# Non-invasive brain stimulation as an intervention for traumatic brain injury

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# Transcranial Direct Current Stimulation (tDCS)

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# Disclosures

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The contents of this presentation do not represent the view of the Department of Veteran Affairs or the United States Government.

# Presentation Outline

Where did Transcranial Direct Current Stimulation (tDCS) come from?

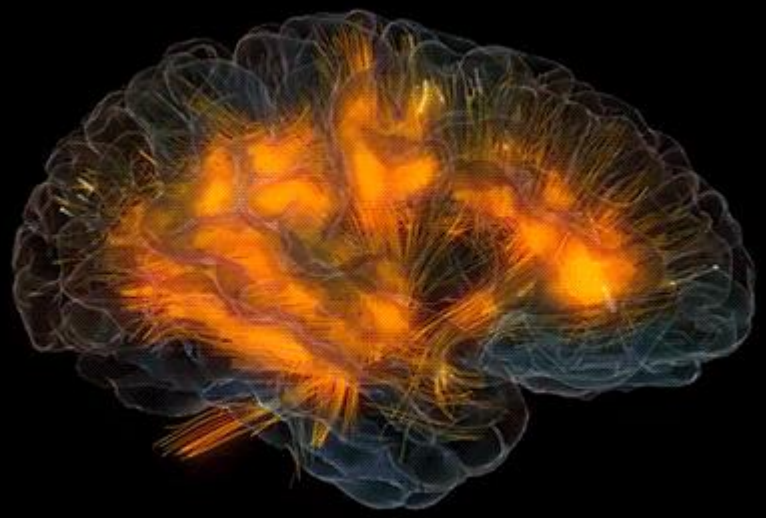
How does Transcranial Direct Current Stimulation (tDCS) work?

How do we use Transcranial Direct Current Stimulation (tDCS)?

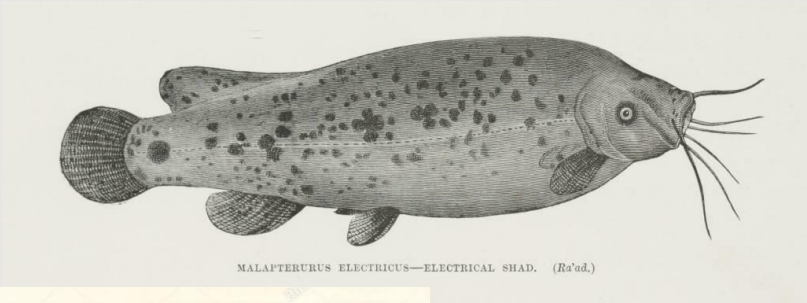
Can we change behavior using Transcranial Direct Current Stimulation (tDCS)?

