
2019
21-23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE
Neuromodulation as a treatment for chemotherapy-induced neuropathy
MASCC/ISOO
Annual Meeting on Suppportive Care in Cancer
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MASCC
Multinational Association of Supportive Care in Cancer
ISOO
INTERNATIONAL SOCIETY of ORAL ONCOLOGY
#MASCC19

Conflict of Interest Disclosure

Sarah Prinsloo, PhD

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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)

Image credit: Wikipedia, Painted by Girodet

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

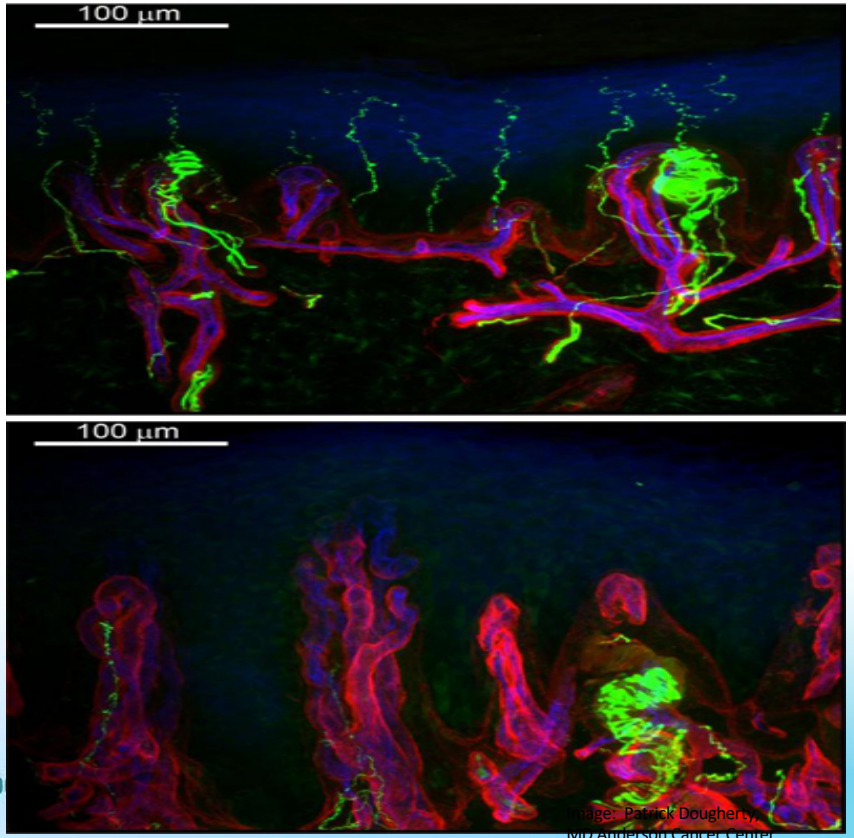
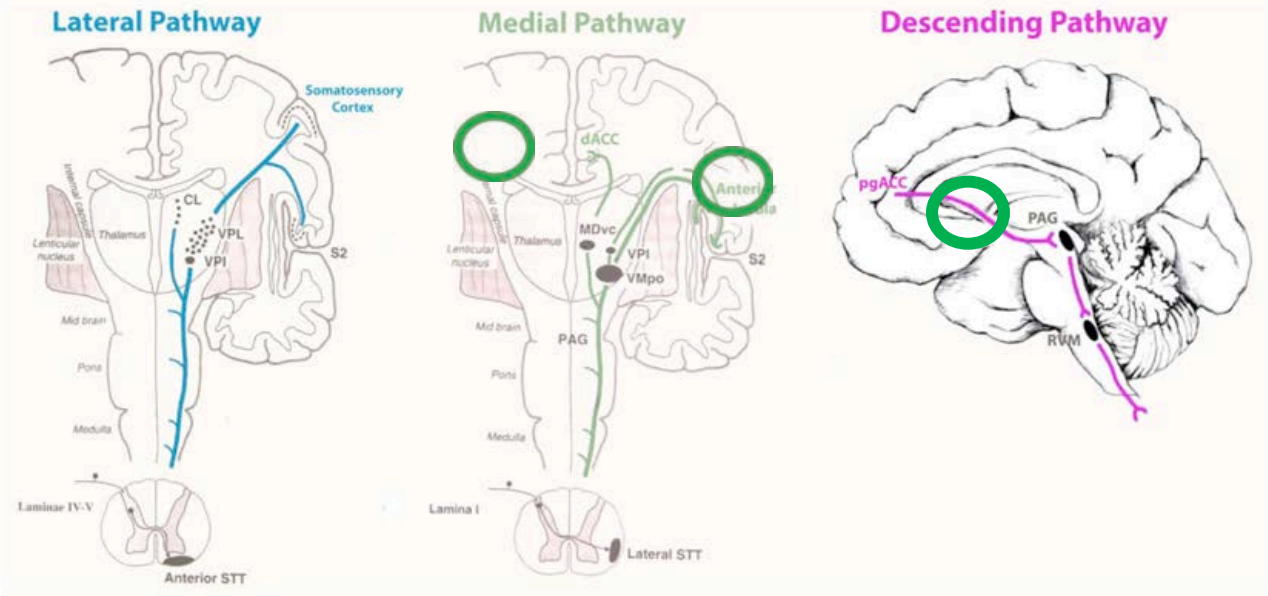


Image: Patrick Dougherty, MD Anderson Cancer Center

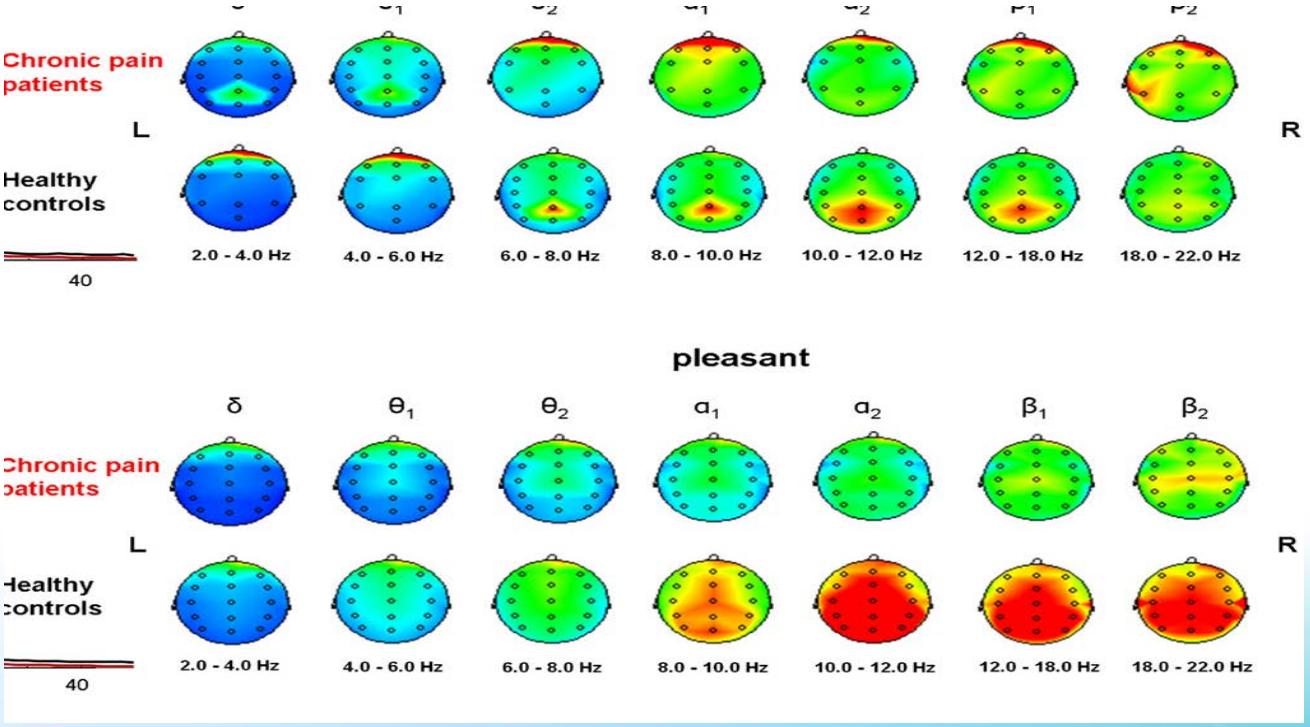
3 pain pathways: Pain can be predicted by only 3 brain regions

Global pain = painfulness + suffering - pain suppression



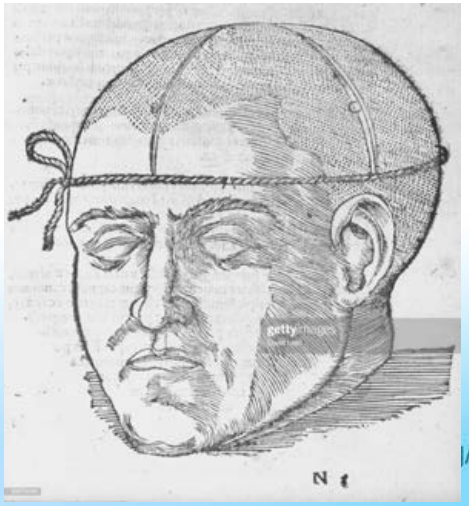
DeRidder, 2015

Quantitative Imaging – qEEG (cortical)



Philosophy

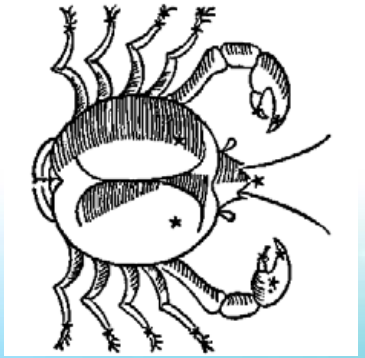
- If the brain is capable of *modifying itself* such that pain becomes chronic, it should be able to also modify itself to gain relief from pain.



