Neuromodulation for Addiction

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Disclosures

1. None

Learning Objectives

1. List current FDA approved neuromodulation addiction treatments
2. Explain Hebb's Rule
3. Describe how neuromodulation can enhance plasticity

Outline

- Neuromodulation Primer
- FDA approved neuromodulation treatments for addiction
- Research
  - tDCS

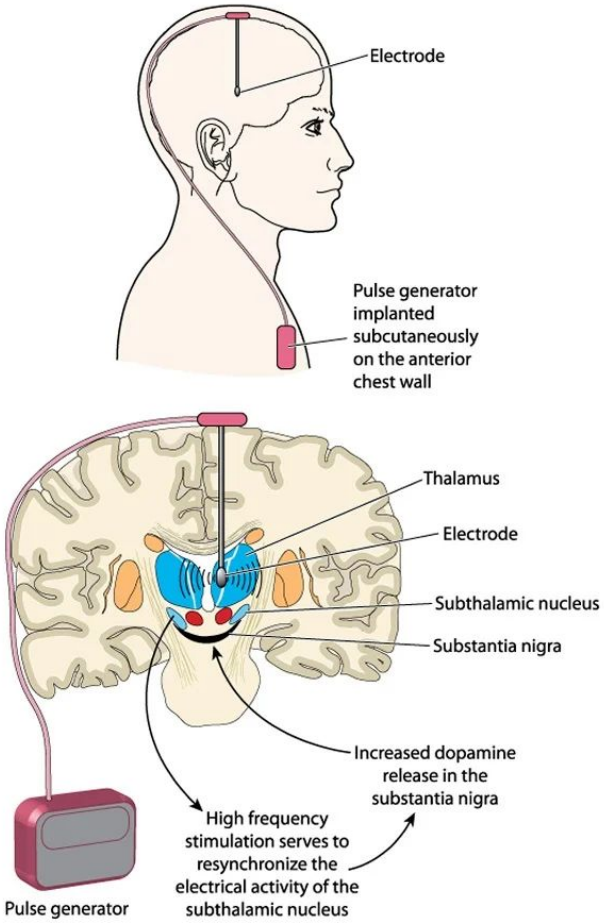
Neuromodulation

"...the alteration—or modulation—of nerve activity by delivering electrical or pharmaceutical agents directly to a target area"

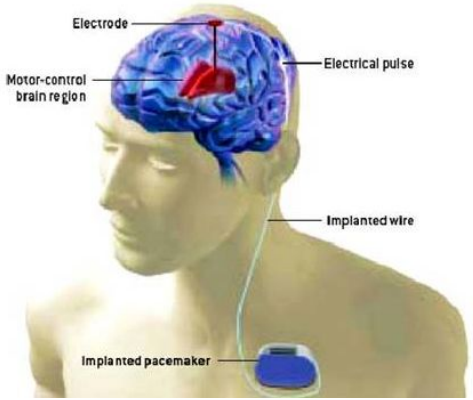
International Neuromodulation Society (neuromodulation.com)

Neuromodulation

- DBS – deep brain stimulation
- VNS - vagus nerve stimulation
- ECT – electroconvulsive therapy
- TMS – transcranial magnetic stimulation
- TCS – transcranial current stimulation



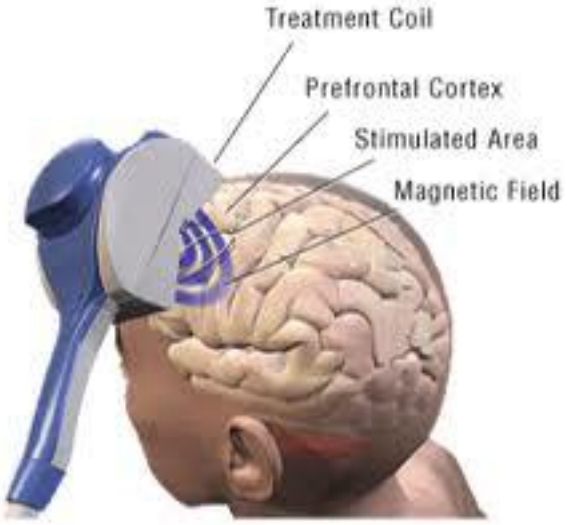
https://www.news-medical.net/health/What-does-deep-brain-stimulation-involve.aspx



- Deep Brain Stimulation of Nucleus Accumbens on Heroin-Seeking Behaviors: A Case Report. Zhou et al. 2011, Biological Psychiatry
- 24 yo male; 5year hx of IV Heroin Use
- Implanted for 2.5 years
- Drug free for 6 six year f/u
- IQ: 86 to 100
- No change in personality (MMPI)

Transcranial Magnetic Stimulation (TMS)

