Long-term Outcomes in Fibromyalgia Patients Treated with Cortical Electrostimulation

Presentation made by Cerephex Chief Scientific Officer Dr. Jeff Hargrove at the 2011 American College of Rheumatology Annual Meeting in Chicago, IL USA

Evidence Based Medicine (EBM)

Centralized Pain in Fibromyalgia (FM)

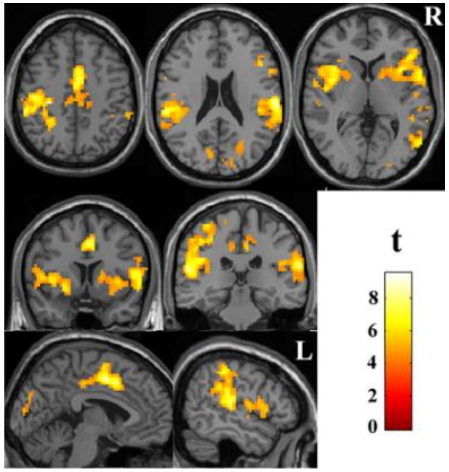
- Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther 2011;13:211.

Clinical Studies Involving Cortical Stimulation Treatment

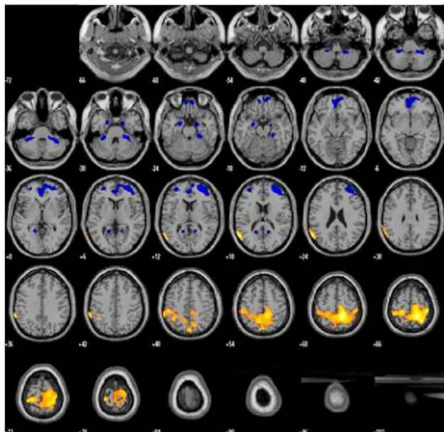
- Fregni F et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum. 2006 Dec;54(12):3988-98.
- Passard A et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain. 2007 Oct;130(Pt 10):2661-70.

Neuroimaging: Central Pain in FM

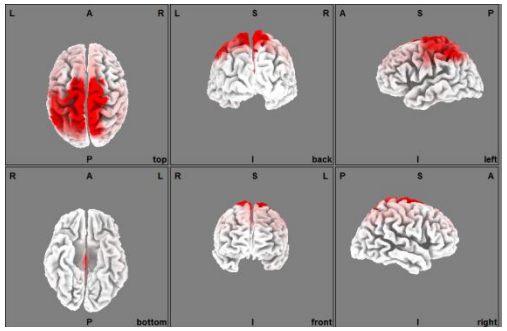
- Fibromyalgia: central nervous system pain mechanisms are well documented – FM has emerged as a prototypical central pain disease
- Abnormal brain function potentially associated with central sensitivity has been demonstrated in numerous neuroimaging studies and in cortical function analysis using electroencephalography (EEG)



fMRI image showing FM patient response to 4 kg/cm^2 pressure applied to the thumb[1]



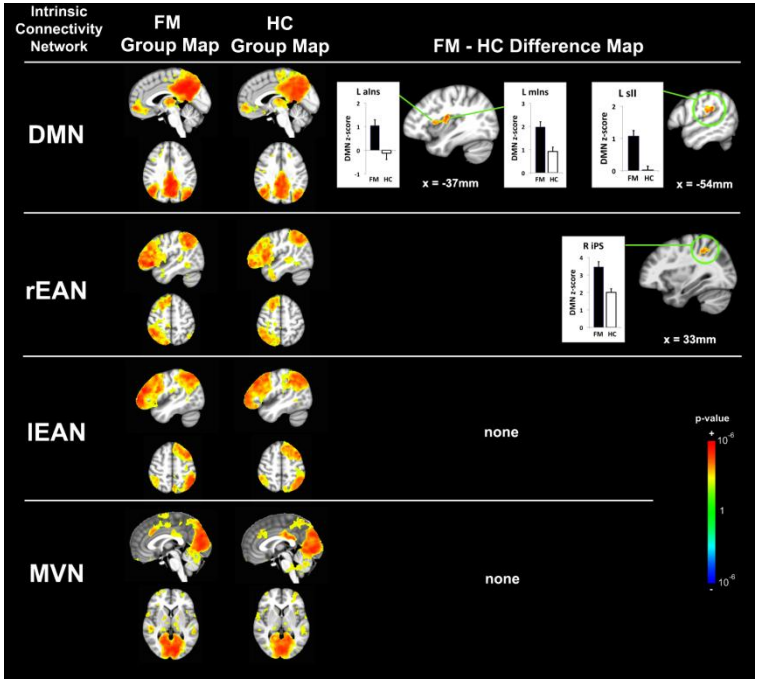
SPECT imaging shows posterior hyperperfusion including the somatosensory cortex in FM, hypoperfusion in frontal cortices[2]