# Where did Transcranial Direct Current Stimulation (tDCS) come from?

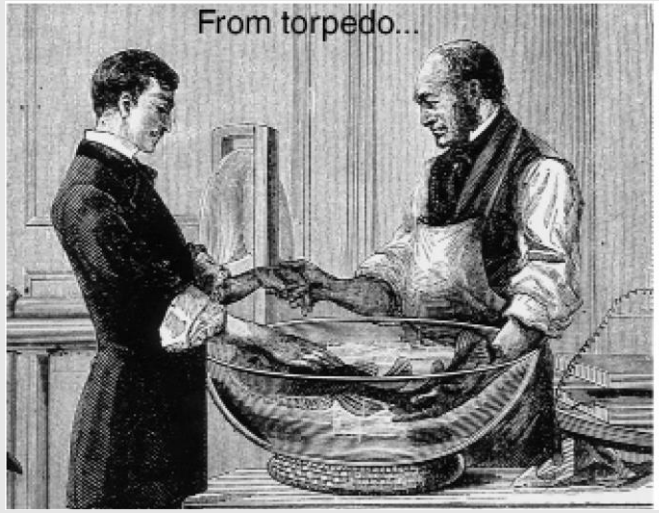
# Electrical Activity

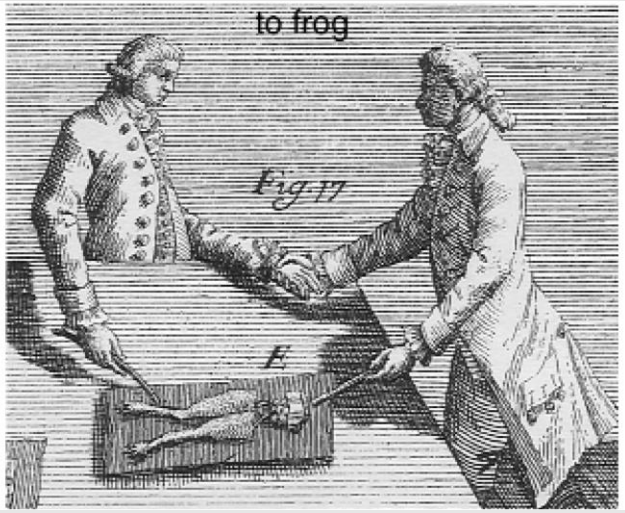


## Ancient Egypt, Greece, Rome

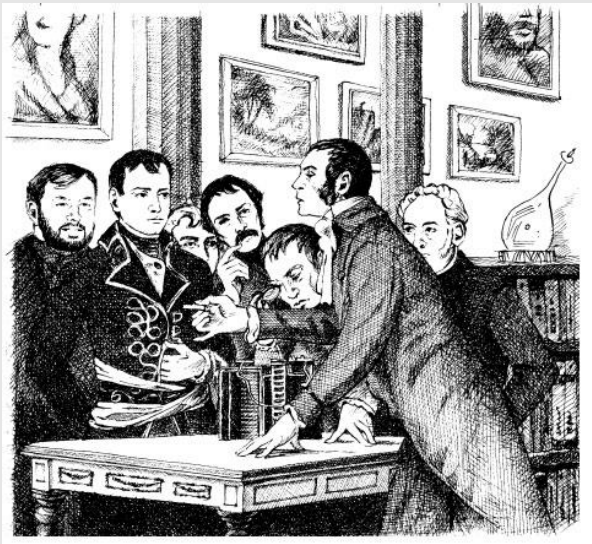






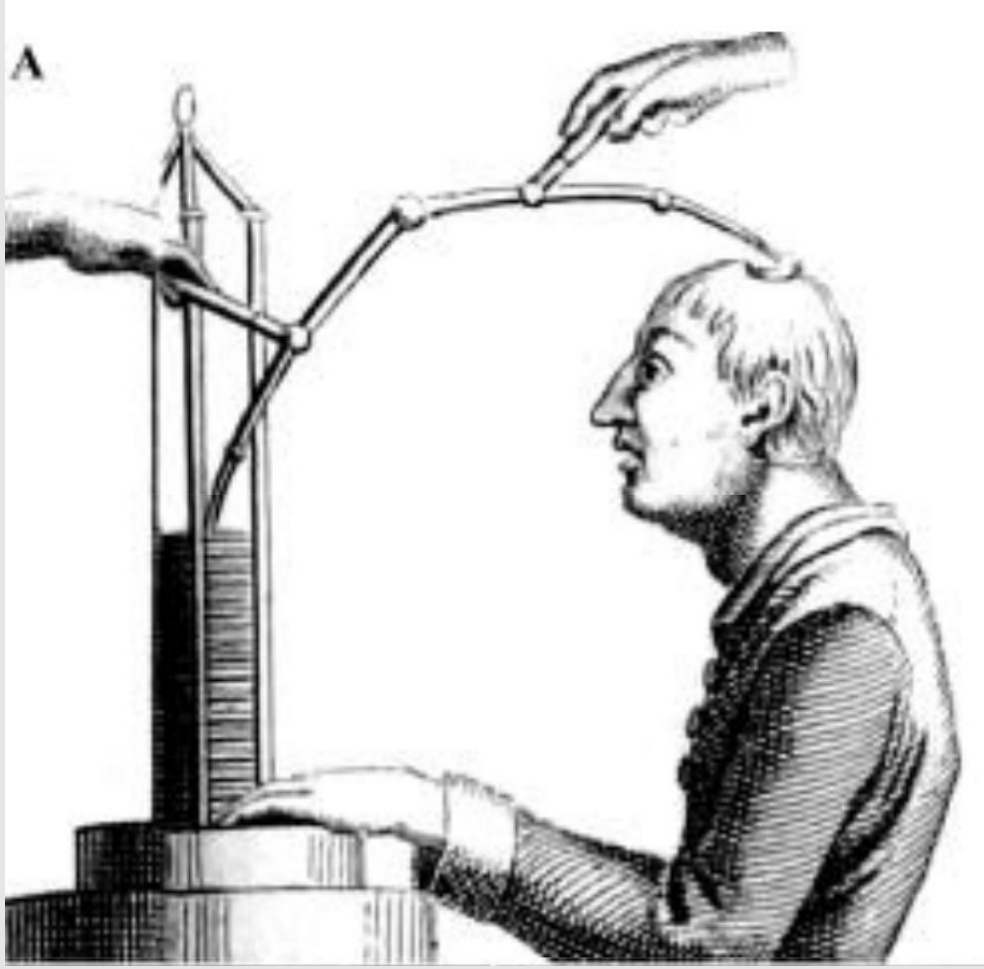