- Strong electromagnet used to create time varying magnetic field that produces current flow
- Can cause depolarization
- Repetitive TMS
  - High frequency increases neuronal excitability
  - Low frequency decreases neuronal excitability



The NeuroStar TMS Therapy® System

Deep TMS for Smoking

BrainSway - FDA approved August 2020

Deep TMS Treatment Sessions

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
5 treatments	*5 treatments*	*5 treatments*	*1 treatment*	*1 treatment*	*1 treatment*

18 treatments

Each session typically takes 25-30 minutes and includes:

Provocation Administration + ***18 Minute TMS Protocol*** + ***Brief Counseling***

Assessments

Number of cigarettes should be assessed daily

Craving should be assessed using a Visual Analog Scale before provocation, after provocation, and after treatment for the first session and periodically thereafter

Changing Behavior

Habit

- A routine of behavior that is repeated regularly and tends to occur subconsciously
- Repeated behavior can become automatic:
  - efficiency
  - lack of awareness

Habit

- Good Habits
  - –Brushing and flossing teeth daily
  - –Exercising regularly
  - –Eating a healthy diet

Habits Impact Health

- 40% of all deaths in America can be attributed:
  - to smoking
  - poor exercise habits
  - inadequate diet
  - alcohol misuse

Change is Hard

New Year’s Resolutions

a. Top 5: Exercise, Lose Weight, Eat Better, Save Money, Self Care
b. 35% of New Year’s Resolution broken by the end of January

Change is Hard

1. Our physiology doesn’t like change (homestasis)
    a. Temperature is constant
    b. Blood glucose is in range
    c. Thinking processes don’t change much
    d. Even bad behaviors are really hard to change
2. Alcohol Abuse
    a. 67% will relapse within a year following treatment
    b. At two years of abstinence 15% will relapse

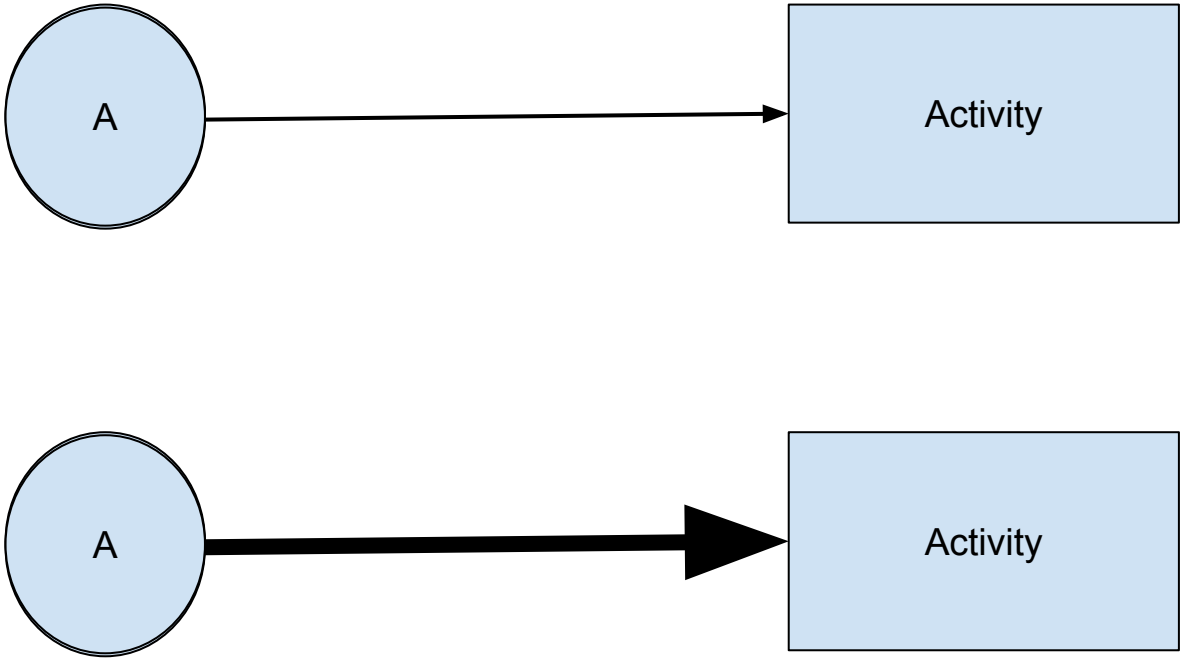
Neuroscience of Learning (Habits)

Donald Hebb

- Father of neuropsychology
- 1904-1985
- Sought to explain behavior in terms of brain function

Hebb’s Rule

- “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.”
  - Hebb 1949
- "neurons wire together if they fire together"
    - Löwel and Singer 1992
- “Spike-timing-dependent plasticity”


