans with chronic low back pain.

# Study Setting

## VA Ann Arbor Healthcare System

- VA Ann Arbor Medical Center
- Toledo CBOC
- Flint CBOC

# Study Methods

## Randomized controlled trial

## Recruiting 300 Veterans with chronic low back pain

- Inclusion Criteria: 1) aged 18 years or older; 2) non-specific low back pain confirmed through electronic medical records (i.e., ICD-10 codes: M54.5, M54.40, 41, 42, M54.89,); 3) reported pain severity of  $\geq 4/10$  that has persisted for at least 3 months and present on most days; 4) medically stable (no hospitalizations in the past month lasting 3 or more days); 5) no changes in pain medication regimen in past 4 weeks; and 6) no planned surgery or injections for back pain during the next 10 weeks.
- Exclusion criteria: 1) pregnant, as this could cause pain unrelated to CLBP; 2) had back surgery in the past 2 years; 3) received acupuncture or acupressure in past 3 months; and 4) evidence of cognitive impairment that could interfere with the ability to provide consent and follow the study protocol (defined as a score of  $\geq 3$  using the Callahan et al. 6-item screener).

150 randomized to 'intervention' and 150 randomized to wait list control

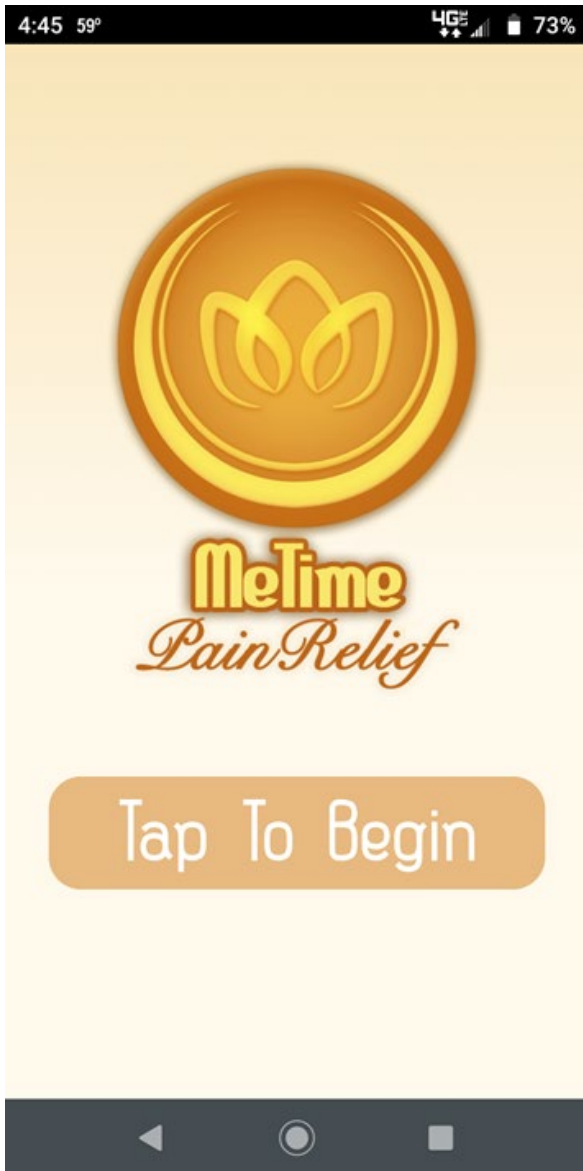


Figure 1. MeTime Acupressure App



# Intervention

Each of the ten acupoints will be stimulated for 3 minutes per point for a total treatment time of 30 minutes daily. The acupoints are:

- Kidney 3 (K3) (Right and Left/bilaterally): inside of ankle
- Si Shen Chong (Unilaterally): top of the head
- Conception Vessel 6 (CV6) (Unilaterally): two finger widths below the navel on the centerline
- Large Intestine 4 (LI4) (Right and Left/bilaterally): back of the hand
- Stomach 36 (ST36) (Right and Left/bilaterally): lower leg below the knee on the outside of the leg
- Spleen 6 (SP6) (Right and Left/bilaterally): inside of lower leg

# Questions

Sarah Krein

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