EEG source localization analysis shows abnormal posterior spectral power and network connectivity in FM[3]

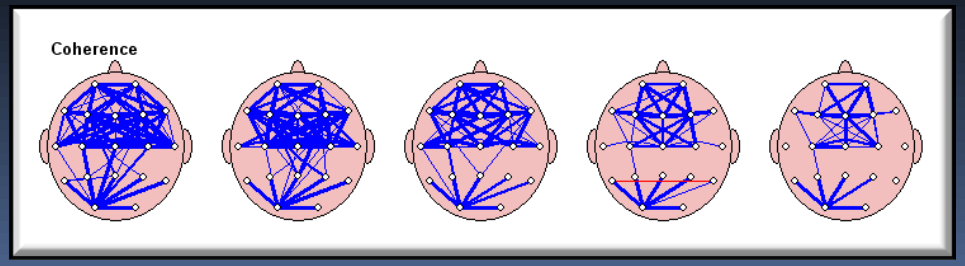
1. Pujol et al PLoS One. 2009;4(4):e5224.
2. Guedj et al Eur J Nucl Med Mol Imaging (2007) 34:130–134.
3. Hargrove et al Clin EEG Neurosci. 2010 Jul;41(3):132-9. Image not previously published.

Emerging: Functional Connectivity in FM



In FM versus healthy controls (HC), DMN and rEAN show greater intrinsic connectivity within component DMN and rEAN, as well as limbic and sensorimotor regions outside of the traditionally defined network boundaries[1]

- Functional network connectivity in pain processing brain areas has been shown to be increased in chronic pain patients
- In FM, resting brain activity within multiple networks is associated with spontaneous clinical pain (left image, fMRI study[1])
- EEG coherence provides another quantitative measure of functional connectivity; FM patient coherence (image below[2]) shows a significantly higher number of functional network connections (blue lines) compared to age/gender matched normal controls



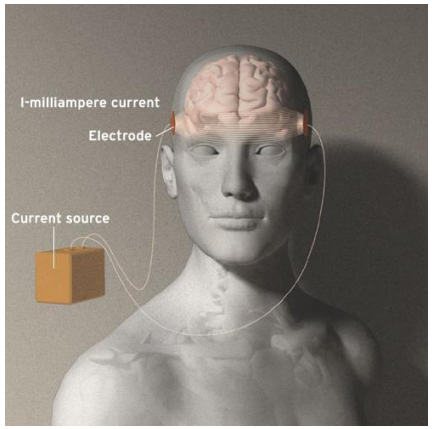
1. Napadow et al Arthritis Rheum. 2010 Aug;62(8):2545-55.
2. Hargrove et al. Unpublished image.

Targeted Therapy: Cortical Stimulation

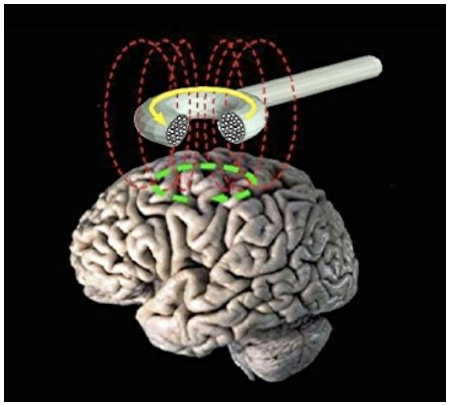
- **These findings establish a rationale for cortical stimulation therapies designed to target relevant brain areas and functions**
- **Cortical stimulation mechanisms of action are increasingly clarified and understood:**
  - **Stimulation of the brain is known to modulate cortical activity (e.g. neuron firing rates and thresholds) and influence network connectivity**
- **Literature supports rationale, safety, provides examples of modest success in reduction of pain and FM symptom improvement following cortical stimulation therapy**

RINCE™ Signal Technology

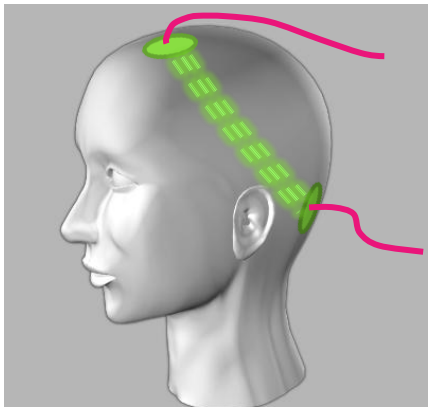
- **Primary technical limitation of noninvasive cortical stimulation techniques: poor conductivity of outer tissues**
- **We have studied an innovative signal form called *Reduced Impedance Noninvasive Cortical Electrostimulation* (RINCE)**