Non-invasive Neuromodulation

Brain computer interface
    Neurofeedback
Transcranial Magnetic Stimulation

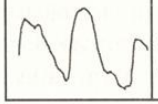
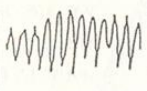
Pipeline:
1. Measure brain activity/compare to norms
2. Create a map of brain regions
3. Design a brain-computer interface



EEG

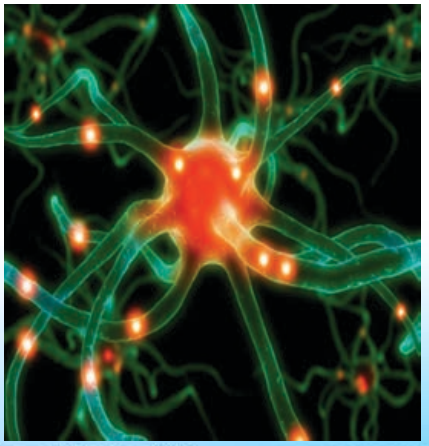
Image: Wikimedia, Santiago Romon y Cajal

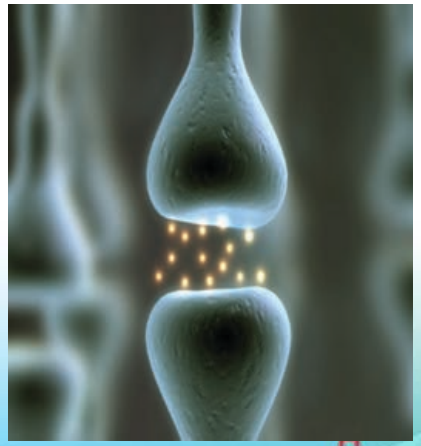
cps = cycles per second, or Hertz

DELTA Less than 4 cps	THETA 4–8 cps	ALPHA 8–12 cps	SMR 12–15 cps	BETA 15–18 cps	HIGH BETA more than 19 cps
Sleep	Drowsy	Relaxed Focus	Relaxed Thought	Active Thinking	Excited
					

Measure Brain Activity

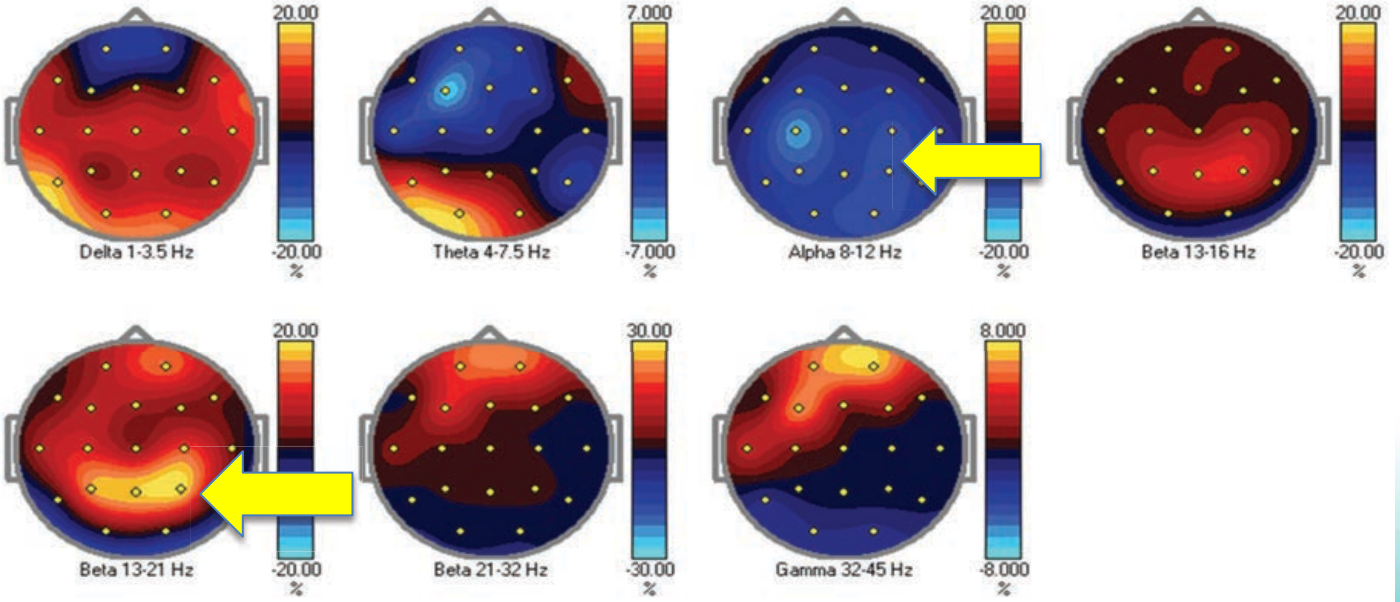
- 98% percent of the brain's communication involves electrical exchange, 2% involves chemical
- 100% of medications work on 2% of the brain's potential
- EEG (Electroencephalogram) – Electrical activity of the brain recorded on the scalp.
- Read from the synchronous activity of thousands to millions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





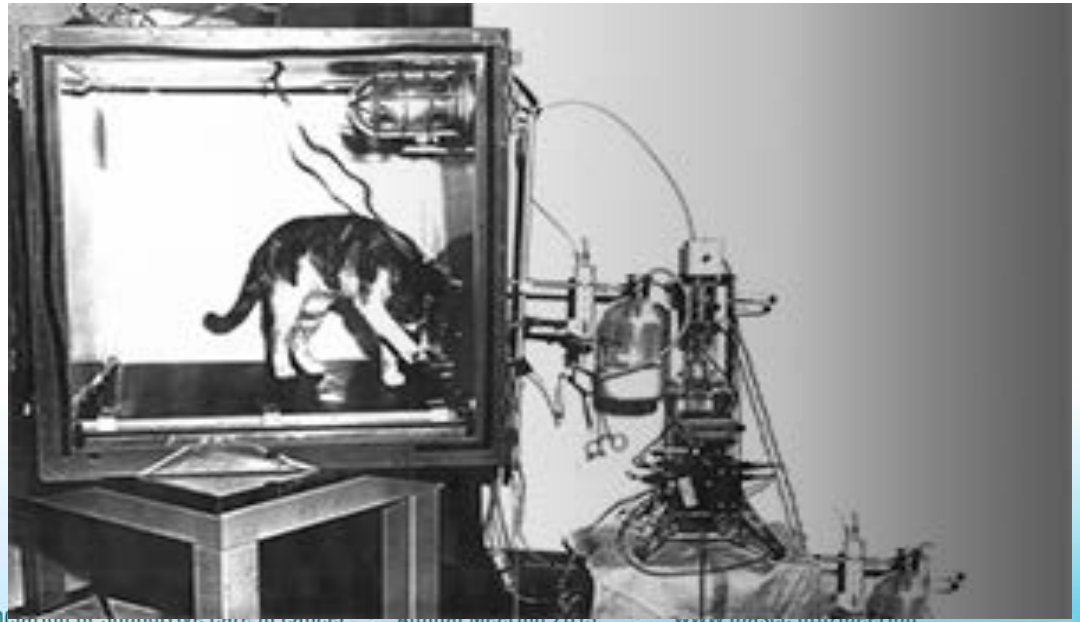
Create a map of brain regions

- qEEG (individual; normative database-brain map)



Design a brain/computer interface

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



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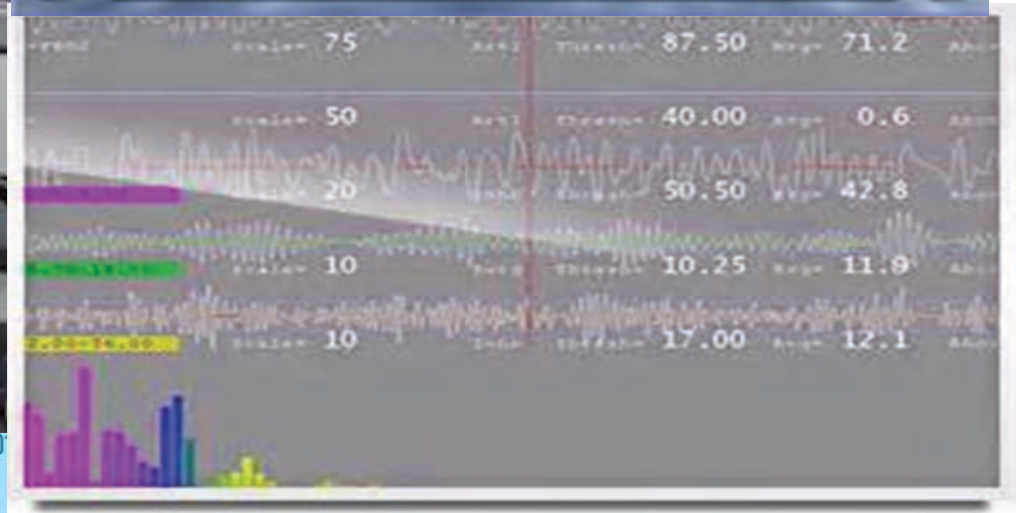
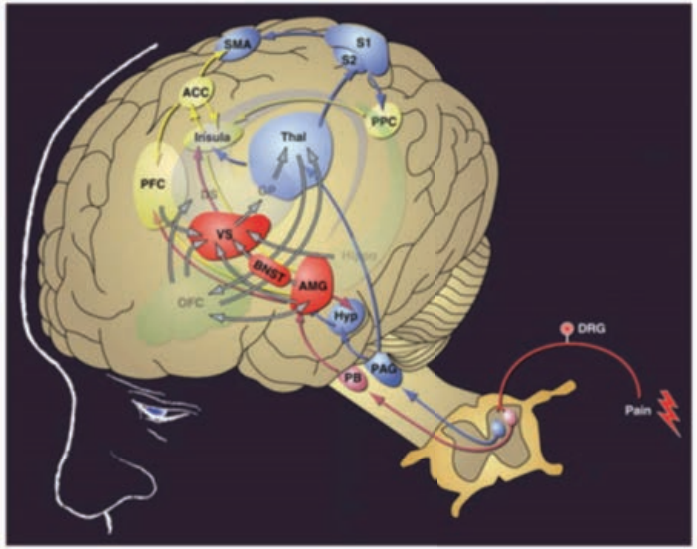
BOAT RACE
51