A
Activity
A
Activity

Practice Makes Perfect

- Leon Fleisher (1928-2020)
- Early 20s, recording contract
- Pianists can practice 5 hours a day
- Age 36, lost use of right hand due to focal dystonia

Addiction as a Habit

- Early stages of drug use - pleasurable (reward system)
- Later stages of drug use - no longer pleasurable (compulsive use - negative reinforcement)

Koob et al, Science 1997

Alcohol Relapse Study

Imaging study of:

- short term abstinent (11 weeks)
- long term abstinent (7 years)
- non dependent

Examine Nucleus accumbens to prefrontal connectivity

Camchong et al, 2014

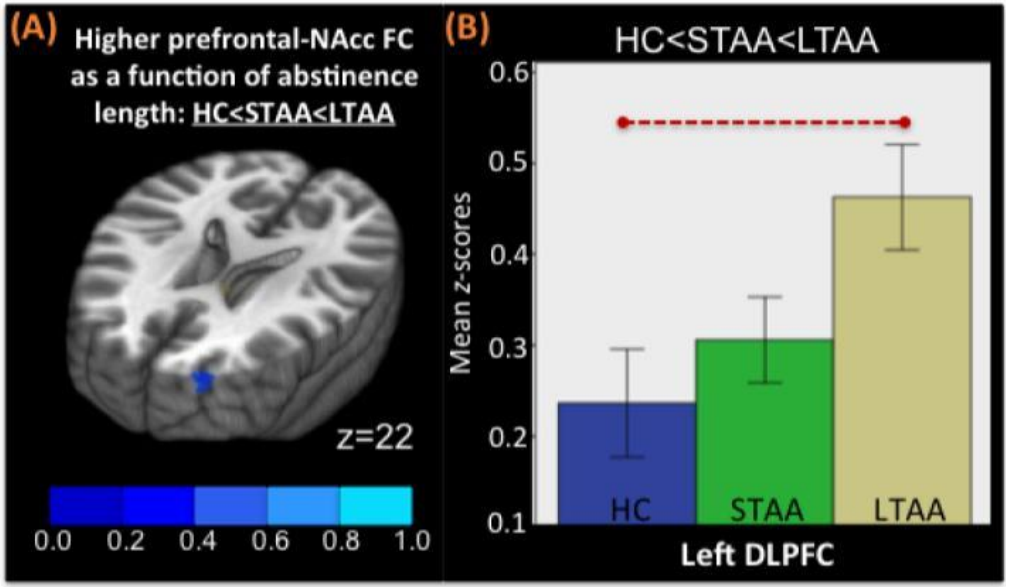


Figure 2. Higher frontal-striatal RSFC in long-term abstinent AUD (LTAA) vs. healthy controls (HC). (A) Dorsolateral prefrontal cortex (DLPFC; blue) region that showed higher RSFC with striatal regions (nucleus accumbens, NAcc) in LTAA vs. HC, with intermediate FC in short-term abstinent AUD (STAA). (B) Bar graph (standard error) illustrating strength of prefrontal-striatal RSFC. Dashed line above bar graph represents significant group differences ($p<0.05$) (Camchong et al 2013).

