Neuromodulation as a treatment for chemotherapy-induced neuropathy
Conflict of Interest Disclosure

Sarah Prinsloo, PhD

Has no real or apparent conflicts of interest to report.

Funding through NCCIH K01
Rising Tide Foundation
Importance of the brain

- From the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant...

- Hippocrates (460-370 BC)
Current Treatments

Review Article
Supportive Care in Cancer
March 2016, Volume 24, Issue 3, pp 1439-1447

First online: 19 December 2015

National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons

Neil Majithia, Sarah M. Temkin, Kathryn J. Ruddy, Andreas S. Beutler, Dawn L. Hershman, Charles L. Loprinzi

14 of 15 trials results in a “failure to provide an evidence based approach” to prevention or treatment
Peripheral Damage
3 pain pathways: Pain can be predicted by only 3 brain regions

Global pain = painfullness + suffering - pain suppression

DeRidder, 2015
Quantitative Imaging – qEEG (cortical)
Philosophy

• If the brain is capable of *modifying itself* such that pain becomes chronic, it should be able to also modify itself to gain relief from pain.
Non-invasive Neuromodulation

Brain computer interface
   Neurofeedback
Transcranial Magnetic Stimulation

Pipeline:
1. Measure brain activity/compare to norms
2. Create a map of brain regions
3. Design a brain-computer interface
## EEG

![Neuronal Image](Image: Wikimedia, Santiago Ramón y Cajal)

<table>
<thead>
<tr>
<th>DELTA</th>
<th>THETA</th>
<th>ALPHA</th>
<th>SMR</th>
<th>BETA</th>
<th>HIGH BETA</th>
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</thead>
<tbody>
<tr>
<td>Less than 4 cps</td>
<td>4–8 cps</td>
<td>8–12 cps</td>
<td>12–15 cps</td>
<td>15–18 cps</td>
<td>more than 19 cps</td>
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<tr>
<td>Sleep</td>
<td>Drowsy</td>
<td>Relaxed Focus</td>
<td>Relaxed Thought</td>
<td>Active Thinking</td>
<td>Excited</td>
</tr>
</tbody>
</table>

cps = cycles per second, or Hertz
Measure Brain Activity

- 98% percent of the brain’s communication involves electrical exchange, 2% involves chemical
- 100% of medications work on 2% of the brain’s potential
- EEG (Electroencephalogram) – Electrical activity of the brain recorded on the scalp.
- Read from the synchronous activity of thousands to millions of pyramidal cells in the cortex under the skull
Create a map of brain regions

• qEEG (individual; normative database-brain map)
Design a brain/computer interface

- Neurofeedback=NFB; 1960s
- Barry Sterman: inspired by Pavlov; EEGs and monomethyl hydrazine
Objectives

- Test the ability of cancer patients to control brainwaves responsible for pain.
- Examine brain changes before and after neurofeedback
Methods

• Eligibility
  – Pain of a 4 or greater on 0-10 scale or 3 or greater grade on NCI neuropathy scale
  – Off active chemotherapy for at least 3 months

• Measures
  – Brief Pain Inventory (BPI)
  – Pain Quality Assessment Scale (PQAS)
  – Quantitative EEG (QEEG)

• Timepoints
  – Baseline
  – Post-TX (20 sessions of NFB for TX group, rolling average number of weeks from baseline for Control group)
Methods

- Randomly assigned to nfb or wait-list (assessed at similar timepoints)
- EEG neurofeedback: 45 minute sessions; auditory and visual rewards.
- A minimum of twice weekly, with a maximum of 5 sessions per week.
Results

Randomized controlled trial of neurofeedback on chemotherapy-induced peripheral neuropathy: A pilot study.

Prinsloo S¹, Now D², Driver L³, Lyle R³, Ramondetta L⁴, Eng C⁵, McQuade J⁶, Lopez G¹, Cohen L¹.

Author information

Abstract

BACKGROUND: Chemotherapy-induced peripheral neuropathy (CIPN) is a significant problem for cancer patients, and there are limited treatment options for this often debilitating condition. Neuromodulatory interventions could be a novel modality for patients trying to manage CIPN symptoms; however, they are not yet the standard of care. This study examined whether electroencephalogram (EEG) neurofeedback (NFB) could alleviate CIPN symptoms in survivors.