75
87.50
71.2
50
40.00
0.6
20
50.50
42.8
10
10.25
11.9
10
17.00
12.1

Objectives

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

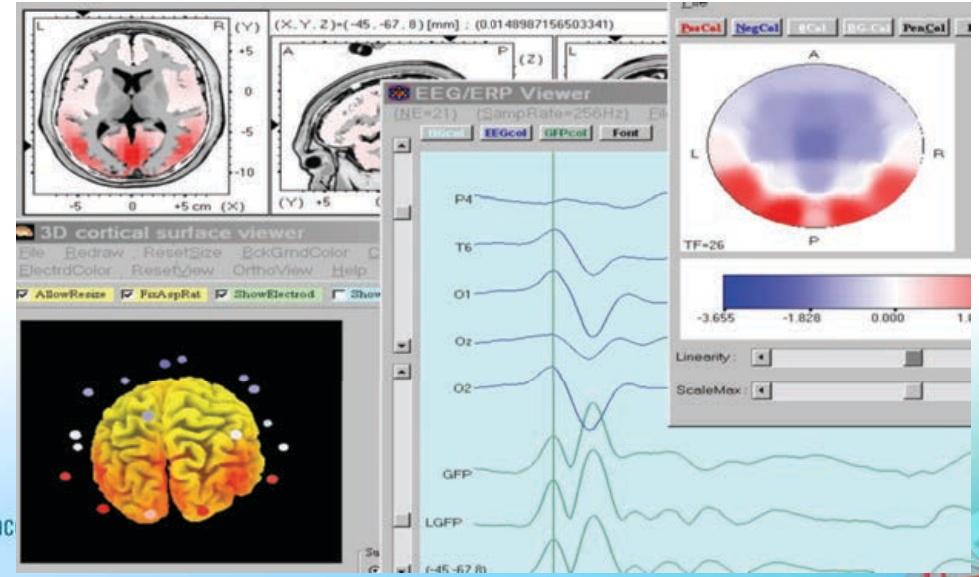


Methods

- 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

Cancer. 2017 Jun 1;123(11):1989-1997. doi: 10.1002/cncr.30649. Epub 2017 Mar 3.

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

Prinsloo S[1], Novy D[2], Driver L[2], Lyle R[3], Ramondetta L[4], Eng C[5], McQuade J[6], Lopez G[1], Cohen L[1].

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 -0.90]; P =·.001; effect size, 0.83).

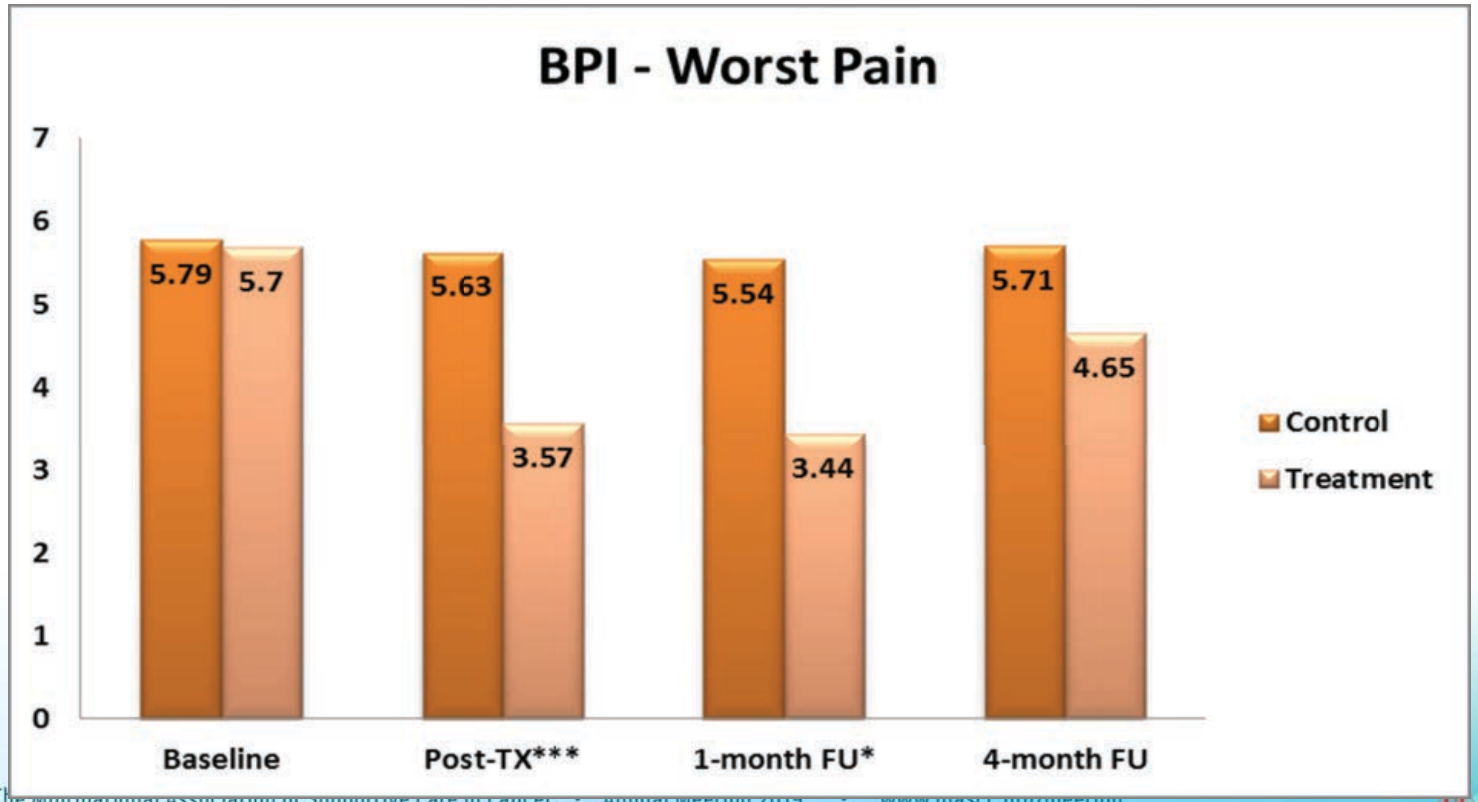
CONCLUSIONS: NFB appears to be effective at reducing CIPN symptoms. There was evidence of neurological changes in the cortical location and in the bandwidth targeted by the intervention, and changes in EEG activity were predictive of symptom reduction. Cancer 2017;123:1989-1997. © 2017 American Cancer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