Traditional direct current stimulators: severe signal attenuation and diffusion



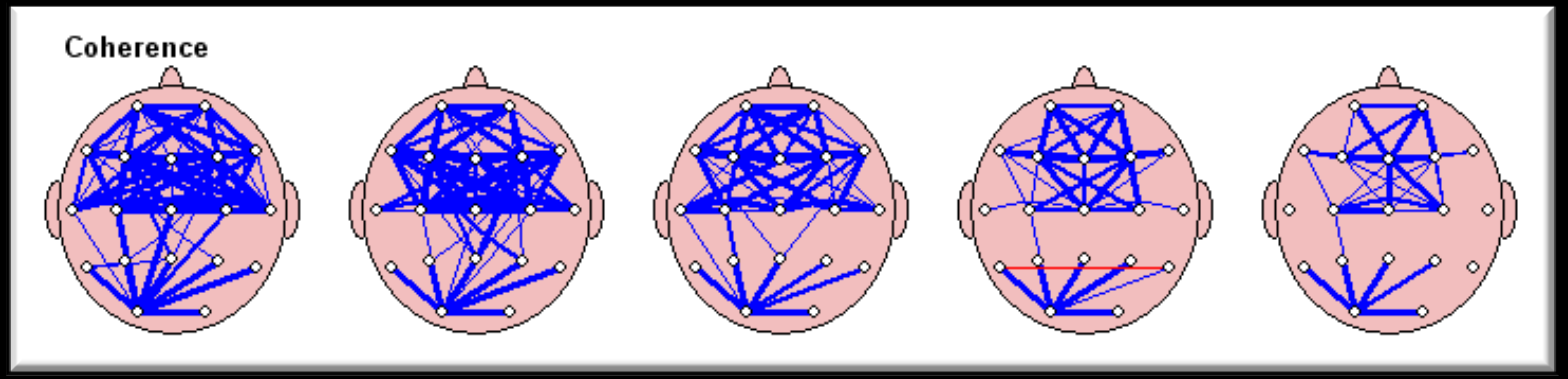
Transcranial magnetic stimulation overcomes outer tissue impedance, but control and depth of signal penetration is poor



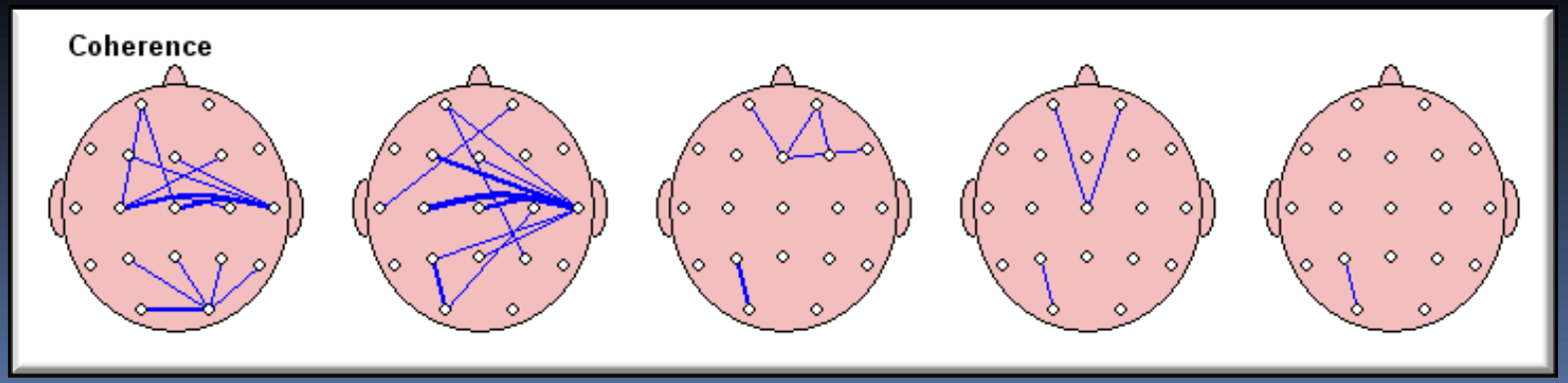
RINCE uses proprietary signal modulation to overcome outer tissue impedance with good control and signal penetration