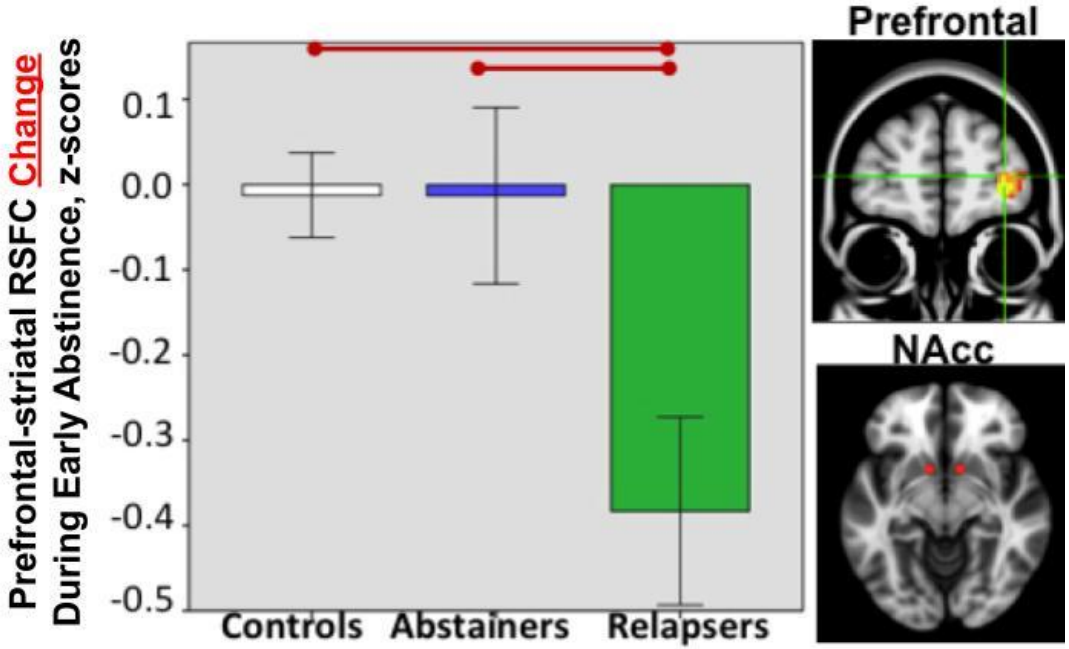


Figure 4. Larger frontal-striatal resting state functional connectivity (RSFC) reduction during early abstinence in subsequent relapsers (green) vs. subsequent abstainers (blue) and healthy controls (white). FC measured during early abstinence (at 5 and 13 weeks of abstinence). Error bars are ±1 SE. Red bars show significant group differences ($p<0.05$). (Camchong et al 2014).

Could Functional Connectivity be a Treatment Target

Would increasing functional connectivity between NAcc and Prefrontal cortex improve alcohol treatment outcomes?

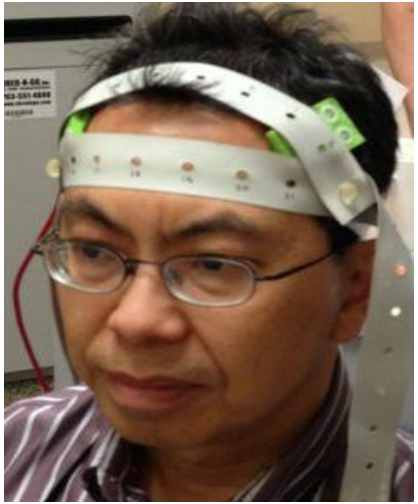
Neuromodulation

"...the alteration—or modulation—of nerve activity by delivering electrical or pharmaceutical agents directly to a target area"

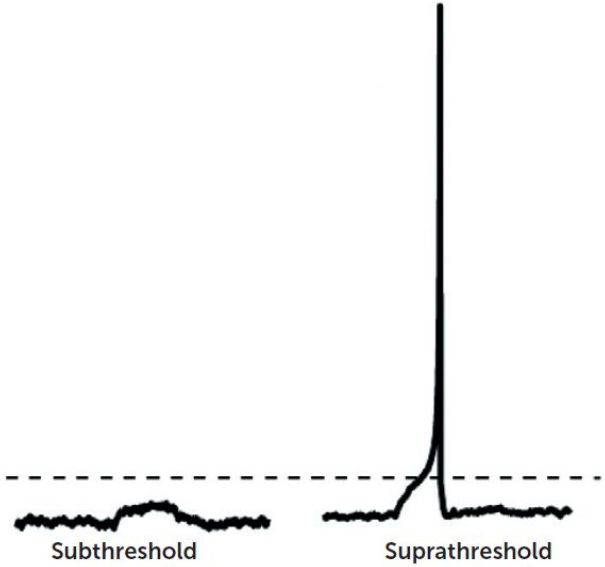
International Neuromodulation Society (neuromodulation.com)

Transcranial Direct Current Stimulation (tDCS)

- Applied to the scalp via saline dampened sponge electrodes
  - Electrical current typically 1.0-2.0mA for up to 20 minutes
  - Various electrode montages can be used to modulate different areas of activity in the brain
  - Low risk of adverse reaction to stimulation

