SYMPTOM IMPROVEMENT IN FIBROMYALGIA PATIENTS IS RELATED TO REDUCED NETWORK CONNECTIVITY AS MEASURED BY EEG COHERENCE

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- Dr. Hargrove is the Chief Scientific Officer of Cerephex Corporation, the company developing the cortical stimulation technology discussed in this presentation, and has stock ownership in that company.

- Drs. Clauw, Bennett and Mashour are unpaid consultants to Cerephex, and have no further relevant financial interests or relationships to disclose.

- Ms. Briggs is a graduate student and has no financial interests or relationships to disclose.
Evidence Based Medicine


2010: RINCE TREATMENT OF FIBROMYALGIA

- RINCE: Reduced Impedance Noninvasive Cortical Electrostimulation
- RINCE is a new paradigm in neuromodulation, overcomes key technology limitations
- RINCE signals pass through poorly conducting outer tissues without loss, target specific brain areas
- RINCE targeting the somatosensory cortex has been studied in 77 fibromyalgia (FM) patients (Pain Med. 2012 Jan;13(1):115-24.)
2010: CLINICAL OUTCOMES

• Two centers (2005-8), randomized, double blinded, sham controlled design

• RINCE-treated subjects improved in all OMERACT core symptoms for FM (evaluated using the FIQ, tender point assessment, modified Jenkins Sleep VAS questionnaire)

• No SAEs, only mild side effects that all resolved without intervention

<table>
<thead>
<tr>
<th></th>
<th>Population Baseline</th>
<th>RINCE Intragroup</th>
<th>RINCE Intergroup</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIQ Pain VAS (0-10)</td>
<td>6.6 (P=0.89)</td>
<td>-2.0 (P&lt;0.001)</td>
<td>-1.5 (P=0.03)</td>
<td>-0.6 (P=0.20)</td>
</tr>
<tr>
<td>FIQ Total Score (0-100)</td>
<td>59.8 (P=0.45)</td>
<td>-16 (P&lt;0.001)</td>
<td>-10 (P=0.03)</td>
<td>-6 (P=0.05)</td>
</tr>
<tr>
<td>FIQ Fatigue (0-10)</td>
<td>7.8 (P=0.21)</td>
<td>-2.1 (P&lt;0.001)</td>
<td>-2.0 (P=0.02)</td>
<td>-0.4 (P=.35)</td>
</tr>
<tr>
<td>FIQ Sleep (0-10)</td>
<td>7.9 (P=0.03)</td>
<td>-2.1 (P&lt;0.001)</td>
<td>-1.4 (P=0.02)</td>
<td>-0.7 (P=.10)</td>
</tr>
<tr>
<td>FIQ Stiffness (0-10)</td>
<td>7.4 (P=0.97)</td>
<td>-1.5 (P=0.02)</td>
<td>-0.4 (P=0.57)</td>
<td>-1.1 (P&lt;0.01)</td>
</tr>
</tbody>
</table>

1 - P-values here are between groups at baseline
## 2011: 45-Month Follow Up Data

### Respondent FIQ Scores

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>EOS</th>
<th>45-month follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FIQ Score</td>
<td>52.6</td>
<td>35.7</td>
<td>31.8</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>6.0</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Fatigue VAS</td>
<td>7.7</td>
<td>6.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Sleep VAS</td>
<td>7.9</td>
<td>6.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Stiffness VAS</td>
<td>6.8</td>
<td>4.7</td>
<td>4.0</td>
</tr>
</tbody>
</table>

### Significance (ANOVA)

<table>
<thead>
<tr>
<th></th>
<th>Baseline-EOS</th>
<th>Baseline-follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
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<tr>
<td>P</td>
<td>&lt; 0.01</td>
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</tr>
<tr>
<td>P</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Correlation

<table>
<thead>
<tr>
<th></th>
<th>R-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FIQ Score</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fatigue VAS</td>
<td>0.69</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep VAS</td>
<td>0.51</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Stiffness VAS</td>
<td>0.49</td>
<td>0.01</td>
</tr>
</tbody>
</table>

1. Improvement since post-treatment is significant at $P < 0.02$.
2. Correlation between changes from baseline at EOS and follow up.

### Reported Change in Pain Medicine Use

- 38% No longer takes pain medicine
- 19% Takes much less pain medicine
- 5% No change in pain medicine use
- 38% Takes more pain medicine now

### Reported Change in Physician Care for Fibromyalgia

- 33% No longer seeing doctors or caregivers
- 25% Much less need to see doctors or caregivers
- 38% No change in doctor / caregiver use
- 4% Increased need for doctors / caregivers
CORTICAL STIMULATION IN FIBROMYALGIA

• Other cortical stimulation modalities have shown some degree of promise:
  • Transcranial Magnetic Stimulation (TMS)
  • Transcranial Direct Current Stimulation (tDCS)

1. Why does cortical stimulation affect FM?
2. What changes? What are the mechanisms involved?
3. Do the mechanisms relate to functional abnormalities?
FUNCTIONAL NETWORK CONNECTIVITY IN THE BRAIN

Brain functional network connectivity is increased in pain processing areas in FM

FM group functional magnetic resonance imaging (fMRI) reveals network connectivity increases in the default mode network (DMN) and the right executive action network (rEAN)

In FM patients, fMRI reveals greater DMN and rEAN intrinsic network connectivity compared to controls

Pain reduction correlates with reduced DMN connectivity

Electroencephalography (EEG) and Functional Network Connectivity

• The relevance of EEG testing in chronic pain, and particularly FM, is a relatively new - and growing - area of scientific investigation.