Results

- 71 patients total consented over a 3 year period

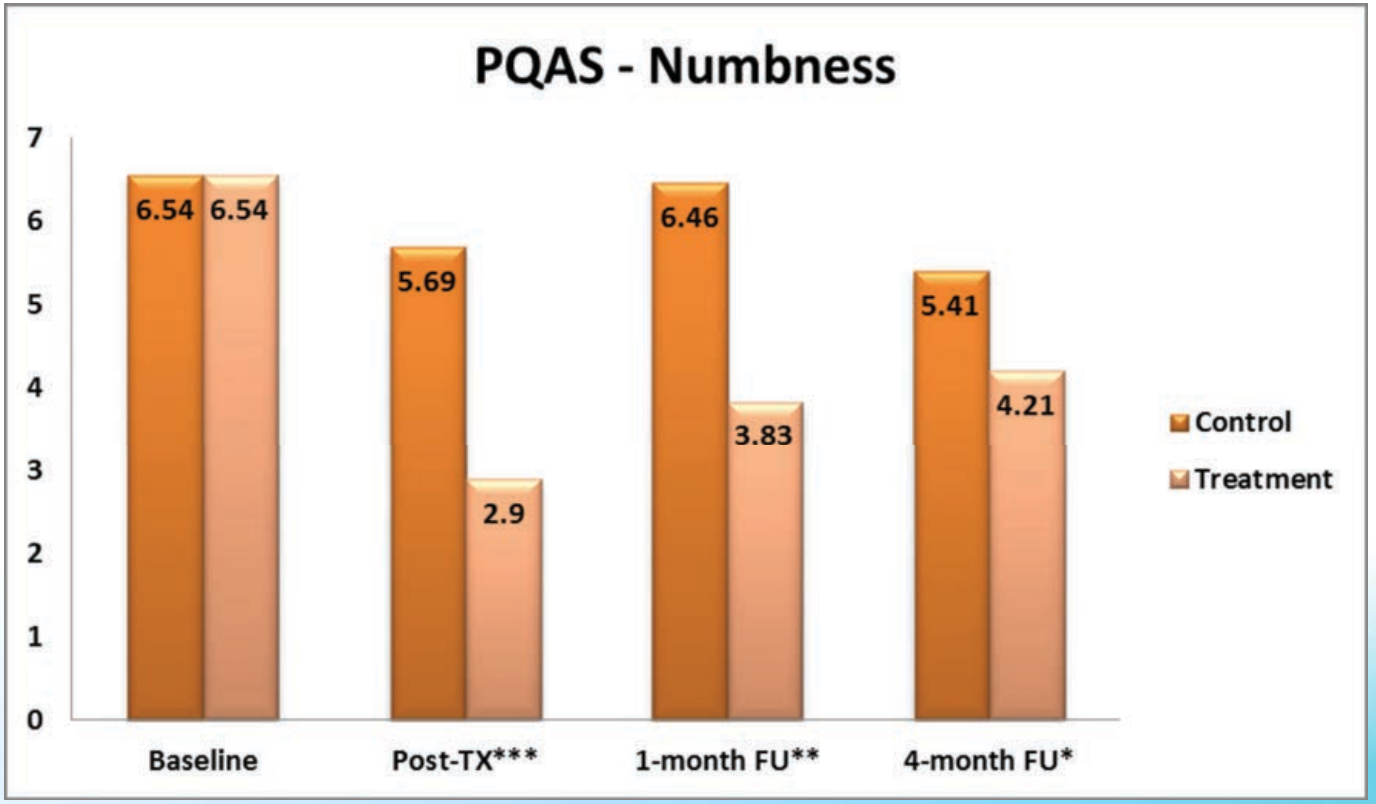
Demographic Factors	Participant
Age, years (+/- SD)	62.6 (+/- 10.5)
Female, n (%)	63 (88%)
Anglo/European, n (%)	55 (80%)
Months since chemo (+/- SD)	24.8 (+/- 18.3)
Breast Cancer, n (%)	51 (72%)
Stage	
I	10 (15%)
II	33 (49%)
III	25 (37%)

Primary Outcome



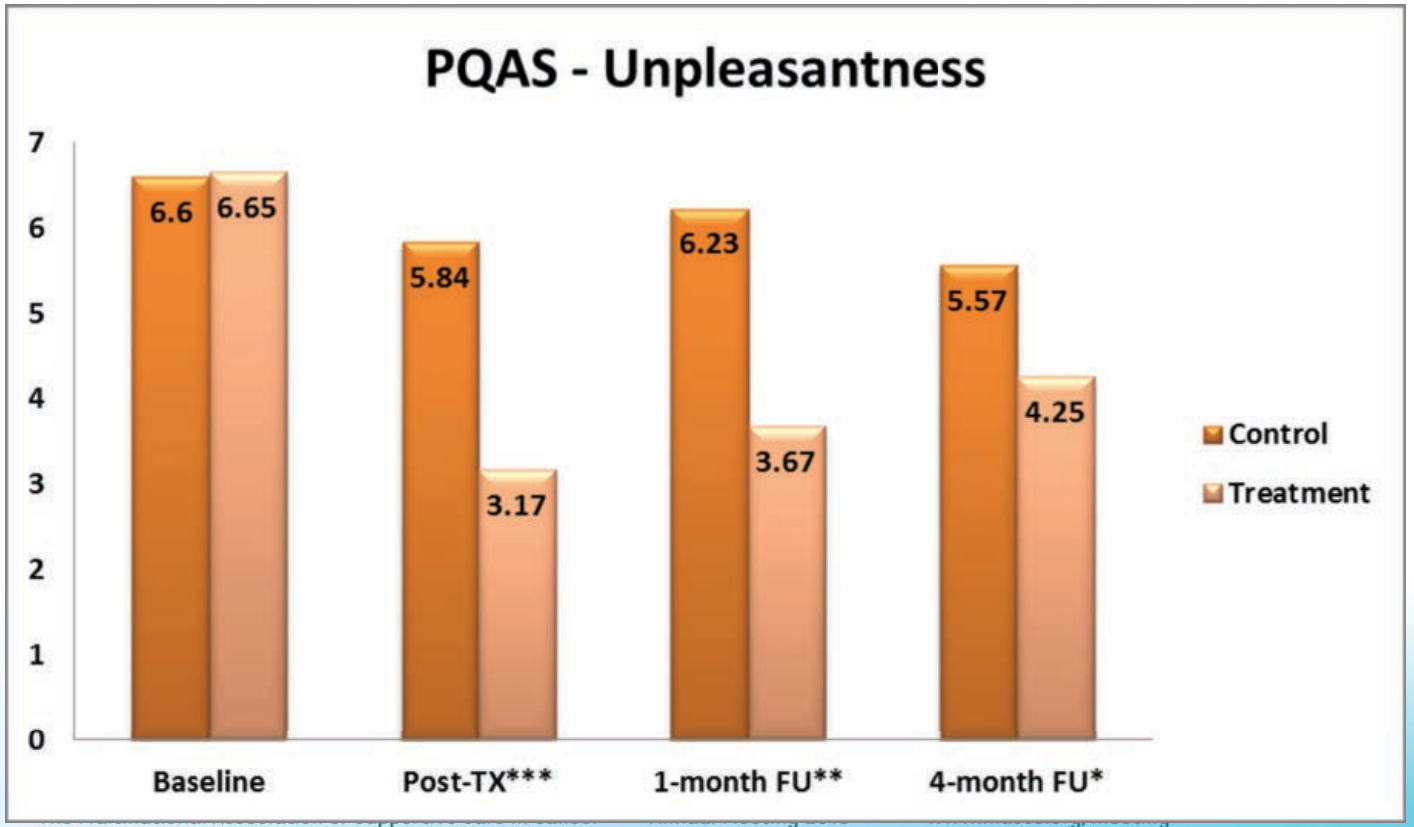
*** p <.001 *p<.05

Other common symptoms



***p<.001 ** p <.01 *p<.05

Other common symptoms



***p<.001 ** p <.01 *p<.05

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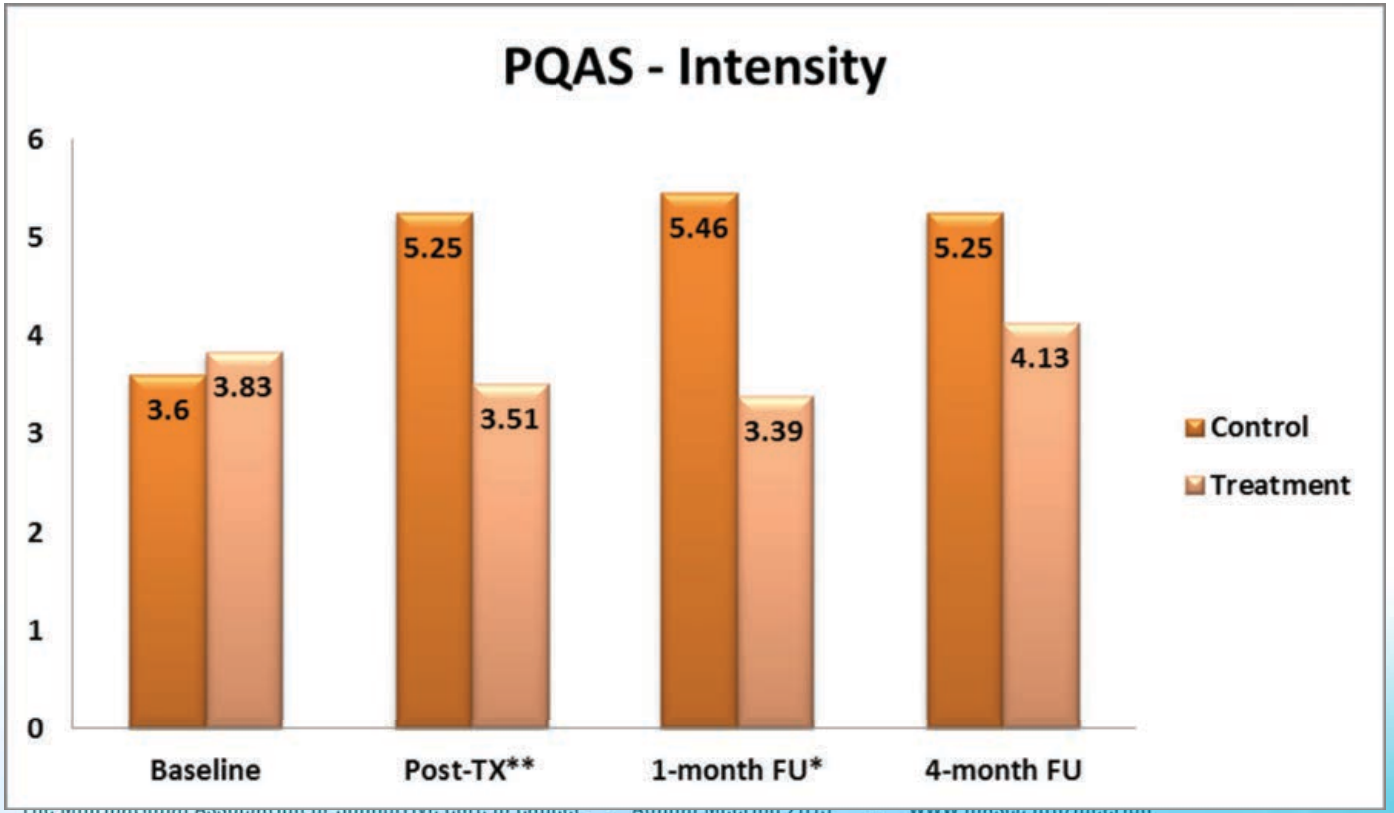
Other common symptoms