## Electricity in Physiology



## Volta's DC battery

## 1801: Treating *Melancholia* with “tDCS”




## Today: Wireless multi-channel tDCS

# How does Transcranial Direct Current Stimulation (tDCS) work?

## Synaptic Plasticity in the Brain

**Synaptic plasticity** is the ability of synapses to strengthen or weaken over time, in response to increases or decreases in their activity.

## 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)

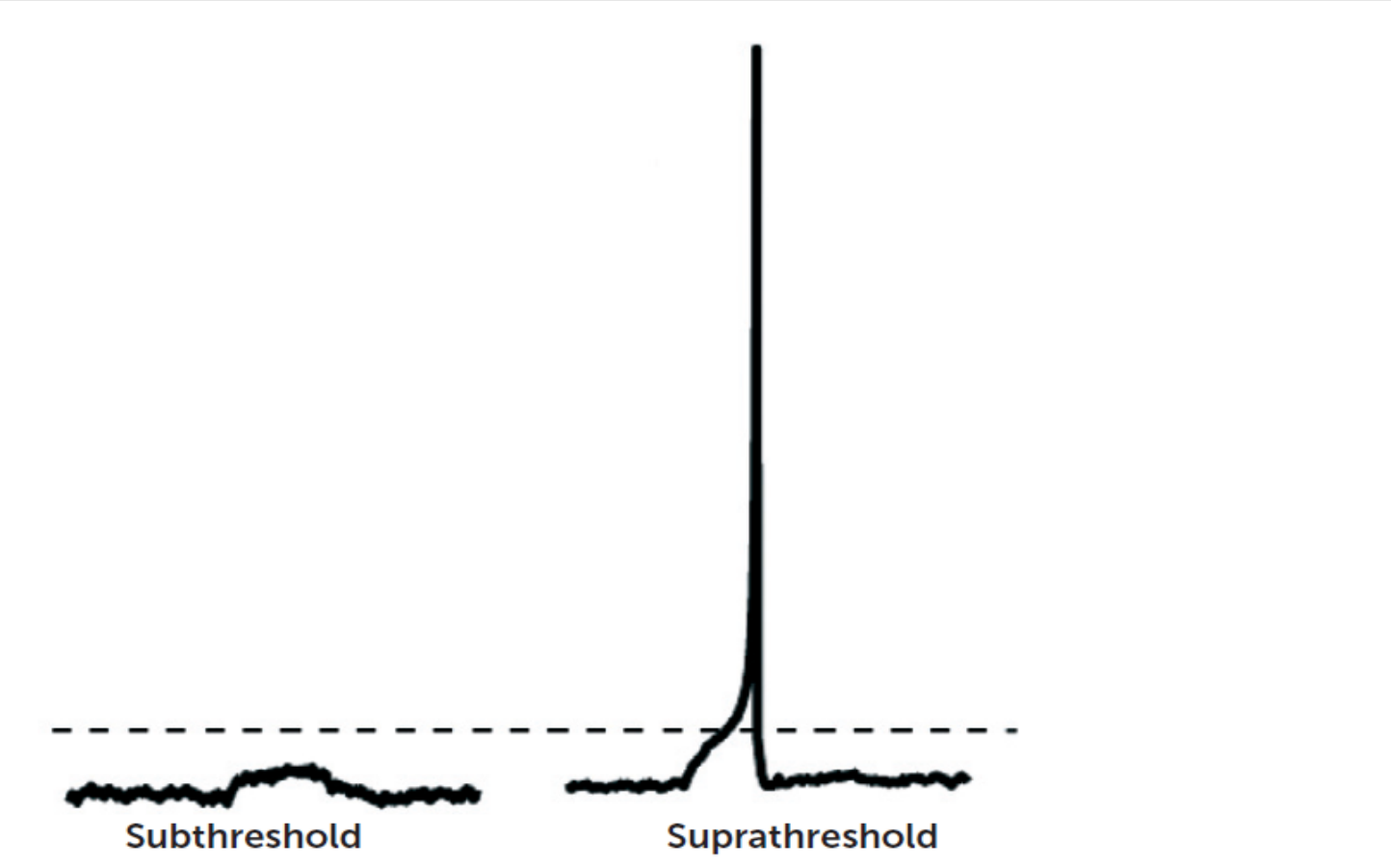
- Applied to the scalp via damp sponge electrodes
- Electrical current typically 1.0 - 2.0 mA for up to 30 mins
- Various electrode montages can be used to modulate different areas of activity in the brain
- Low risk of adverse reaction to stimulation

