


# Pre-clinical Models of Central Pain Syndromes

Steven Harte, PhD



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## Didactic Outline

1. Overview of Central Pain Syndromes
2. Overview of Pre-clinical Models
  - Types
  - Advantages/Limitations
  - Proposed Pre-clinical Models of Central Pain
3. Acid Model of Chronic Widespread Pain
  - Behavioral Studies
  - Neuroimaging Studies

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## Central Pain Syndromes

What are we talking about?

- Patients with...
  - chronic widespread pain (CWP)
  - fibromyalgia (FM)
  - temporomandibular disorder (TMD)
  - chronic pelvic pain
  - irritable bowel syndrome (IBS)
  - chronic headache/unexplained facial pain

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### Central Pain Syndromes

Also called...

- functional somatic syndromes
- chronic multi-symptom illnesses
- allied spectrum disorders
- idiopathic pain
- medically unexplained symptoms

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### Central Pain Syndromes

Features and Characteristics

- Widespread or localized chronic pain
- Diffuse hyperalgesia and/or allodynia
- Fatigue
- Non-specific peripheral pathology
- Co-aggregation and familial aggregation of symptoms and syndromes
- More common in women
- Respond to similar type of therapies (eg, tricyclic compounds, NSRIs, cognitive-behavioral interventions)
- Augmented central nervous system processing of pain
- Dyscognition
- Sleep disturbances
- Psychiatric comorbidity

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University of Michigan

### Central Pain Syndromes

What we are NOT talking about?

- Patients with clear peripheral pathology, examples include:
  - peripheral nerve damage
  - arthritis
  - acute post-surgical pain
  - herniated disk
- Nociceptive pain

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### Defining the Preclinical Animal Model

- Subject – Type of animal used
  - strain
  - sex
  - mutation
- Assay – Procedure used to produce a pain state
  - surgical techniques (eg, chronic constriction injury, CCI)
  - disease states (eg, cancer)
  - inflammatory techniques (eg, CFA)
- Measure – Method used to assess nociception
  - reflex tests (eg, tail flick, hotplate, von Frey)
  - spontaneous "pain-like" behaviors
  - operant behaviors

See: Mogil JS, *Nat Rev Neurosci* 10, 2009

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### Why Use Animal Models?

- High level of experimental control
- Short life span
- No recruitment issues
- Cost effective
- Repeated assessments
- Intrauterine access
- Drug screening and toxicology
- Invasive techniques
- Proof-of-Concept studies
- Mechanistic studies

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### Limitations of Animal Models

Understanding the gap between the bench and the bedside

- Animals are NOT human
- Models have poor validity and/or reliability
- Species, strain, and sex differences
- Unknown or uncontrollable confounds
- Inadequate measurement tools and strategies

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## Pre-Clinical Models of Central Pain

How do you develop an animal model for a disorder of which little is known concerning its underlying mechanisms?

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## "Proposed" Pre-clinical Models of Central Pain

- **Stress Paradigms**
  - Forced swimming [eg, Quintero et al., *Pharm Biochem Behavior* 67, 2000]
  - Thermal stress [eg, Satoh et al., *Pain* 49, 1992]
  - Water Avoidance [Bradesi et al., *Physiolol Gastrointest Liver Physiol* 289, 2005]
  - Restraint [daSilva Torres et al., *Neurosci Res* 45, 2003]
- **Neurochemical Modulation**
  - Catechol-O-methyltransferase (COMT) inhibition [Nackley et al., *Pain* 128, 2007]
- **Physical Trauma/Muscle Insult**
  - Acid Model of Chronic Widespread Pain [Sluka et al., *Muscle Nerve* 24, 2001]

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## Acid Model

- Persistent and diffuse mechanical hyperalgesia produced following repeated intramuscular injections of acidic saline (pH 4.0)
- Non-inflammatory stimulus
- Unremarkable muscle pathology

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### Acid Model, cont.

- Face Validity
- CNS Plasticity

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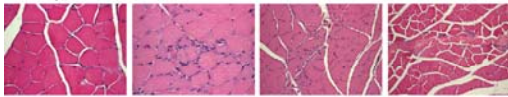
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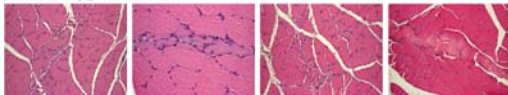
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### Representative Muscle Pathology

ACID Group\_ Left Gastrocnemius



CONTROL Group\_ Left Gastrocnemius



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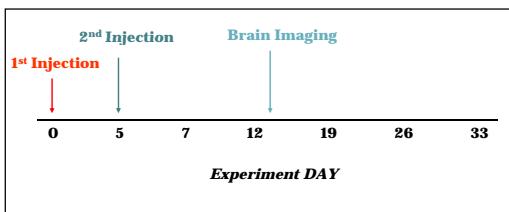
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### Protocol



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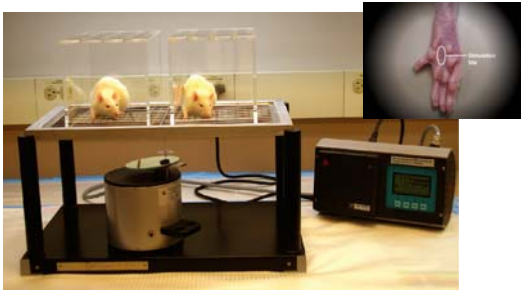
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### Assessment of Mechanical Hyperalgesia