** p <.01 *p<.05

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Results

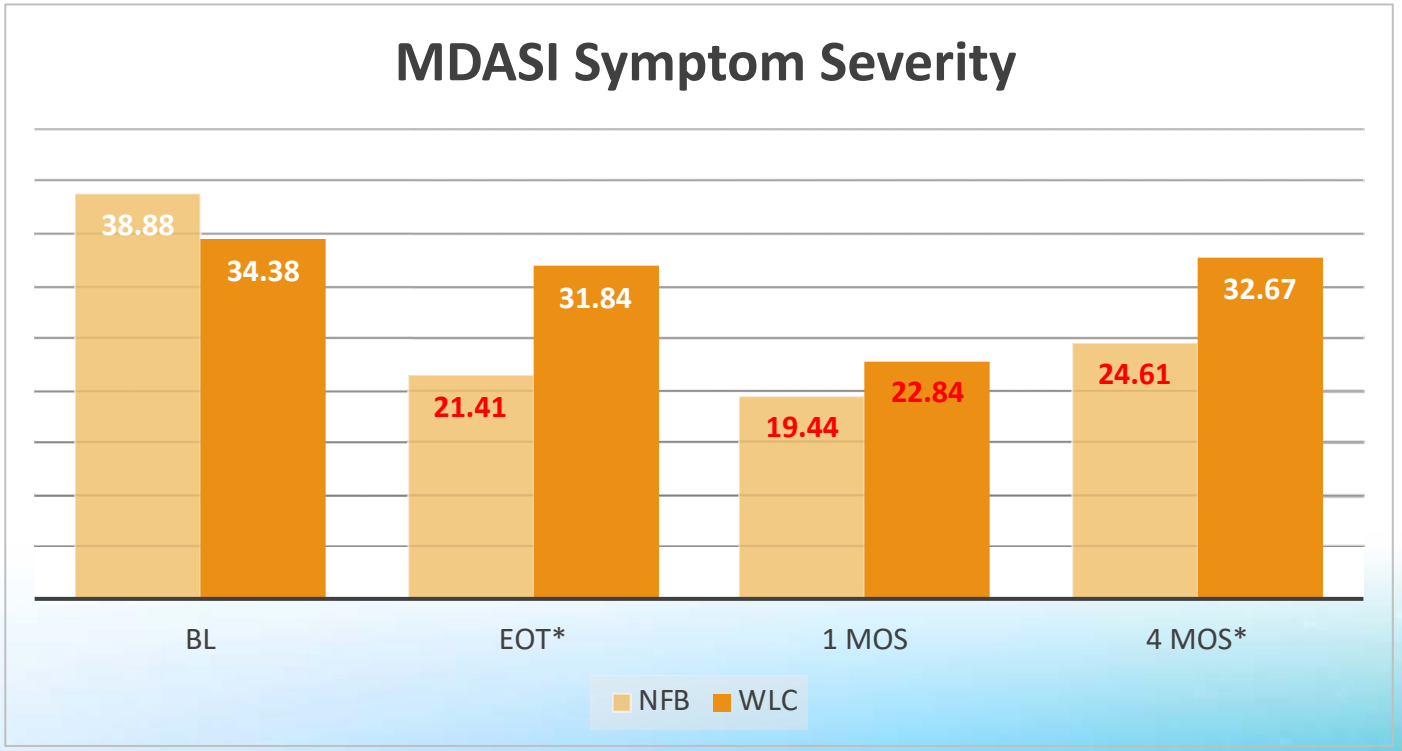
Original Article

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



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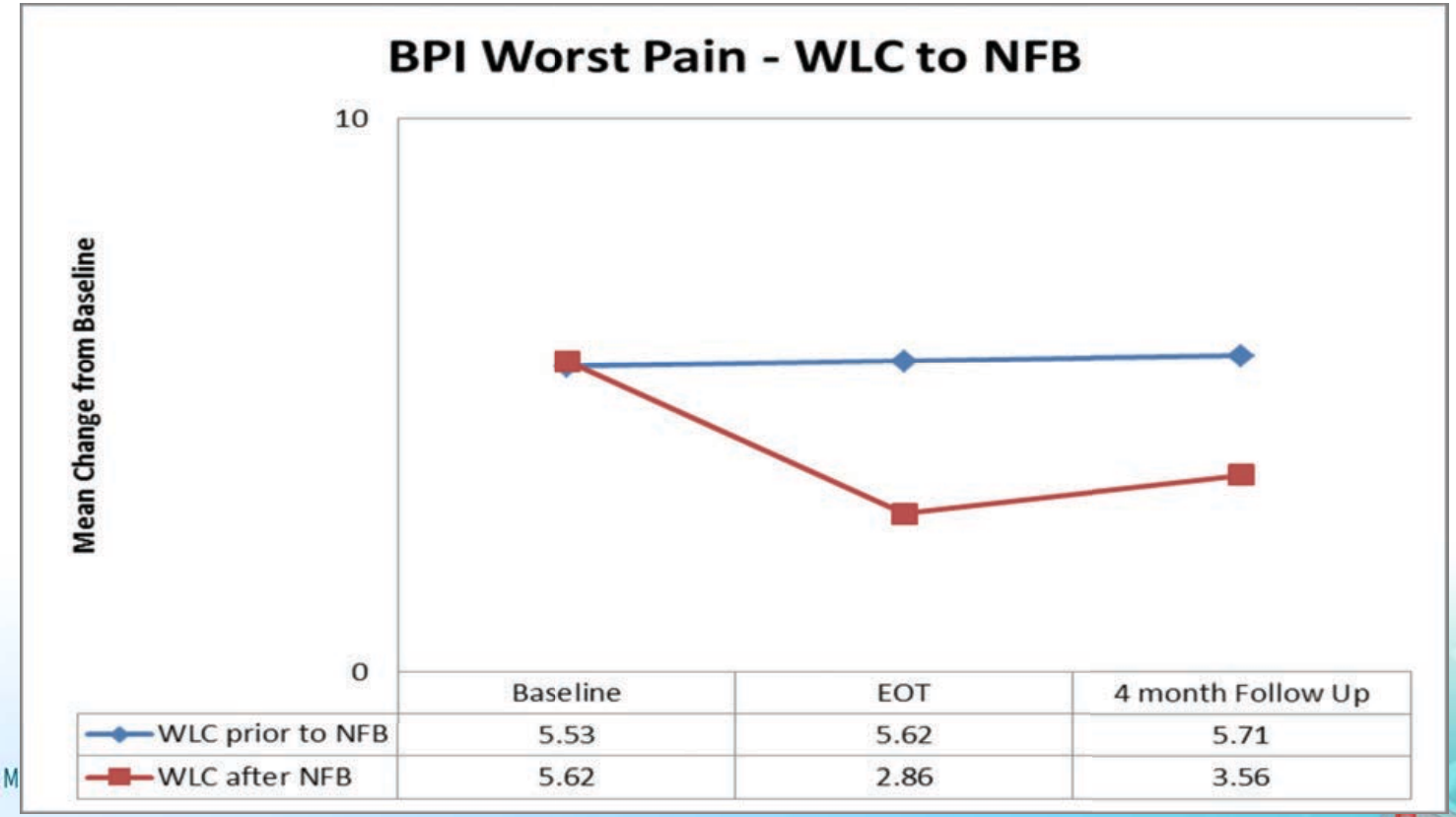
And then we treated the waitlist…



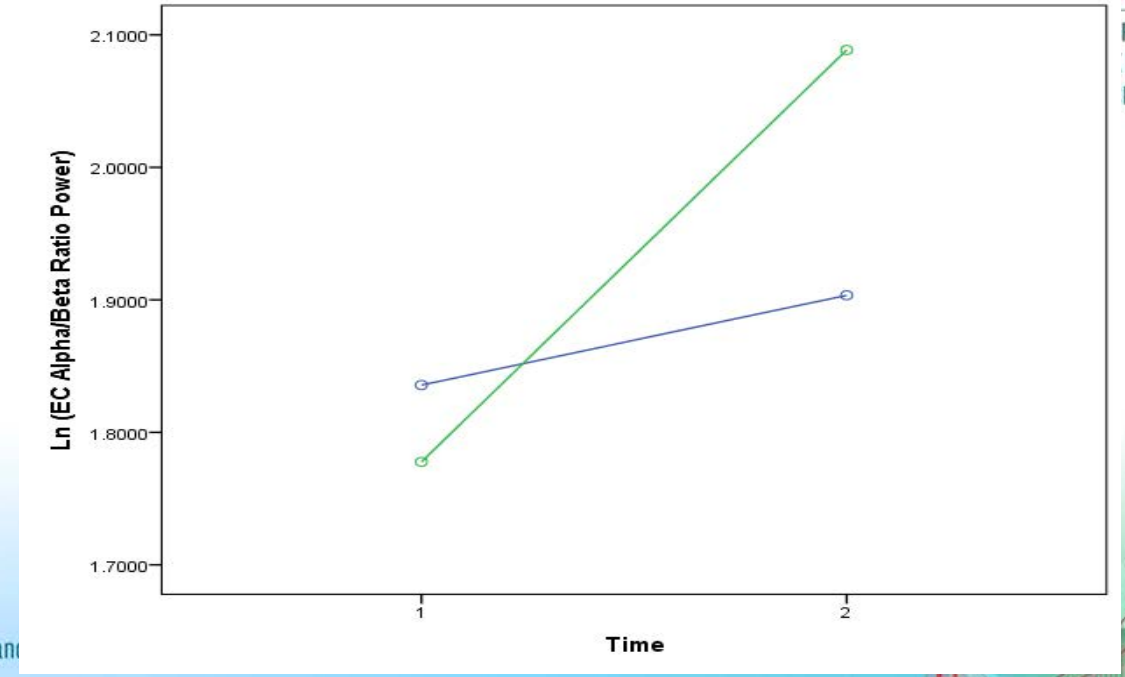
	Baseline	EOT	4 month Follow Up
WLC prior to NFB	5.53	5.62	5.71
WLC after NFB	5.62	2.86	3.56