# How does tDCS work?

**Threshold**

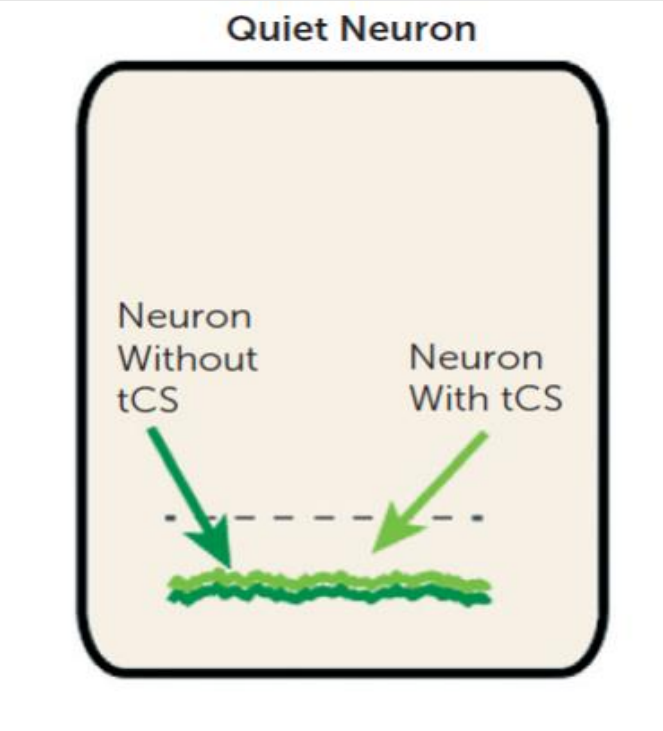

Philip et al., *AJP*, 2017

# How does tDCS work?



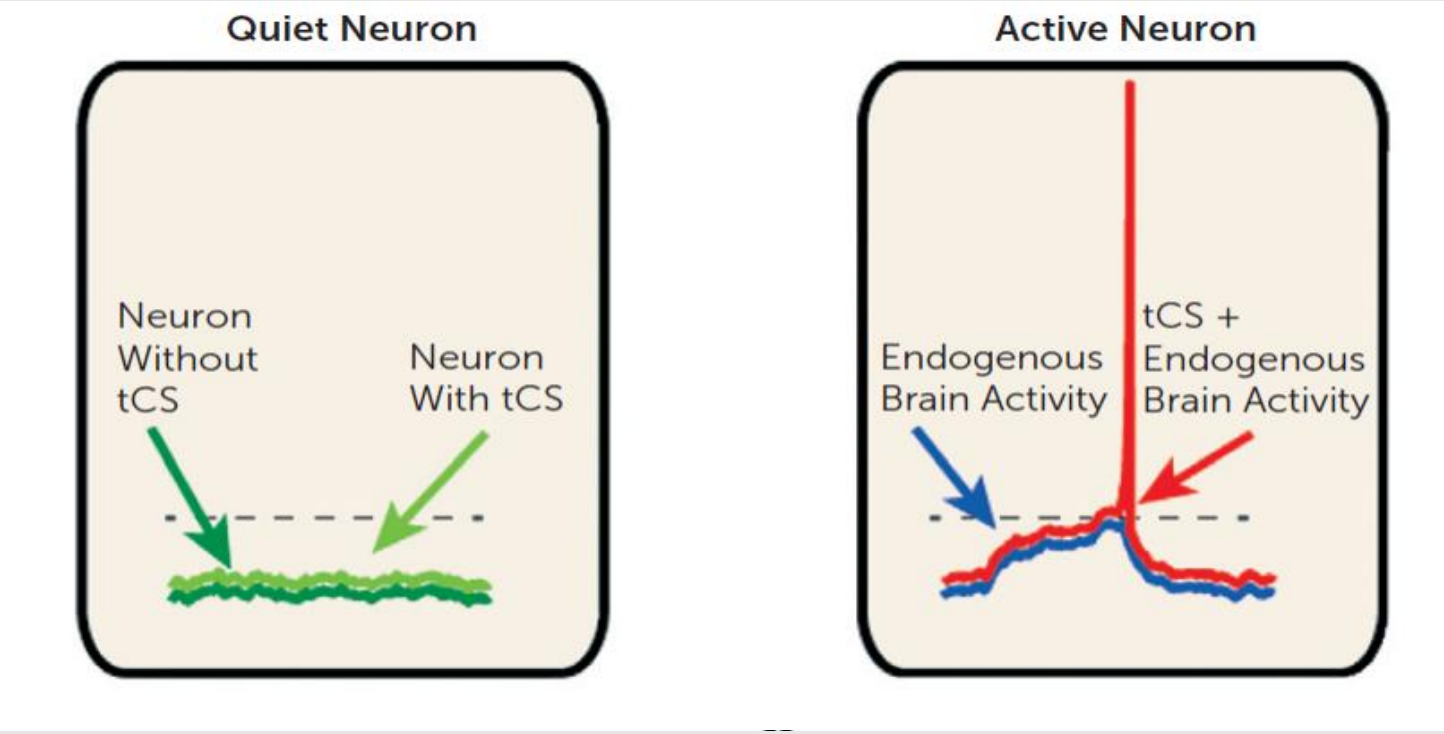

Philip et al., *AJP*, 2017

# How does tDCS work?




Philip et al., *AJP*, 2017

# How does tDCS work?




Philip et al., *AJP*, 2017

# How do we use Transcranial Direct Current Stimulation (tDCS)?

## How do we use tDCS?

- Effects are activity-dependent
- Facilitate learning

- Combine tDCS with an appropriate cognitive task

# Can we change behavior using Transcranial Direct Current Stimulation (tDCS)?

# tDCS + Cognitive Task to Reduce Impulsivity

- Common following a TBI
- No effective treatments

- Can we reduce impulsivity by combining tDCS with a task?

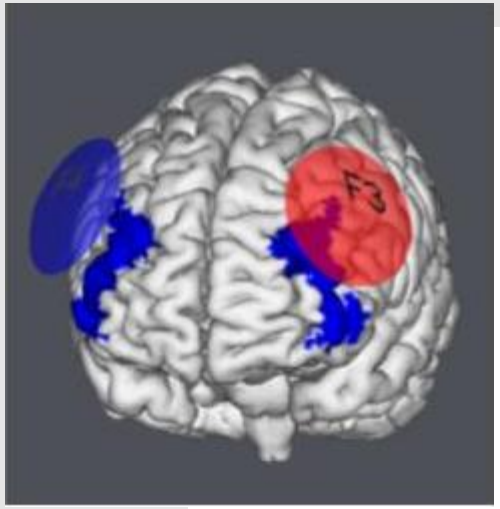
## tDCS to Reduce Impulsivity

30 clinically-referred Veterans with Impulsivity

- 15 Active tDCS (60.4 ±6.6 years old)
- 15 Sham tDCS (58.3 ±7.6 years old)