Dynamic Plantar Aesthesiometer, Ugo Basile)

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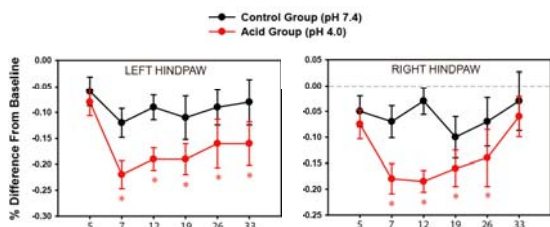
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### Gastrocnemius Acid Injections Produce Hindpaw Mechanical Hypersensitivity in Pain-Naive, Juvenile Rats



\* Decreased Compared to Baseline Pressure Threshold,  $p < 0.05$ .

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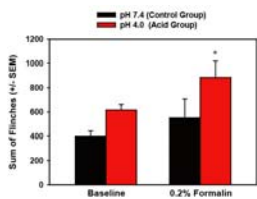
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### Acid Model Response to Formalin-Induced Inflammation



Automated Nociception Analyzer (Yaksh et al., 2001)

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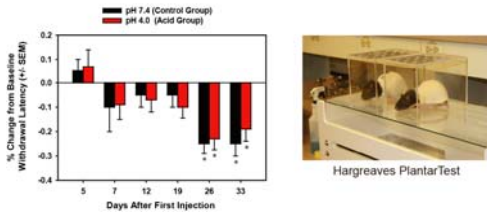
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### Acid Model Response to Thermal Stimulation




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### A Modified Acid Model

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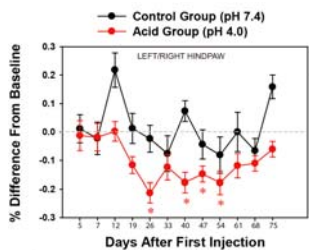
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Acid Injections into the Neck Muscles of Pain-Experienced, Adult Rats Produce a Persistent Increase in Hindpaw Mechanical Sensitivity




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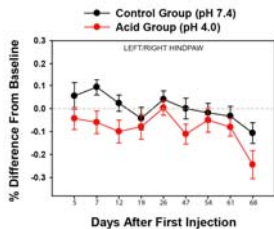
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Acid Neck Injections Do Not Alter Mechanical Sensitivity in the Hindpaws of Pain-Naive, Juvenile Rats




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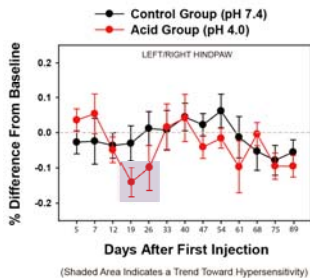
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Acid Neck Injections May Produce a Transient and Modest Increase in Hindpaw Mechanical Sensitivity in Pain-Naive, Adult Rats




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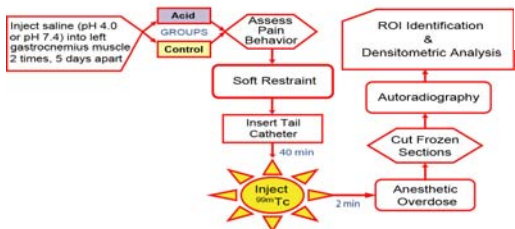
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Autoradiographic Functional Brain Imaging




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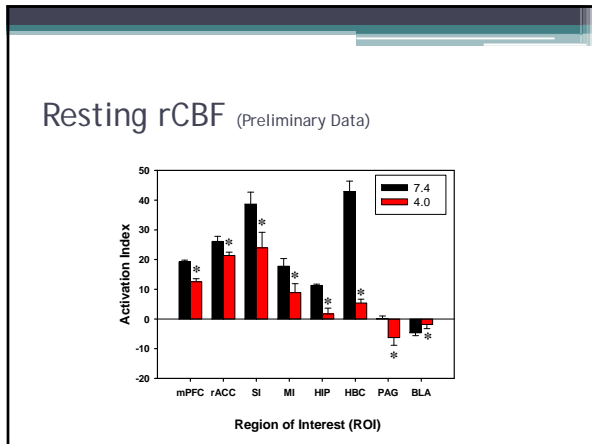
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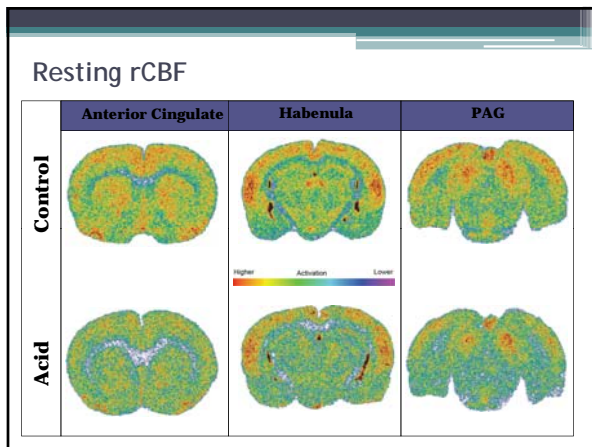
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### Summary

Is the Acid Model a reasonable assay of central pain?

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