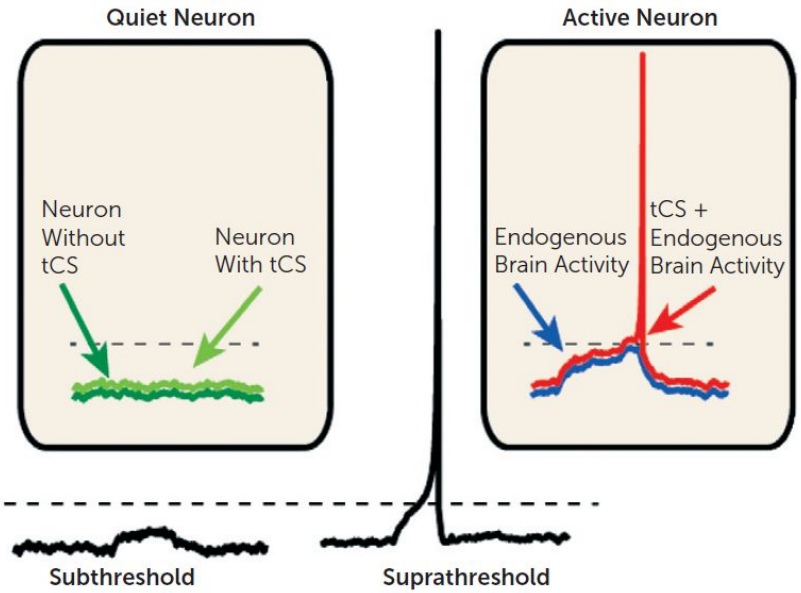


Action Potential



Philip et al., AJP, 2017

Effect of anodal stimulation



Philip et al., AJP, 2017

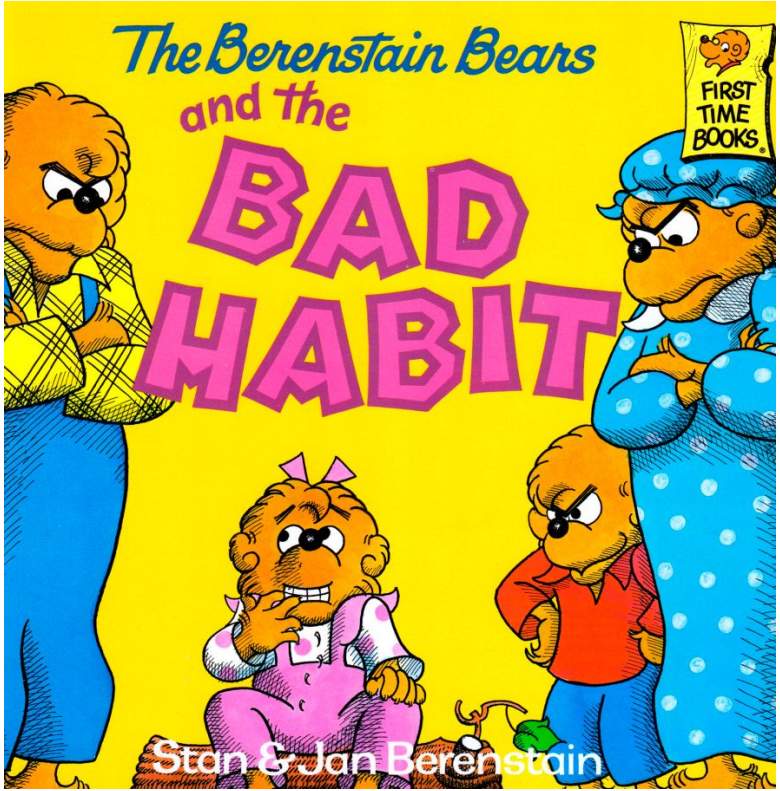
Effects of tDCS

- Modulation of cortical neuronal excitability
  - Increases excitability at anode electrode
- Increases Brain Derived Neurotrophic Factor (BDNF) secretion – important for synaptic plasticity (Fritsch et al. 2010)
- Activity dependent
- Effect is to facilitate learning (neuronal change)

Brain Circuit Related to Alcohol Relapse

1. Communication between Prefrontal Cortex (Cognitive Control) and Nucleus Accumbens (Reward Center)
2. Poor (low) communication is associated with future relapse
3. Can we increase the communication to improve outcome?

Bad Habit

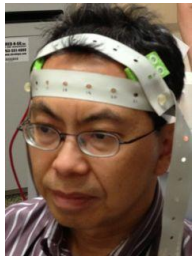

The Berenstain Bears
and the
BAD
HABIT
FIRST
TIME
BOOKS
Stan & Jan Berenstain

"Well," said Mama, "it's sort of like this path. I've wheeled this barrow over it so many times that it's worn a deep rut right down the middle. And it keeps getting deeper every time I use it. Why, it's so deep now that I can't get out of it without a little help.

From Berenstain Bears and the Bad Habit

Strategy for Changing the Brain

1. Take advantage of Hebbs Rule
   “Neurons that fire together wire together”
2. Easy way to get neurons to fire together is to think:
   Perform a cognitive task that gets the desired connection firing
3. To overcome homeostasis, give the brain a nudge with non-invasive neuromodulation to make it easier to fire (tDCS)



From Berenstain Bears and the Bad Habit

Approach

1. Use tDCS as tool for enhancing neural plasticity
2. tDCS has coarse spatial anatomical targeting
3. How to gain greater specificity?
   a. Hebb's rule – "cells that fire together, wire together"
   b. Use training task related to targeted behavior to gain circuit specificity (functional targeting)
4. Strengthen that circuit and the associated behavior

Alcohol tDCS Study

- Primary alcohol use disorder
- 2 weeks abstinence
- RCT - 5 days of treatment with tDCS plus a **reversal learning task and decision making task**
  - pre treatment fMRI
  - post treatment fMRI
  - Followup for 4 months
- N=51

