How Neurotechnologies are Providing New Insights In Vivo Into the Treatment of Migraine and other Chronic Pain Disorders

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Biologic & Materials Sciences Department, University of Michigan School of Dentistry
Disclosure: MoxyTech Inc (Co-Founder)
116 Million Americans With Chronic Pain

Costs $635 billion a year

Costs per patient additional $4.5-7.7 thousand in health care expenditures
What Are We Measuring?

<table>
<thead>
<tr>
<th></th>
<th>VAS</th>
<th>GeoPain Average</th>
<th>Area</th>
<th>P.A.I.N.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.9</td>
<td>1.4</td>
<td>7.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>6.3</td>
<td>2.0</td>
<td>5.5%</td>
<td>3.6%</td>
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<tr>
<td></td>
<td>5.7</td>
<td>2.1</td>
<td>36.4%</td>
<td>25.7%</td>
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</table>
MRI
Neuroplasticity in Migraine

Limbic System
- Cognition
- Mood

Visual System
- Aura

Inhibitory System
- Allodynia

Sensorimotor System
- Headache

Neuroimage
- ACC
- MT/V5
- PAG
- Thal

Prescot et al, 2009
DaSilva et al, 2006
DaSilva et al, 2007
DaSilva et al, 2007
Background

Positron Emission Tomography (PET Studies)

Endogenous Mu-opioid

$[{_{^{11}}}C]$ Carfentanil

No pain

Pain
Methods

Participants

- Ictal (headache)
- Interictal (non-headache)
- HC (healthy control)

Imaging

- EM-Ictal
- EM-Interictal
- PET 90 min
- Early Phase (Rest)
- Late Phase (Allodynia)
- MRI
- HC

Challenge

- Sustained Thermal Pain Threshold

(Allodynia)
Spontaneous Migraine Attacks
μ-Opioid Activation

Migraine Attacks During PET

Migraine Rating Average

μ-Opioid Activation

Severe
Moderate
Mild

mPFC

NIH-NINDS K23 NS062946
NIH-NINDS R01 NS094413
DANA Foundation’s Brain Award
Migraine Research Foundation

DaSilva et al, 2014
Nascimento et al, 2014
H.O.P.E. Lab, University of Michigan
Spontaneous Migraine Attacks

μ-Opioid Activation during Allodynia

Migraine Allodynia

μ-Opioid Activation

<table>
<thead>
<tr>
<th>Average Threshold Temperature (Celsius)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>AVE</th>
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<tr>
<td>Interictal</td>
<td>49.44</td>
<td>48.78</td>
<td>48.87</td>
<td>40.62</td>
<td>46.87</td>
<td>47.78</td>
<td>47.06</td>
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<tr>
<td>Ictal</td>
<td>45.2</td>
<td>45.91</td>
<td>39.53</td>
<td>36.45</td>
<td>34.33</td>
<td>40.68</td>
<td>40.35</td>
</tr>
</tbody>
</table>

NIH-NINDS K23 NS062946
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Chronic Migraine Attacks
Mu-Opioid Dysfunction

A Pain Area + Intensity (P.A.I.N.S)

Chronic Migraine (CM)

Episodic Migraine (EM)

B PET Neuroimaging

μ-Opioid Activity during Migraine Attacks & Thermal Challenge

HC vs CM

EM vs CM

Thalamus
MNI: -10, -14, 8

Caudate
MNI: -14, 18, -8

Amygdala
MNI: 22, -2, -16

Parahippocampal
MNI: 24, 6, -30

Under preparation
Migraine Attacks – Variance for Amygdala Type of Migraine, Severity, Allodynia

A Explained Variance for Amygdala $\mu$OR-BP$_{ND}$

B Individual Impact of Type of Migraine, Attack Severity or Allodynia on Amygdala $\mu$OR-BP$_{ND}$

Under preparation
Migraine Attacks - Limbic

Increase Endogenous μ-opioid Release during Chronic Migraine Attack and Allodynia in vivo