RINCE Affects Functional Connectivity

- FM patient EEG coherence measures of functional connectivity before RINCE signal therapy



- Same patient following therapy: widely reduced functional connectivity with far less significant deviation from levels in normal controls



Results of Therapy (End-of-Study)

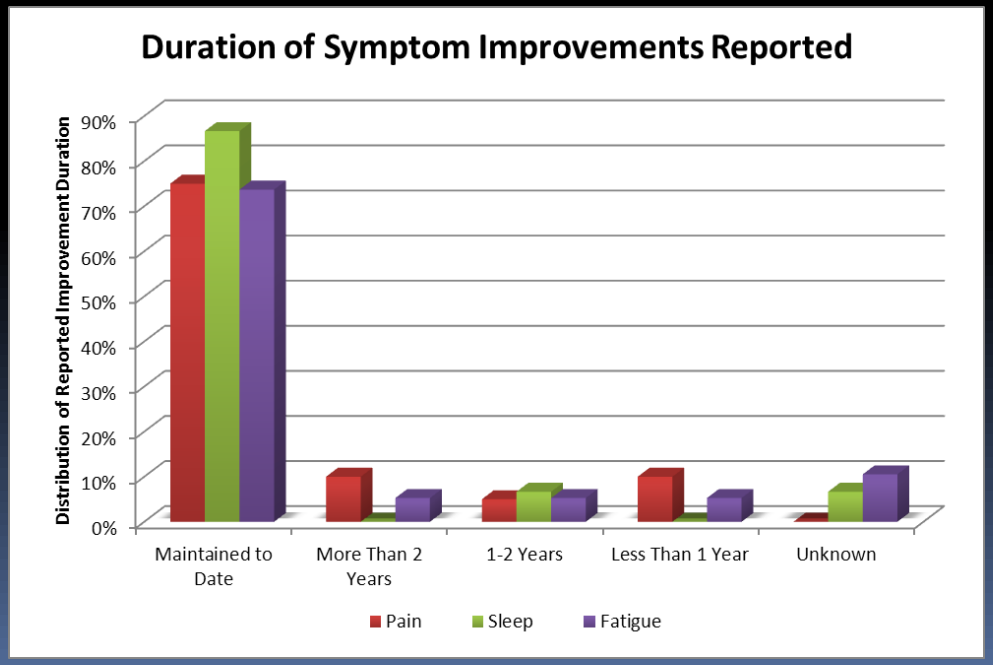
- **End-of-study results of a randomized, blinded, sham controlled study on RINCE treatment of 77 FM subjects were reported at the 2010 ACR Annual Meeting** (Arthritis Rheum 2010;62(10 Suppl):269-70)
  - These clinical results are published in *Pain Medicine* (January 2012 issue)
  - All subjects met ACR criteria and underwent 22 treatment sessions over an 11 week period between 2006-2008
  - All elements of the OMERACT core symptom set for FM were evaluated (FIQ, tender point assessment, modified Jenkins Sleep VAS questionnaire)
- **Significant end-of-study within- and between-group intervention improvement over sham in all core symptoms**
- **No serious adverse events, only a few mild side effects that all resolved without intervention**

Long-Term Follow Up: Methods

- **January-March 2011: under IRB-approval, subjects treated with RINCE were asked to complete an un-blinded follow-up survey and the FIQ**
- **39 subjects were mailed surveys, 25 were returned (64%)**
- **In addition to the FIQ, survey responses provided patient self-report data on:**
  - **duration of symptom improvement**
  - **incidence of side effects**
  - **changes in pain medicine use and physician visits**

Long-Term Follow Up: General Results

- **Average time since completion of therapy: 45 months (range 31-60)**
- **Subjects reported symptom improvement lasting at least two-years in pain (68%) sleep (56%) and fatigue (60%)**
  - **Improvement was defined as either *much improved* or *somewhat improved* using a 5-point Likert scale**



Distribution of the *duration* of symptom improvements among those reporting improvement