Camchong, unpublished

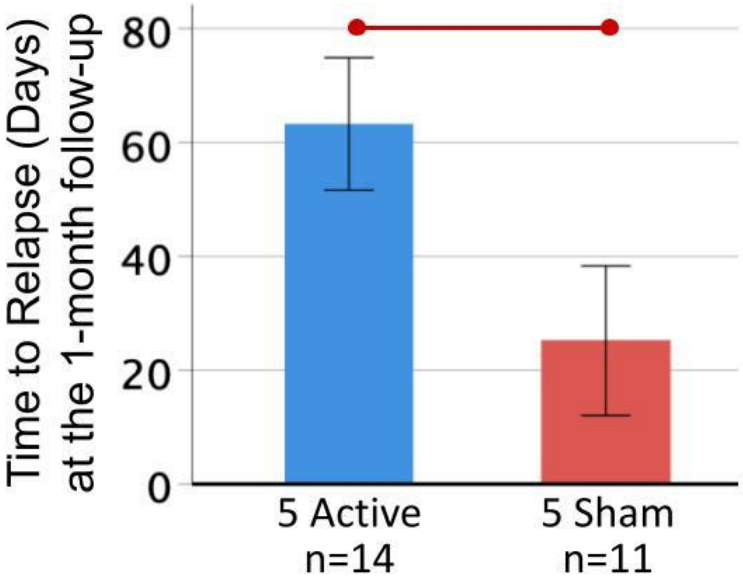


Figure 5. Among AUD that relapsed, those assigned to 5 sessions of active tDCS (F3 anode, F4 cathode) showed longer time to relapse vs. those assigned to 5 sham sessions. Error bars: ±1 SE. Red line: Significant group difference after controlling for sex (p=0.043) **(Camchong K01 clinical trial).**

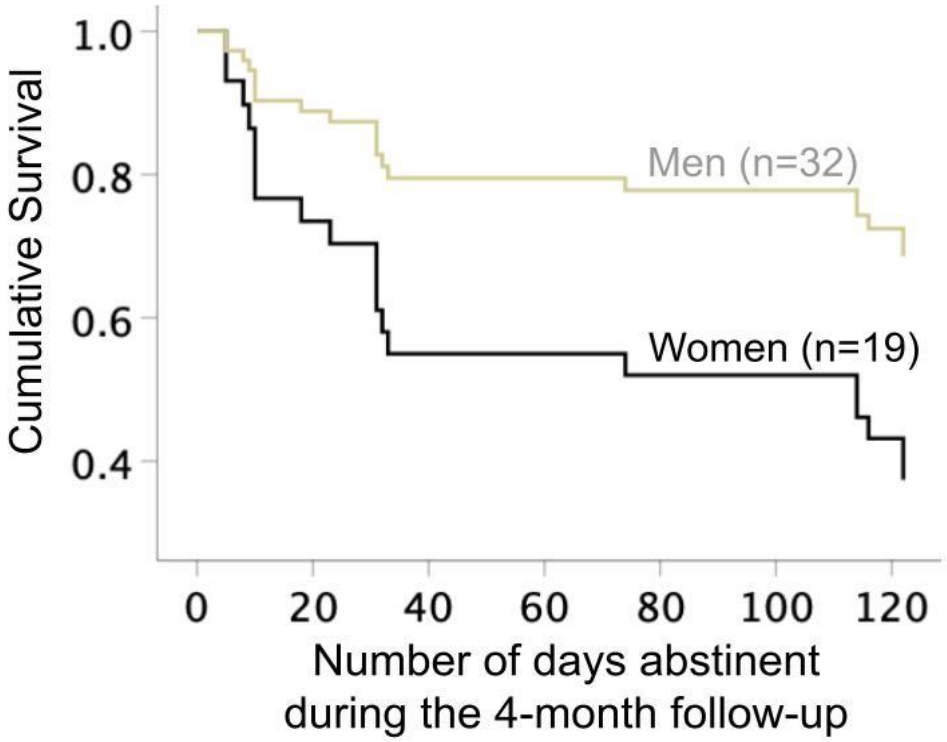
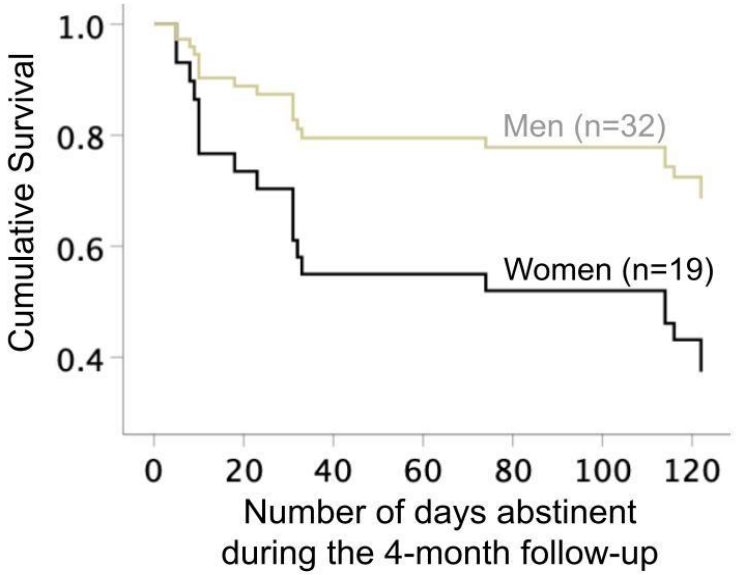


Figure 6. Significantly different survival curves between sexes (**Camchong K01 clinical trial**).