Healthy Controls  
Migraine (Ictal Phase)  
Increase in endogenous μ-opioid release in the limbic system

- μ-opioid (endogenous)
- [11C]carfentanil
- μ-opioid receptor
- [11C]carfentanil BPND

Under preparation
Spontaneous Migraine Attacks
Dopamine D2/D3 Decrease

Spontaneous migraine attacks during PET
Decreased endogenous dopamine release

Putamen
Caudate

Spontaneous Migraine Attacks
Dopamine D2/D3 Imbalance

Interictal phase
(No headache)

Migraine attack
(Headache at rest)

Cutaneous allodynia
(Headache + STPT challenge)

- Dopamine (D2/D3 (endogenous))
- ($^{11}$C)raclopride
- D2/D3 receptor
- ($^{11}$C)raclopride BP

Neuromodulation
Non-invasive Brain Stimulation

Transcranial Direct Current Stimulation (tDCS)

Continuous weak electric
Anode and Cathode
Resting neuronal membrane
Fibromyalgia, neuropathic pain, depression

DaSilva et al, 2011
tDCS and Chronic Migraine

Results
INVASIVE Motor Cortex Stimulation In The Treatment Of Chronic Pain.
Non-Invasive H.O.P.E. lab M1 HD-tDCS Montage for Chronic Pain.
# TMD: MONTH FOLLOW-UP

## VAS 50% Responders from Week 1 to Week 6

<table>
<thead>
<tr>
<th>Group</th>
<th>Active</th>
<th>Sham</th>
<th>Total</th>
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<tbody>
<tr>
<td>&lt;50% VAS decrease</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>≥50% VAS decrease</td>
<td>9</td>
<td>4</td>
<td>13</td>
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<tr>
<td><strong>Total</strong></td>
<td>12</td>
<td>12</td>
<td>24</td>
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</table>

Chi-Square: \(X^2=4.1958\) \(p=0.04\)

Donnell et al, 2015
H.O.P.E. Lab, University of Michigan
<table>
<thead>
<tr>
<th>Location</th>
<th>Time Frame</th>
<th>Effect</th>
<th>Pain Sum</th>
<th>Ave Pain</th>
<th>Pain Area</th>
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<tbody>
<tr>
<td>Bilateral</td>
<td>Study</td>
<td>Week Group</td>
<td>0.0042</td>
<td>&lt;0.0001</td>
<td>0.0027</td>
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<tr>
<td></td>
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<td>Week*Group</td>
<td>0.0851</td>
<td>0.9845</td>
<td>0.1057</td>
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<tr>
<td></td>
<td>Treatment</td>
<td>Day Group</td>
<td>0.0071</td>
<td>&lt;0.0001</td>
<td>0.0052</td>
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<tr>
<td></td>
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<td>Day PrePost</td>
<td>0.1186</td>
<td>0.4078</td>
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<tr>
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<td>Day PrePost*Group</td>
<td>0.2945</td>
<td>0.0084</td>
<td>0.2237</td>
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<td>0.1176</td>
<td>0.3567</td>
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<td>Ipsilateral</td>
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<td>Week*Group</td>
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<td>Treatment</td>
<td>Day Group</td>
<td>0.1713</td>
<td>0.0013</td>
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<tr>
<td></td>
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<td>Day PrePost</td>
<td>0.2058</td>
<td>0.6991</td>
<td>0.1932</td>
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<tr>
<td></td>
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<td>Day PrePost*Group</td>
<td>0.2871</td>
<td>0.7001</td>
<td>0.4564</td>
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<tr>
<td></td>
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<td>Day PrePost*Group</td>
<td>0.2107</td>
<td>0.9903</td>
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<td>Contralateral</td>
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<td>Week Group</td>
<td>0.0083</td>
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<td>0.9820</td>
<td>0.0758</td>
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<tr>
<td></td>
<td>Treatment</td>
<td>Day Group</td>
<td>0.0005</td>
<td>&lt;0.0001</td>
<td>0.0057</td>
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<tr>
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<td>Day PrePost</td>
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<td>0.4471</td>
<td>0.0553</td>
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<td>Day PrePost*Group</td>
<td>0.0007</td>
<td>&lt;0.0001</td>
<td>0.0035</td>
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</tbody>
</table>