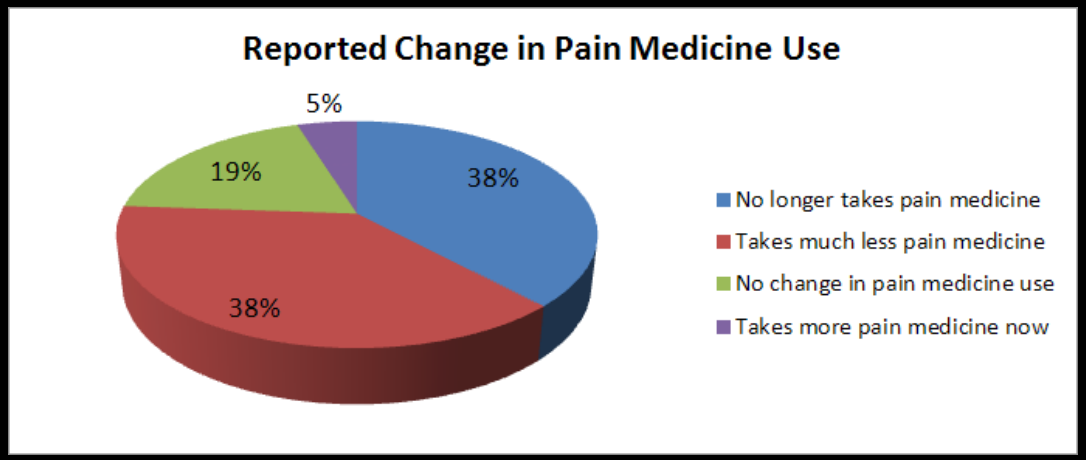
Long-Term Follow Up: FIQ Findings

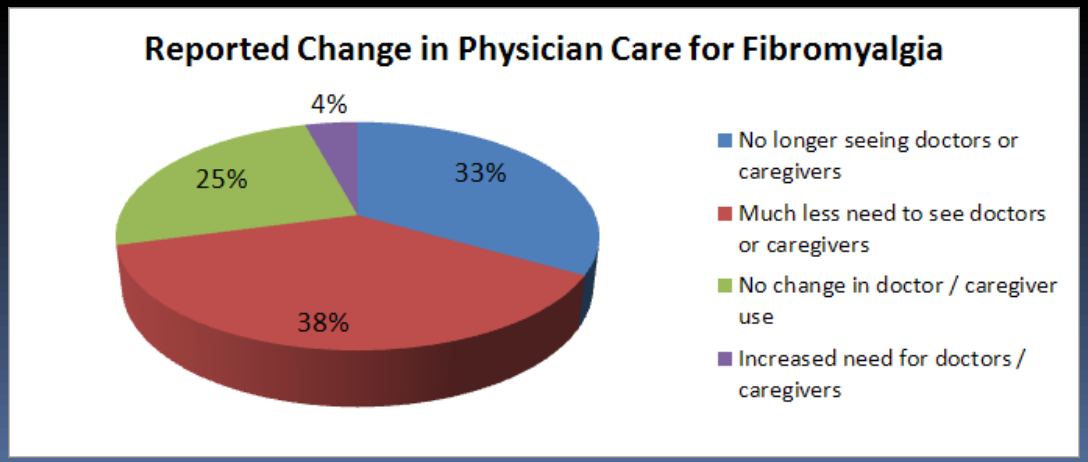
- **The mean total FIQ score was 53 at baseline, 36 at end-of-study and 32 at follow-up (P<0.001)**
- **The change from baseline FIQ scores at end-of-study and follow-up were significantly correlated (R=0.78, P<0.001)**

	Pre-Tx	Post-Tx	45-month Follow Up	*Significance (ANOVA)* Pre / Post	Pre / FU
Total FIQ Score	52.6	35.7	31.8	P < 0.001	P < 0.001
Pain VAS	6.0	4.0	3.6	P < 0.01	P < 0.001
Fatigue VAS	7.7	6.0	4.5*	P < 0.01	P < 0.001
Refreshing Sleep VAS	7.9	6.2	5.0	P < 0.01	P < 0.001
Stiffness VAS	6.8	4.7	4.0	P < 0.01	P < 0.001
Anxiety VAS	4.0	1.8	2.6	P < 0.001	P = 0.03
Depression VAS	3.5	1.7	1.9	P < 0.001	P < 0.01

* - Improvement since post-treatment is significant at P = 0.02

Patient Reported Changes in Medicine and Healthcare Resource Usage





- **76% of respondents reported that they had reduced or completely eliminated medicine use for pain**
- **71% of respondents indicate reduced or eliminated need to see physicians for FM**

Conclusions

- A high percentage of FM patients treated with RINCE continued to experience improvement in FM symptoms at a 45-month follow-up
- Sustained benefits were accompanied by significant reductions in pain medicine use and physician visits
- Follow-up total FIQ scores demonstrated durability of treatment effect when compared to baseline and end-of-study
- A strong correlation between total FIQ scores at end-of-study and follow-up suggests the initial response to RINCE is predictive of a long lasting therapeutic benefit
- Cortical electrostimulation is a non-pharmacological modality that continues to show promise in the long-term management of FM patients