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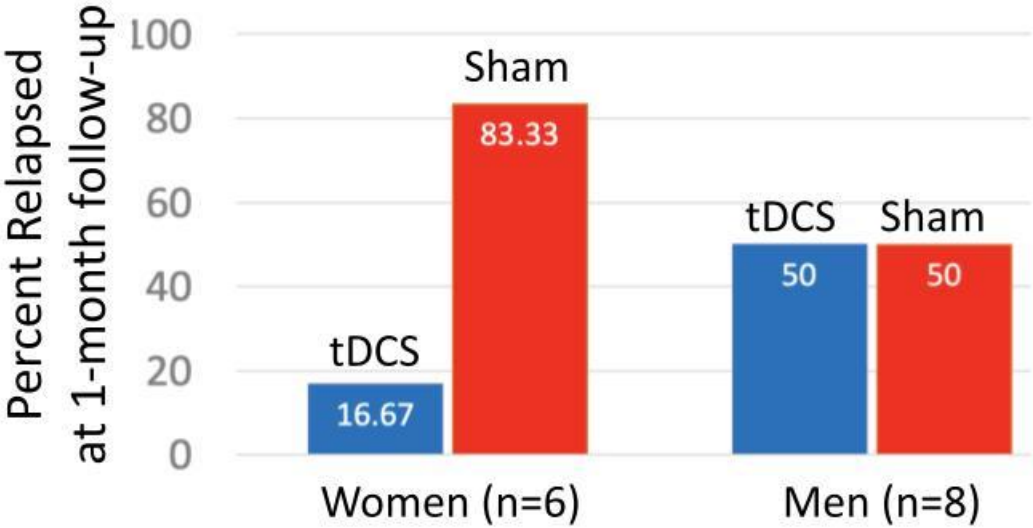

Figure 7. Among AUD that relapsed: Significantly lower relapse rate in AUD women who received 5 active tDCS intervention sessions vs. 5 sham sessions. No effect observed in men **(Camchong K01 clinical trial).**

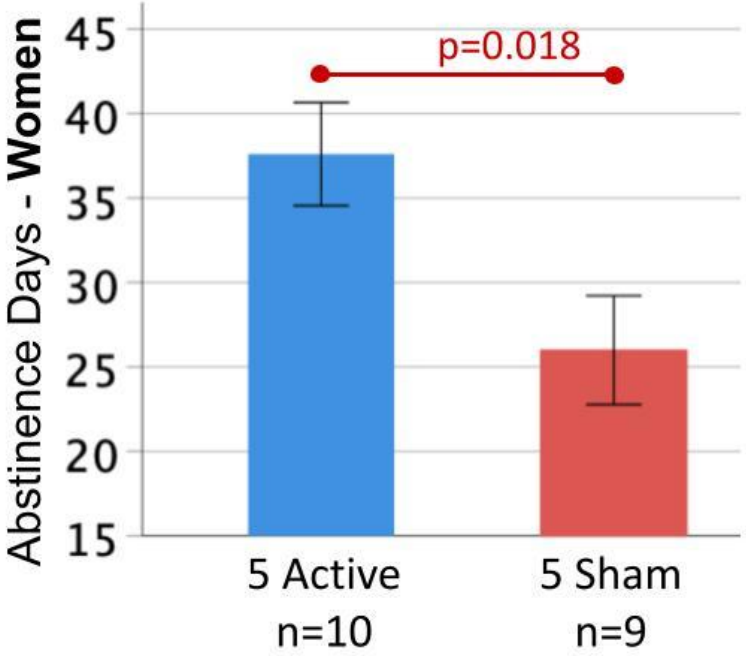

Figure 8. Among AUD women: Longer abstinence after 5 Active (F3 anode, F4 cathode) vs. 5 Sham tDCS interventions. No effect was observed in men. Error bars: ±1 SE. **(Camchong K01 clinical trial).**