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

Treatment

Control:

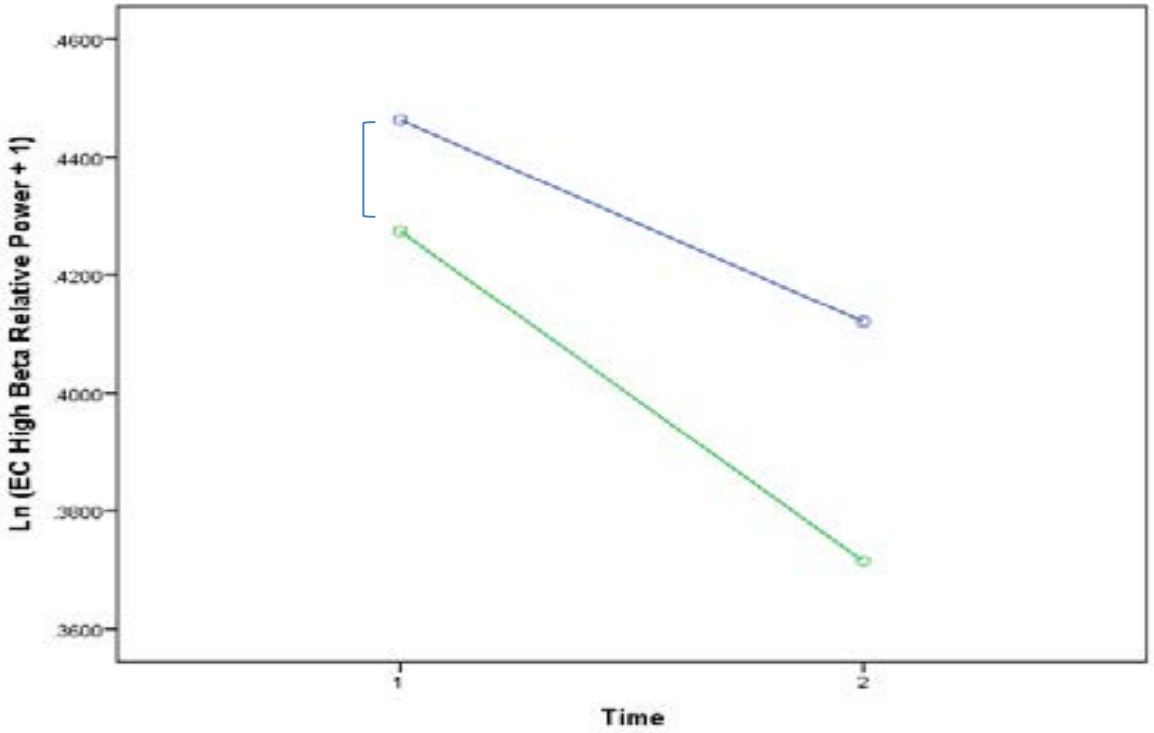


Results: Beta 2 reduction

Treatment

Control:

p=.02



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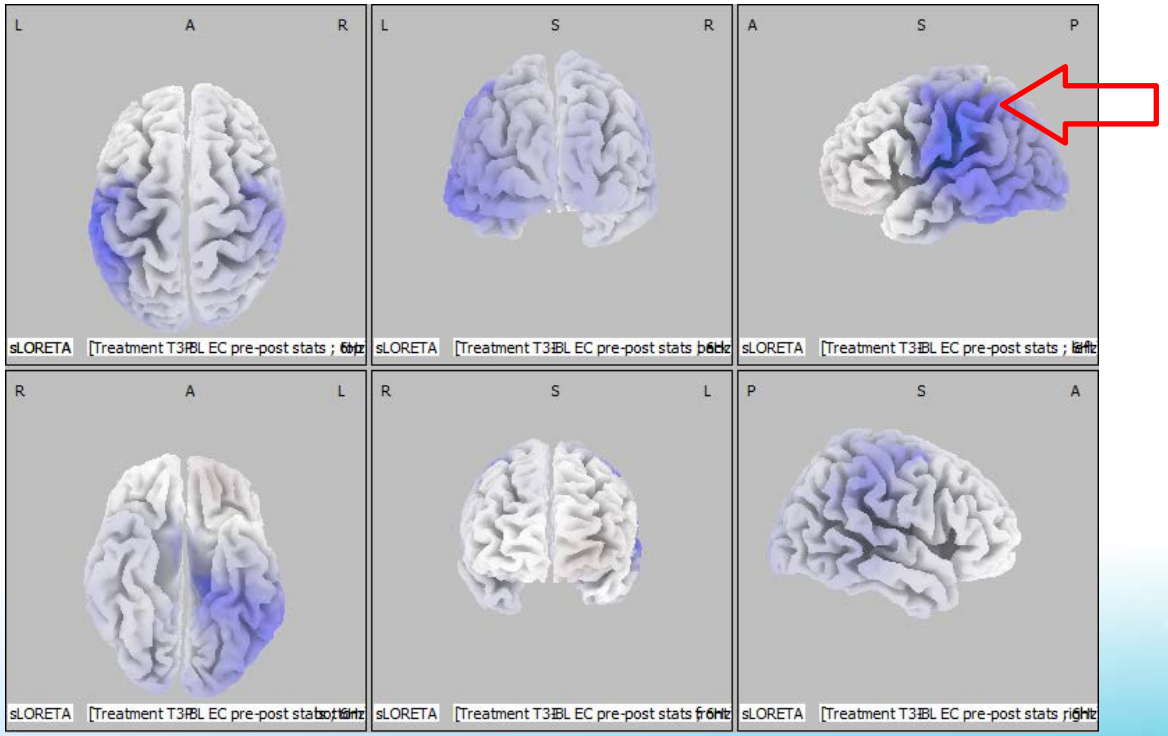
Results: Association between decreased symptom report and brain activity



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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."

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Placebo controlled trial

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

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Effect Sizes

Table 2. Effect sizes of primary and secondary endpoints.

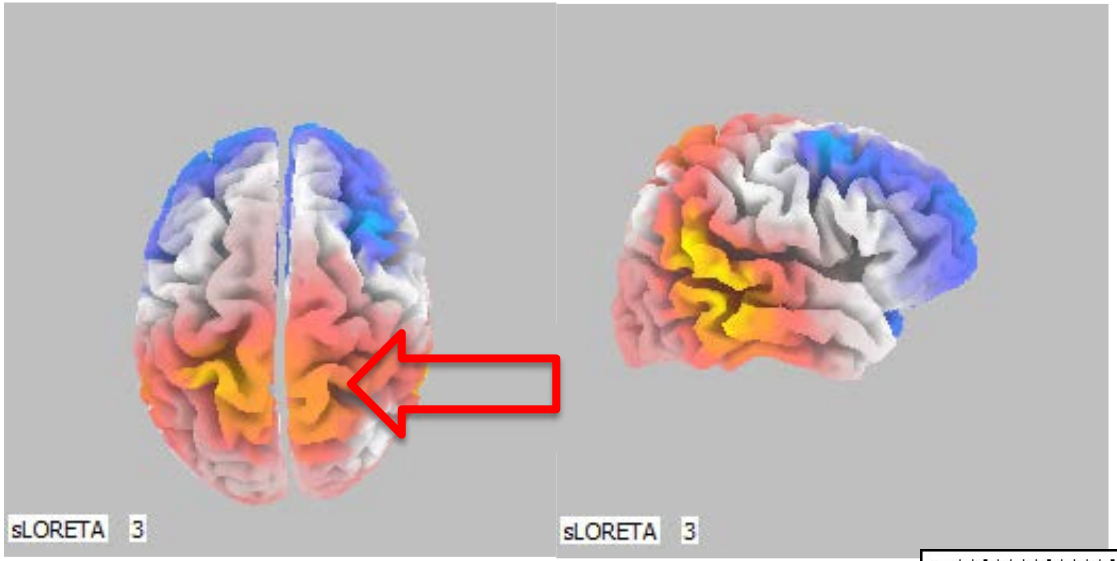
	Mean (SE)				
	Neurofeedback (n=25)		Placebo (n=27)		Waitlist Control (n=24)
Measure	Mean	Effect^ v WL	Mean	Effect v WL	Mean
PQAS					
Unpleasantness	4.08 (.61)	1.03	4.37 (.66)	0.9	6.96 (.51)
Numbness	3.60 (.62)	0.8	4.89 (.63)	0.33	5.92 (.60)
Tingling	3.72 (.56)	0.6	5.07 (.64)	0.12	5.46 (.68)
Intensity	4.08 (.54)	0.8	4.59 (.56)	0.6	6.21 (.49)
Tenderness	1.52 (.48)	0.6	2.48 (.61)	0.3	3.46 (.73)
Sensitive	1.52 (.43)	0.12	1.78 (.60)	0.004	1.79 (.48)
Itchy	0.64 (.26)	0.3	1.74 (.53)	0.2	1.13 (.45)
Sharp	3.16 (.57)	0.6	2.96 (.67)	0.6	4.92 (.64)
Hot	1.76 (.47)	0.6	2.56 (.56)	0.3	3.46 (.72)
Dull	3.16 (.61)	0.6	2.00 (.58)	0.3	4.75 (.58)
Cold	1.80 (.52)	0.4	1.67 (.50)	0.5	3.00 (.64)
Shooting	1.80 (.42)	0.4	3.04 (.66)	0.1	2.79 (.63)
Electrical	2.08 (.53)	0.6	2.89 (.66)	0.3	4.00 (.74)
Cramping	2.32 (.57)	0.05	3.04 (.69)	0.2	2.46 (.68)
Radiating	1.20 (.35)	0.8	2.52 (.62)	0.2	3.29 (.67)
Throbbing	1.76 (.45)	0.7	3.15 (.61)	0.2	3.67 (.70)
Aching	2.80(.55)	0.8	3.37 (.72)	0.5	5.13 (.71)
Heavy	2.48 (.62)	0.3	3.41 (.64)	0.01	3.46 (.64)
Global	2.50 (.38)	0.8	3.26 (.52)	0.3	4.13 (.45)