METHODS: This was a randomized controlled trial with survivors assigned to an NFB group or a wait-list control (WLC) group. The NFB group underwent 20 sessions of NFB, in which visual and auditory rewards were given for voluntary changes in EEGs. The Brief Pain Inventory (BPI) worst-pain item was the primary outcome. The BPI, the Pain Quality Assessment Scale, and EEGs were collected before NFB and again after treatment. Outcomes were assessed with general linear modeling.

RESULTS: Cancer survivors with CIPN (average duration of symptoms, 25.3 mo), who were mostly female and had a mean age of 62.5 years, were recruited between April 2011 and September 2014. One hundred percent of the participants starting the NFB program completed it (30 in the NFB group and 32 in the WLC group). The NFB group demonstrated greater improvement than the controls on the BPI worst-pain item (mean change score, -2.43 [95% confidence interval, -3.58 to -1.28] vs 0.09 [95% confidence interval, -0.72 to -0.09]; P = .001; effect size, 0.83).

CONCLUSIONS: NFB appears to be effective at reducing CIPN symptoms. There was evidence of neurological changes in the cortical location and in the bandwidth targeted by the intervention, and changes in EEG activity were predictive of symptom reduction. Cancer 2017;123:1989-1997. © 2017 American Cancer Society.
Results

- 71 patients total consented over a 3 year period

<table>
<thead>
<tr>
<th>Demographic Factors</th>
<th>Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (+/- SD)</td>
<td>62.6 (+/- 10.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>63 (88%)</td>
</tr>
<tr>
<td>Anglo/European, n (%)</td>
<td>55 (80%)</td>
</tr>
<tr>
<td>Months since chemo (+/- SD)</td>
<td>24.8 (+/- 18.3)</td>
</tr>
<tr>
<td>Breast Cancer, n (%)</td>
<td>51 (72%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>II</td>
<td>33 (49%)</td>
</tr>
<tr>
<td>III</td>
<td>25 (37%)</td>
</tr>
</tbody>
</table>
Primary Outcome

BPI - Worst Pain

- Baseline: 5.79 (Control), 5.7 (Treatment)
- Post-TX: 5.63 (Control), 3.57 (Treatment)
- 1-month FU: 5.54 (Control), 3.44 (Treatment)
- 4-month FU: 5.71 (Control), 4.65 (Treatment)

*** p < .001   *p < .05
Other common symptoms

![PQAS - Numbness chart](chart)

**Statistical Significance:**

- ***p<.001**
- **p <.01**
- *p <.05**
Other common symptoms

![Bar chart](chart.png)

- **PQAS - Unpleasantness**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.6</td>
<td>6.65</td>
</tr>
<tr>
<td>Post-TX**</td>
<td>5.84</td>
<td>3.17</td>
</tr>
<tr>
<td>1-month FU**</td>
<td>6.23</td>
<td>3.67</td>
</tr>
<tr>
<td>4-month FU*</td>
<td>5.57</td>
<td>4.25</td>
</tr>
</tbody>
</table>

***p<.001   ** p <.01     *p<.05
Other common symptoms

**PQAS - Intensity**

- Baseline: Control (3.6), Treatment (3.83)
- Post-TX**: Control (5.25), Treatment (3.51)
- 1-month FU*: Control (5.46), Treatment (3.39)
- 4-month FU: Control (5.25), Treatment (4.13)

** p < .01  *p < .05
Results

Original Article

The Long-Term Impact of Neurofeedback on Symptom Burden and Interference in Patients With Chronic Chemotherapy-Induced Neuropathy: Analysis of a Randomized Controlled Trial

Sarah Prinsloo, PhD, Diane Novy, PhD, Larry Driver, MD, Randall Lyle, PhD, Lois Ramondetta, MD, Cathy Eng, MD, Gabriel Lopez, MD, Yisheng Li, PhD, and Lorenzo Cohen, PhD

Department of Palliative, Rehabilitation, and Integrative Medicine (S.P., G.L., L.C.), The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Pain Medicine (D.N., L.D.), The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Marriage and Family Therapy (R.L.), Mount Mercy University, Cedar Rapids, Iowa; Department of Gynecologic Oncology and Reproductive Medicine (L.R.), The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Gastrointestinal Medical Oncology (C.E.), The University of Texas MD Anderson Cancer Center, Houston, Texas; and Department of Biostatistics (Y.L.), The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
Results: activity, mood, sleep, cognitive function

<table>
<thead>
<tr>
<th></th>
<th>NFB</th>
<th>WLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>38.88</td>
<td>34.38</td>
</tr>
<tr>
<td>EOT*</td>
<td>21.41</td>
<td>31.84</td>
</tr>
<tr>
<td>1 MOS</td>
<td>19.44</td>
<td>22.84</td>
</tr>
<tr>
<td>4 MOS*</td>
<td>24.61</td>
<td>32.67</td>
</tr>
</tbody>
</table>

MDASI Symptom Severity
And then we treated the waitlist...