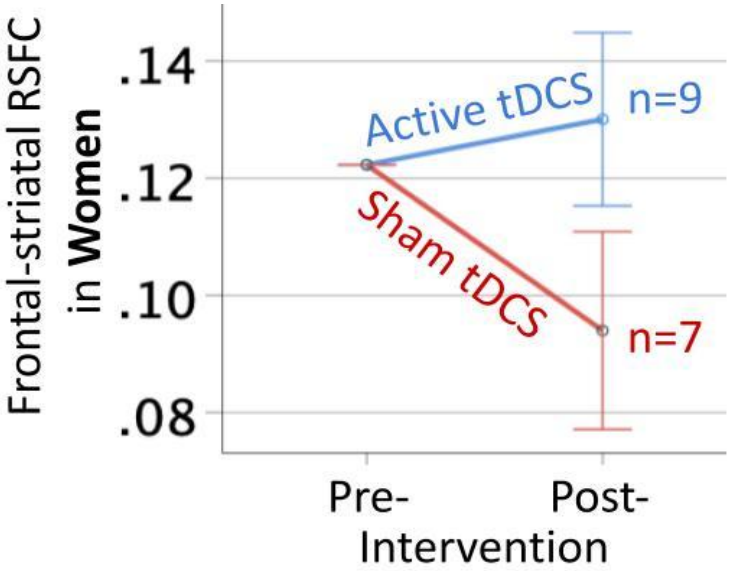

Figure 9. Among AUD women: Group x Time intervention effect on frontal-striatal RSFC (resting state functional connectivity) measured before and after 5 sessions of Active (red) or Sham (blue) tDCS (controlling for baseline). No effect was observed in men. Error bars: ±1 SE. **(Camchong K01 clinical trial).**

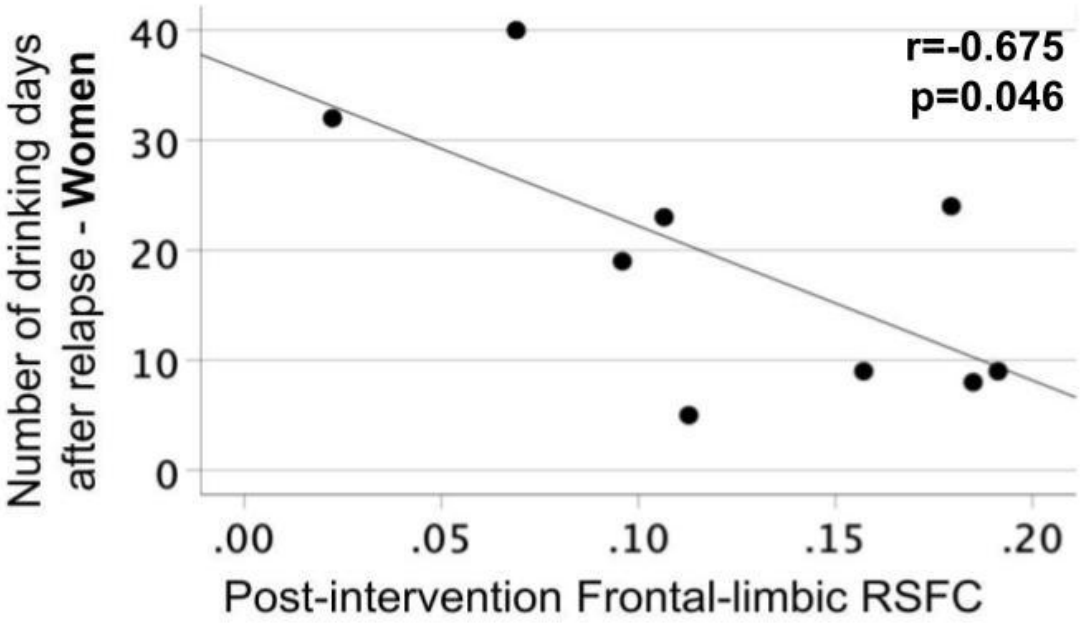

Figure 10. Among AUD women that relapsed: Association between strength of frontal-striatal RSFC (resting state functional connectivity) measured post-intervention and subsequent number of drinking days**.** No effect was observed in men. **(Camchong K01 clinical trial).**

tDCS Alcohol Study Summary

1. Active tDCS increased frontal-limbic connectivity in women but not in men
2. Active tDCS increased abstinence days only in women who relapsed
3. No effect on abstinence for active tDCS in men
4. Even in women who relapsed, those with HIGHER frontal-limbic connectivity had fewer drinks

Neuromodulation Studies

- tDCS Alcohol (VA Merit Lim)
- tDCS Opioid (NIH UG3 Lim)
- tDCS Schizophrenia (NIH R01 Lim/MacDonald)
- tDCS Mild Cognitive Impairment (VA McCarten)
- tDCS Obesity (VA Merit Sibley)
- tDCS Traumatic Brain Injury(VA Gilmore)
- tDCS Phantom Limb Pain (VA Rich)
- TMS Depression (VA Lim)

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