*p-value is for Type 3 test of fixed effect from linear mixed model for particular time frame (over study or over treatment) of particular dependent variable.
Neuromodulation + Neuroimaging
There were no significant differences between sham and active tDCS group.
μ-Opioid Activation During tDCS

DosSantos et al, 2014
H.O.P.E. Lab, University of Michigan
μ-Opioid Activation During tDCS

Sham

Active

DosSantos et al, 2014
H.O.P.E. Lab, University of Michigan
μ-Opioid Activation During tDCS

DosSantos et al, 2014
H.O.P.E. Lab, University of Michigan
What is the Chronic Effect of Sham and Active Neuromodulation?
Pre-Treatment Glx within the Anterior Cingulate Predicts Subsequent Clinical Response to Sham and Active tDCS

Foerster et al, 2015
H.O.P.E. Lab, University of Michigan
Clinical Augmented Reality
Michigan Clinical Augmented Reality Pain Unit (M-CARP)

- Observation Room
- Real-Time Neuroimage
- Non-Invasive Neuromodulation
- Clinical Augmented Reality
- Mobile Applications
- Virtual Reality 3D Breathing
Cooling Stimulus

Lower SI cortex

Upper SI cortex

Dental Pain Evoked Response at SI

* * * * *

Racek et al, 2015

H.O.P.E. Lab, University of Michigan

Colgate-Palmolive
Dental Pain Evoked Response at Left Prefrontal Cortex

Dental Pain Evoked Response at Right Prefrontal Cortex

Racek et al, 2015
H.O.P.E. Lab, University of Michigan
Immediate Functional Connectivity Changes after Dental Pain

- Functional connectivity changed immediately after clinical dental pain
- The orofacial S1 region contralateral to the pain globally increased its functional connectivity
- The S1 homuncular regions ipsilateral to the pain decreased their functional connectivity with the prefrontal regions

Hu et al, Accepted
H.O.P.E. Lab, University of Michigan
Pattern Recognition + Clinical Augmented Reality

Neuroimaging (fNIRS)

- Region 1
- Region 2
- Region 3
- Region 4
- Region 5
- Region 6

Oxy-Hb & Deoxy-Hb

Training trials

Testing trials

Brain Stimulation

Augmented Reality

Predictor

- Painful
- Non-Painful

Predictor 1: K-NN

Predictor 2: K-NN & DT

Accuracy: 80% (Block wide) 70%

K-NN: K Nearest Neighborhood DT: Decision Tree
MICHIGAN CLINICAL AUGMENTED REALITY FOR PAIN UNIT
Conclusions

• Technology has completely expanded the meaning of multidisciplinarity in pain treatment, research and education.

• Novel neuroscience-driven technologies have improved our ability to understand, navigate and modulate, in a non-invasive manner, brain activity related to pain even at molecular level.

• The brain is presenting itself as an objective and reliable target for multiple emerging technologies to advance personalized treatment of chronic pain, even remotely.
Funding

GOVERNMENTAL
• NIH-NINDS R01 NS094413
• NIH-NIDCR U01 DE025633
• NIH-NINDS K23 NS062946
• NIH-NIDCR R56 DE022637

PRIVATE
• DANA Foundation’s Brain and Immuno-imaging award
• Migraine Research Foundation

INTERNAL
• Michigan Institute for Clinical & Health Research Clinical Trial Planning
• CTSA High-Tech funding grant number UL1RR024986
• Transforming Learning for a Third Century, University of Michigan Provost’s Office
• MCubed Award– University of Michigan

INDUSTRY
• Colgate-Palmolive
Thank You

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Facing Virtual Reality
Health care goes high tech