**BPI Worst Pain - WLC to NFB**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>EOT</th>
<th>4 month Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLC prior to NFB</td>
<td>5.53</td>
<td>5.62</td>
<td>5.71</td>
</tr>
<tr>
<td>WLC after NFB</td>
<td>5.62</td>
<td>2.86</td>
<td>3.56</td>
</tr>
</tbody>
</table>

Mean Change from Baseline
Results: 8-12 HZ ratio (this is what we trained them to do)

- Control: 32 pts (age: M=61.91, SD = 11.30; gender: 29 female, 3 male)
- Treatment: 30 pts (age: M=62.97; SD = 9.49; gender: 25 female, 5 male) \( p=.001 \)
Results: Beta 2 reduction

Treatment
Control:  

\[ p = .02 \]
Results: Association between decreased symptom report and brain activity
Comments made by patients

- "I had sequestered myself before. I was able to go (to a wedding this weekend) and have fun, dance." First time since treatment that I’ve gone out like that. Able to wear pretty shoes. Felt feminine."

- "For me, getting my feet back was more about safety. The feel good stuff came later." "The feel good stuff is just that. It gave me back to me."

- "It's a mind/body thing. Being able to feel confident on knowing what my feet are doing."
Placebo controlled trial

- K01 Award; Rising Tide Foundation
- Same study design but breast cancer only
- 3 group design
Effect Sizes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Neurofeedback (n=25)</th>
<th>Placebo (n=27)</th>
<th>Waitlist Control (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>PQAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpleasantness</td>
<td>4.08 (.61)</td>
<td>4.37 (.66)</td>
<td>6.96 (.51)</td>
</tr>
<tr>
<td>Numbness</td>
<td>3.60 (.62)</td>
<td>4.89 (.63)</td>
<td>5.92 (.60)</td>
</tr>
<tr>
<td>Tingling</td>
<td>3.72 (.56)</td>
<td>5.07 (.64)</td>
<td>5.46 (.68)</td>
</tr>
<tr>
<td>Intensity</td>
<td>4.08 (.54)</td>
<td>4.59 (.56)</td>
<td>6.21 (.49)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>1.52 (.48)</td>
<td>2.48 (.61)</td>
<td>3.46 (.73)</td>
</tr>
<tr>
<td>Sensitive</td>
<td>1.52 (.43)</td>
<td>1.78 (.60)</td>
<td>1.79 (.48)</td>
</tr>
<tr>
<td>Itchy</td>
<td>0.64 (.26)</td>
<td>1.74 (.53)</td>
<td>1.13 (.45)</td>
</tr>
<tr>
<td>Sharp</td>
<td>3.16 (.56)</td>
<td>2.96 (.67)</td>
<td>4.92 (.64)</td>
</tr>
<tr>
<td>Hot</td>
<td>1.76 (.47)</td>
<td>2.56 (.56)</td>
<td>3.46 (.72)</td>
</tr>
<tr>
<td>Dull</td>
<td>3.16 (.61)</td>
<td>2.00 (.58)</td>
<td>4.75 (.58)</td>
</tr>
<tr>
<td>Cold</td>
<td>1.80 (.52)</td>
<td>1.67 (.50)</td>
<td>3.00 (.64)</td>
</tr>
<tr>
<td>Shooting</td>
<td>1.80 (.42)</td>
<td>3.04 (.66)</td>
<td>2.79 (.63)</td>
</tr>
<tr>
<td>Electrical</td>
<td>2.08 (.53)</td>
<td>2.89 (.66)</td>
<td>4.60 (.74)</td>
</tr>
<tr>
<td>Cramping</td>
<td>2.32 (.57)</td>
<td>3.04 (.69)</td>
<td>2.46 (.68)</td>
</tr>
<tr>
<td>Radiating</td>
<td>1.20 (.35)</td>
<td>2.52 (.62)</td>
<td>3.29 (.67)</td>
</tr>
<tr>
<td>Throbbing</td>
<td>1.76 (.45)</td>
<td>3.15 (.61)</td>
<td>3.67 (.70)</td>
</tr>
<tr>
<td>Aching</td>
<td>2.80 (.55)</td>
<td>3.37 (.72)</td>
<td>5.13 (.71)</td>
</tr>
<tr>
<td>Heavy</td>
<td>2.48 (.62)</td>
<td>3.41 (.64)</td>
<td>3.46 (.64)</td>
</tr>
<tr>
<td>Global</td>
<td>2.50 (.38)</td>
<td>3.26 (.52)</td>
<td>4.13 (.45)</td>
</tr>
</tbody>
</table>