• Modern EEG analyses provide measures of neuronal firing rates, source localization for estimating origins of neuronal currents.

• EEG “coherence” provides measures of functional network connectivity.
EEG Coherence

EEG coherence is a coefficient-based measure of correlation between the amplitude and phase of EEG signals measured at two different locations.

Coherence is often shown graphically as lines connecting EEG location points where abnormally high or low coherence coefficients exist.

- EEG signals are “coherent” when their peaks and valleys are aligned in time.
- Coherence is decreased as peaks and valleys between two signals are less aligned.
- High coherence indicates a strong functional network connection between EEG measurement locations.
EEG Coherence

Coherence measures indicate functional network connectivity consistent with measures obtained using fMRI

Here, functional network connectivity in networks activated during reading is demonstrated using both fMRI and EEG coherence methods.

Source: NIH/National Institute of Deafness and Other Communication Disorders, A.R. Braun MD, Director
OBJECTIVES OF CURRENT WORK

1. Does RINCE cortical stimulation affect EEG coherence in fibromyalgia patients?

2. Are those changes in coherence related to changes in symptoms resulting from treatment?
**METHODODOLOGY**

- Under IRB-approval, EEG was collected at baseline and end of study from FM subjects that received either RINCE (N=37) or sham (N=35).

- 19-channel EEG was collected at standard electrode sites; third party software used for editing and coherence calculation.

- Non-neighboring electrode pairings (N=118) were analyzed at low EEG frequencies (1-4 Hz) to reduce effects of cortical volume conduction over shorter spatial distances.

- FM symptomatology was assessed with the FIQ and the SF-36.
FINDINGS

• Population baseline coherence showed widespread hyper-coherence, and was consistent between groups in 112 of 118 electrode pairings

• Coherence coefficient mean change from baseline (MCFB) between the RINCE and sham groups; RINCE = 67%, sham = 18% (P<0.001)

• Electrode pairings achieving at least a 50% MCFB response:
  
  **RINCE group:** Pairings achieving response: 79
  Pairings with no response: 39

  **Sham group:** Pairings achieving response: 9
  Pairings with no response: 109

• Significance: $\chi^2 = 86.3$, $P < 0.001$
POST-TREATMENT EEG PAIRINGS WITH SIGNIFICANT DECREASES IN COHERENCE

SHAM GROUP

RINCE GROUP
Significant positive correlations in both inter- and intra-hemispherical electrode pairings between coherence MCFB and improvements in FM symptom domains:

- **FIQ Total Score**
- **FIQ Sleep Index**
- **FIQ Fatigue**
Significant positive correlations in both inter- and intra-hemispherical electrode pairings between coherence MCFB and improvements in FM symptom domains:

**SF-36 Emotional Wellbeing**

**SF-36 Social Functioning**

<table>
<thead>
<tr>
<th>Symptom Measure</th>
<th>Improvement from Baseline (P-value)</th>
<th>Significant Correlations to Reduced Coherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 Emotional Wellbeing Domain (i.e. Mental Health)</td>
<td>+11.7 (+21%) (p=0.001)</td>
<td>EEG Pairs: 4</td>
</tr>
<tr>
<td>SF-36 Social Functioning Domain</td>
<td>+10.1 (+22%) (p=0.02)</td>
<td>EEG Pairs: 19</td>
</tr>
</tbody>
</table>
Subjects experiencing reduced coherence had significantly greater improvements in FIQ and pain VAS compared to those who had stable or increased coherence.
CONCLUSIONS

• FM patient baseline EEG coherence suggests brain functional network connectivity abnormalities consistent with neuroimaging studies

• Subjects treated with RINCE exhibited significant changes in EEG coherence that suggest reductions in functional network connectivity

• Improvements in FIQ total score and pain VAS were greatest in FM subjects showing reductions in functional network connectivity based on reduced EEG coherence
IMPLICATIONS

• This study suggests FM symptom improvements arising from RINCE therapy are related to reductions in abnormal functional network connectivity.

• These results may provide insight into why cortical stimulation therapies have promise as a treatment modality for FM, and possibly other painful conditions where pain has centralized.

• These findings strengthen previous claims that reduced connectivity may be an objective biomarker of improvement in FM clinical trials.

• This study supports the use of EEG for detecting and quantifying abnormal network connectivity.

  • EEG is less costly than fMRI testing, and thus more practical for use in point of care settings.