*P values are from general linear model

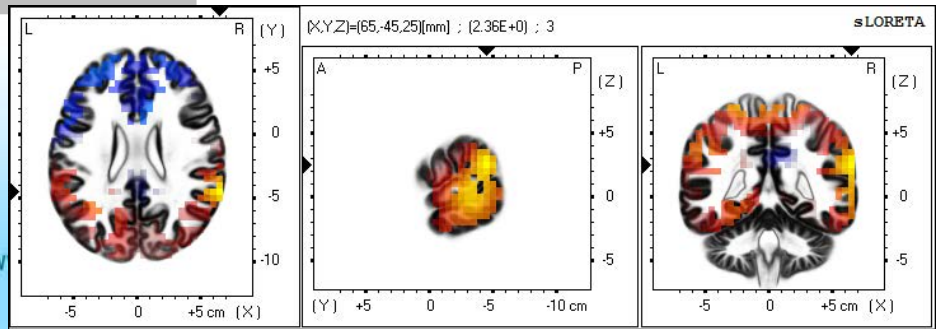
^ Effect sizes are calculated based on group differences in change scores from pre- to post-training using Cohen's d

NFB had a greater effect size than PL in 16 of 19 scales

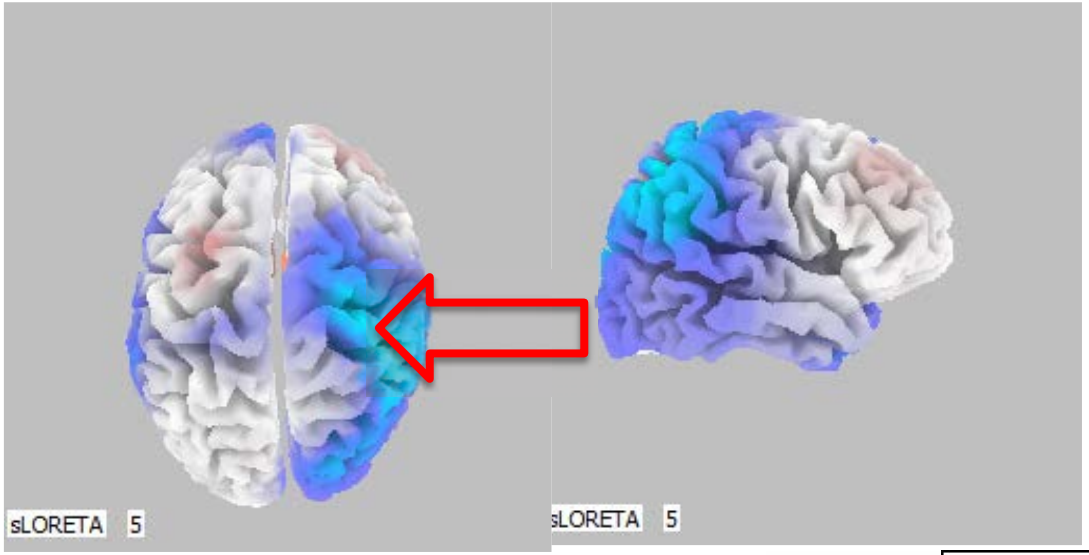
Alpha: NFB compared to PLC; T2-T1



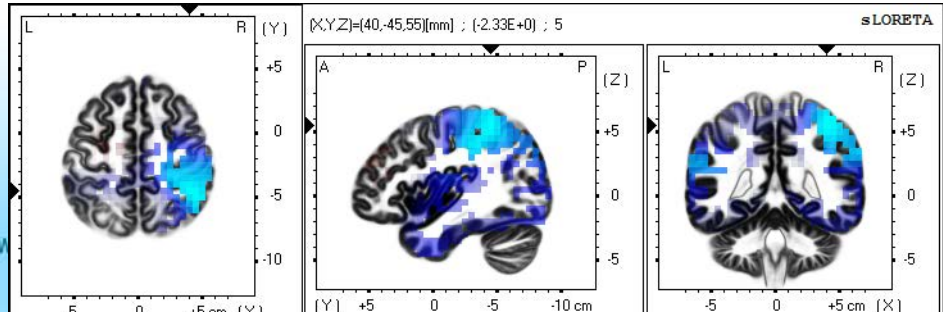
Value= 2.36E+0
(X= 65 , Y= -45 , Z= 25) (MNI coords)
Best Match at 0 mm
Brodmann area 40
Inferior Parietal Lobule
Parietal Lobe



Beta: NFB compared to PLC; T2-T1

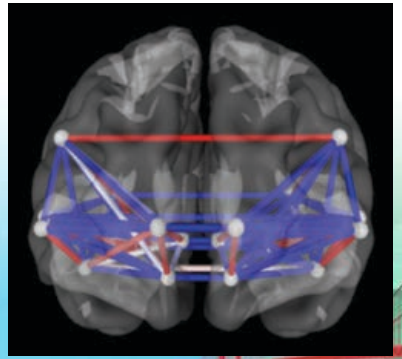


Value= -2.33E+0
(X= 40 , Y= -45 , Z= 55) (MNI coords)
Best Match at 0 mm
Brodmann area 40
Inferior Parietal Lobule
Parietal Lobe



Conclusions

- 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



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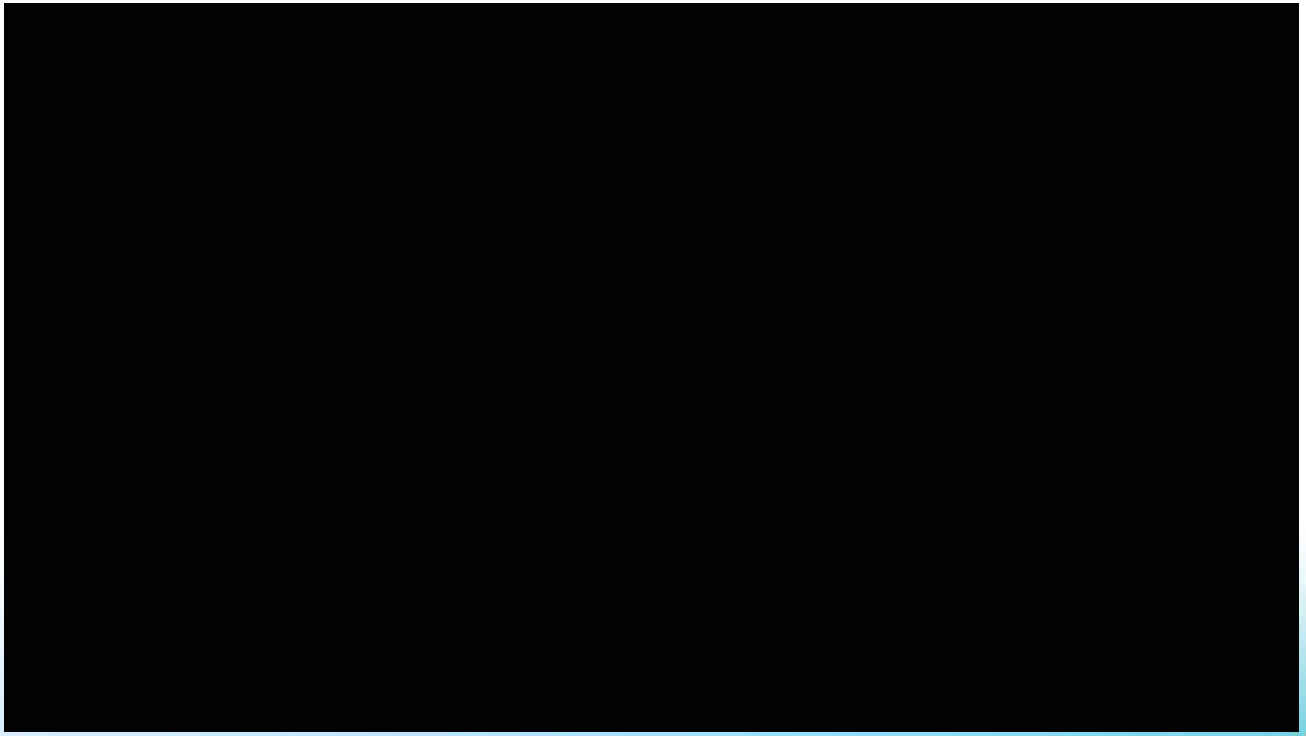
Video