*P values are from general linear model

Effect sizes are calculated based on group differences in change scores from pre- to post-training using Cohan’s d

NFB had a greater effect size than PL in 16 of 19 scales
Alpha: NFB compared to PLC; T2-T1

Value = 2.36E+0
(X = 65, Y = -45, Z = 25) (MNI coords)
Best Match at 0 mm
Brodmann area 40
Inferior Parietal Lobule
Parietal Lobe

The Multinational Association of Supportive Care in Cancer • Annual Meeting 2019 • www
Beta: NFB compared to PLC; T2-T1

Value = -2.33E+0
(X = 40, Y = -45, Z = 55) (MNI coords)
Best Match at 0 mm
Brodmann area 40
Inferior Parietal Lobule
Parietal Lobe

The Multinational Association of Supportive Care in Cancer • Annual Meeting 2019 •
Patients can be taught via neurofeedback to modify their brainwave activity AND decrease the sensations of neuropathy.

Neurofeedback has a larger effect size than either placebo or waitlist; greater reduction in numeric rating scale than duloxetine.

We do have a placebo effect at work in neurofeedback, which is difficult to separate by patient self-report. Brain data supports discreet mechanisms of NFB and PL.

Predictable brain wave patterns, independent of chemo type and disease type.

Cost is approximately $120 per session, equipment is portable.
Video
THANKS

- MD Anderson Patients and Caregivers!
- Collaborators
- Funders
Regions active in placebo: rACC; dIPFC; insula
<table>
<thead>
<tr>
<th>Seeds</th>
<th>ACC sub-regions</th>
<th>MNI coordinates</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
<td></td>
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<tr>
<td>Seed1</td>
<td>Caudal ACC</td>
<td>±5</td>
<td>-10</td>
<td>47</td>
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<tr>
<td>Seed 2</td>
<td>Dorsal ACC</td>
<td>±5</td>
<td>14</td>
<td>42</td>
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<tr>
<td>Seed 3</td>
<td>Rostral ACC</td>
<td>±5</td>
<td>34</td>
<td>28</td>
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<tr>
<td>Seed 4</td>
<td>Perigenual ACC</td>
<td>±5</td>
<td>47</td>
<td>11</td>
<td></td>
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<tr>
<td>Seed 5</td>
<td>Subgenual ACC</td>
<td>±5</td>
<td>25</td>
<td>-10</td>
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</table>

ACC, anterior cingulate cortex.

doi:10.1371/journal.pone.0151879.t001
CONCLUSIONS: modifications of pathways in the brain is possible…

- Patients can be taught via neurofeedback to modify their brainwave activity AND decrease the sensations of neuropathy
  - Duloxetine mean reduction in average pain: 1.06 pts; effect size: 0.51
  - Neurofeedback mean reduction in average pain: 2.2 pts; effect size: 0.88
Conclusions - Clinical significance

Primary outcome: NFB mean reduction in unpleasantness: -2.57 pts

CONCLUSIONS - clinically significant

- Average pain as measured by the BPI
  - Duloxetine mean reduction in average pain: 1.06 pts
  - Neurofeedback mean reduction in average pain: 1.44 pts
  - Placebo mean reduction in average pain: 1.33 pts

- Our primary outcome (PQAN)
  - Clinical significance: decrease by 2 points
  - Neurofeedback mean reduction in unpleasantness: -2.57 pts
  - Placebo mean reduction in unpleasantness: -2.26 pts
  - Waitlist mean reduction in unpleasantness: (gain) .375 points
NFB compared to WLC

Alpha

Beta
Need for pain management in cancer

- Most patients and survivors are taking multiple medications, even into survivorship
  - Side effects
  - Interplay between types medications/efficacy
  - Expense
  - Continued pain despite being medicated
  - Risk of opioid abuse
  - To date, limited targeted interventions. Current treatments effect the entire system