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THANKS

- MD Anderson Patients and Caregivers!
- Collaborators
- Funders

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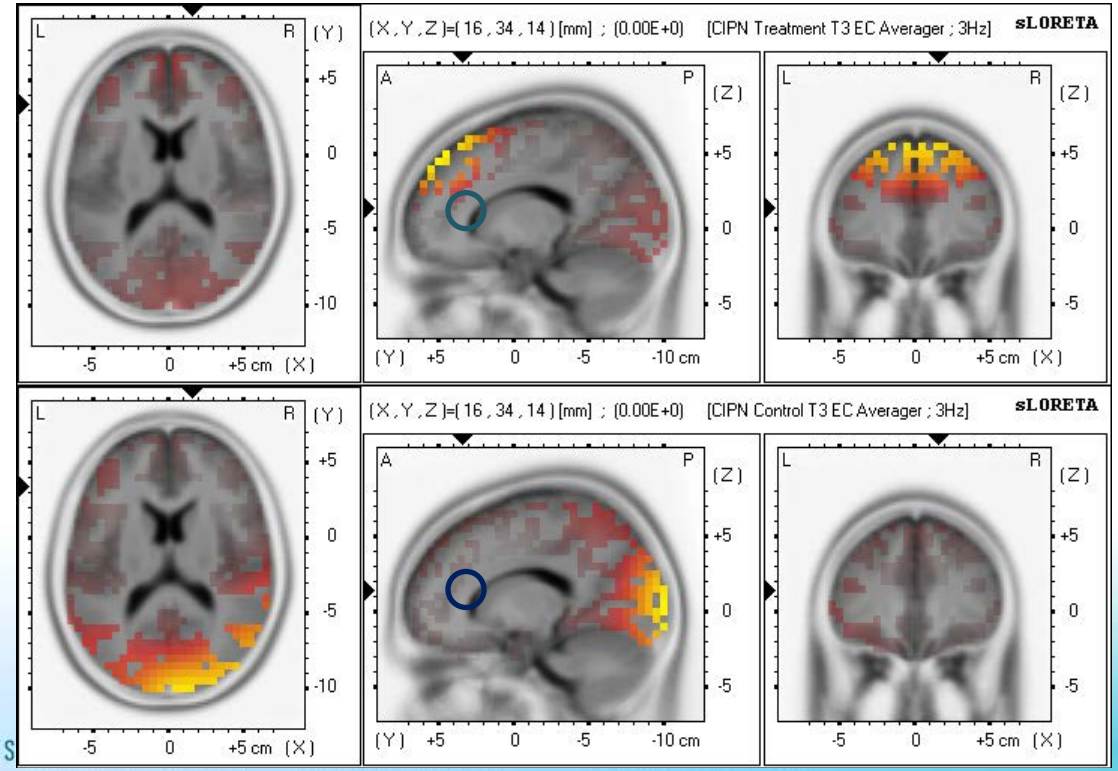
Regions active in placebo: rACC; dlPFC; insula



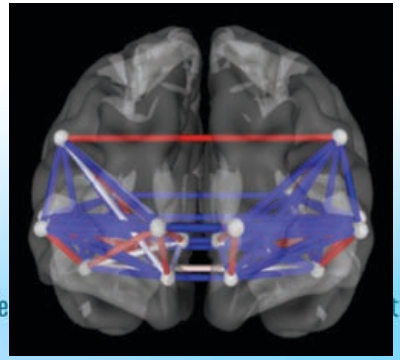
Seeds	ACC sub-regions	MNI coordinates		
		x	y	z
Seed1	Caudal ACC	±5	-10	47
Seed 2	Dorsal ACC	±5	14	42
Seed 3	Rostral ACC	±5	34	28
Seed4	Perigenual ACC	±5	47	11
Seed 5	Subgenual ACC	±5	25	-10

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

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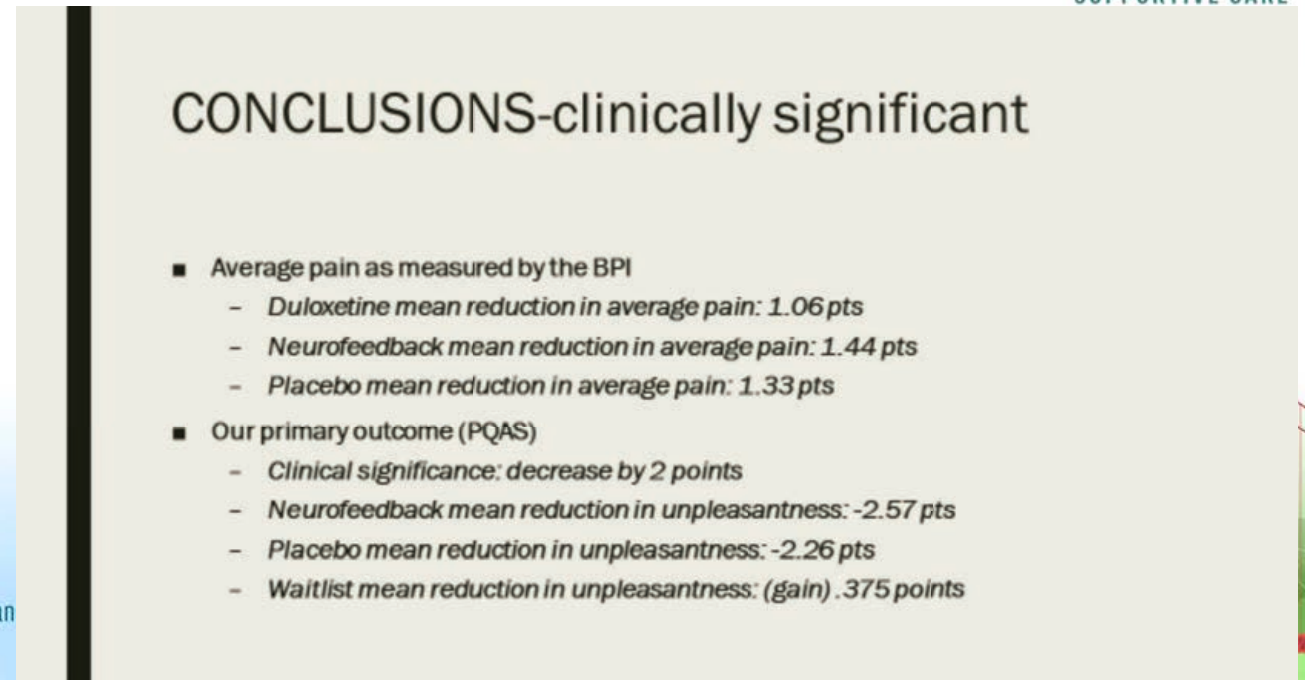
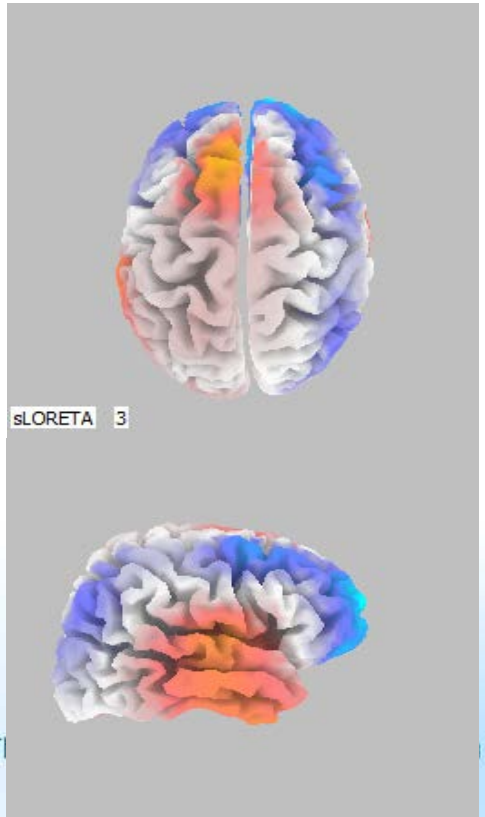
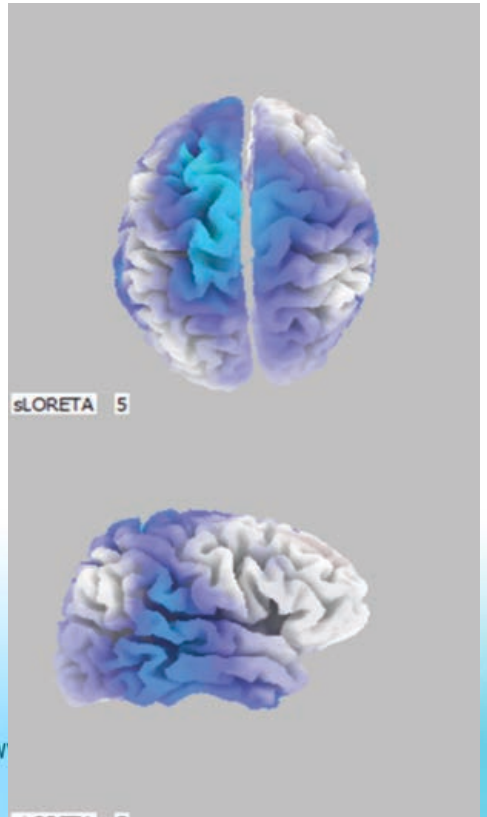


NFB compared to WLC

Alpha



Beta



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MAKES EXCELLENT
CANCER CARE POSSIBLE

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