10 sessions of tDCS + training task (2x day/5 days)

# Trained Task + tDCS





# Untrained Task

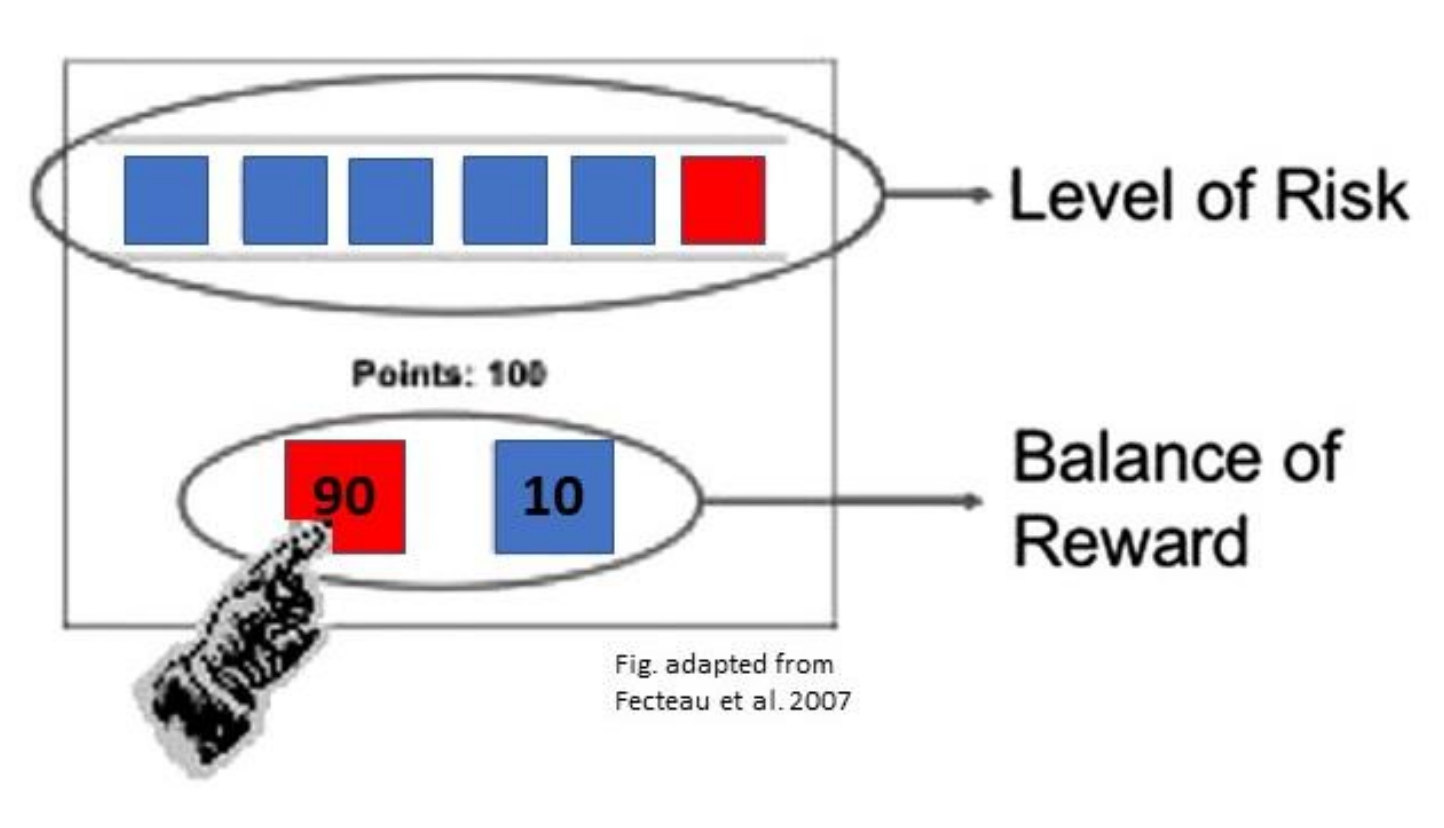
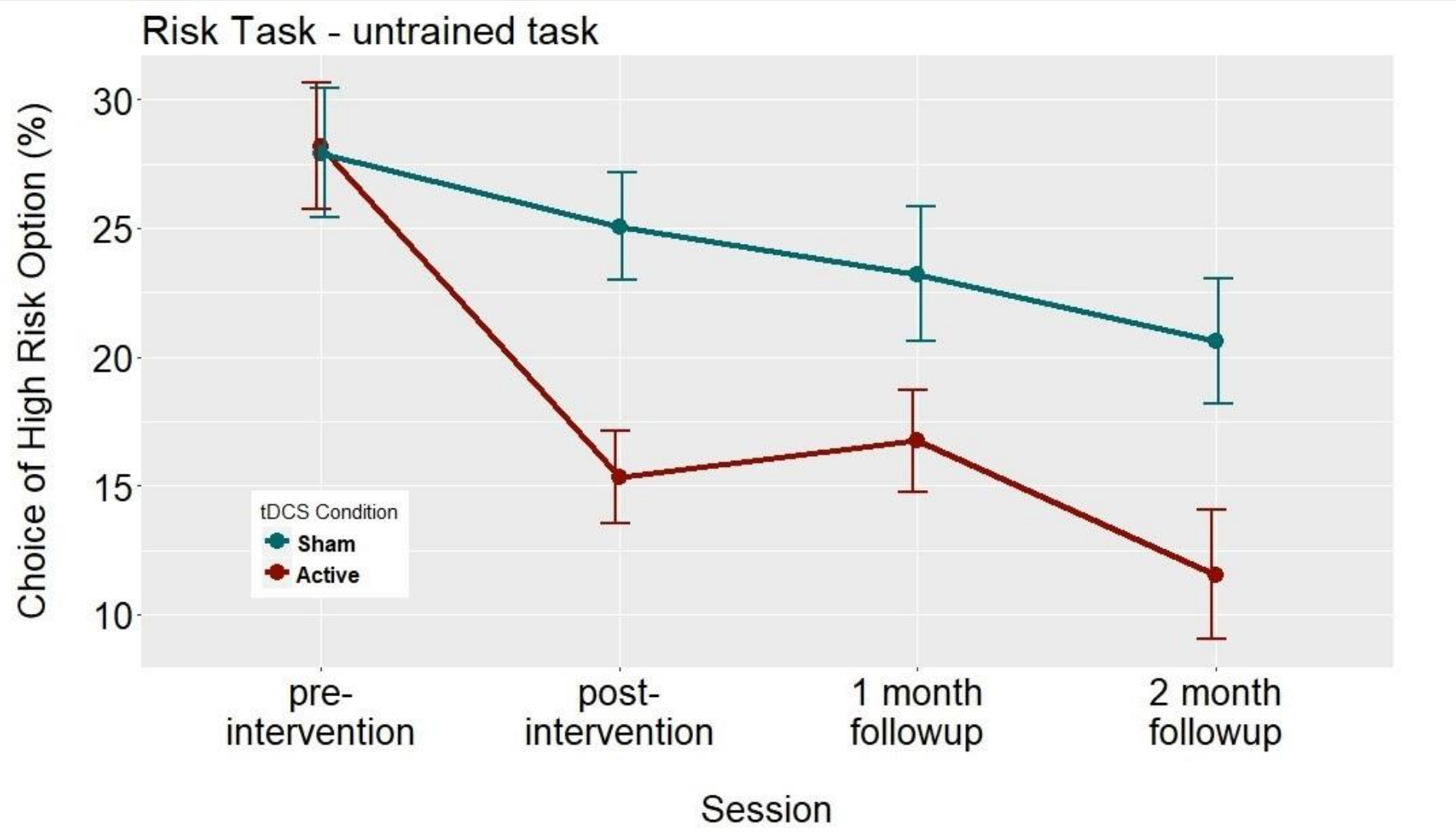



Fig. adapted from Fecteau et al. 2007

# Untrained Task



# tDCS + Cognitive Task to Reduce Impulsivity

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Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample

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# Combining TDCS with Cognitive Training to Promote Generalization of Learning

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# Disclosures

- **Research/Grants**:
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  - State of Minnesota Office of Higher Learning
- **Conflicts of Interest**: None
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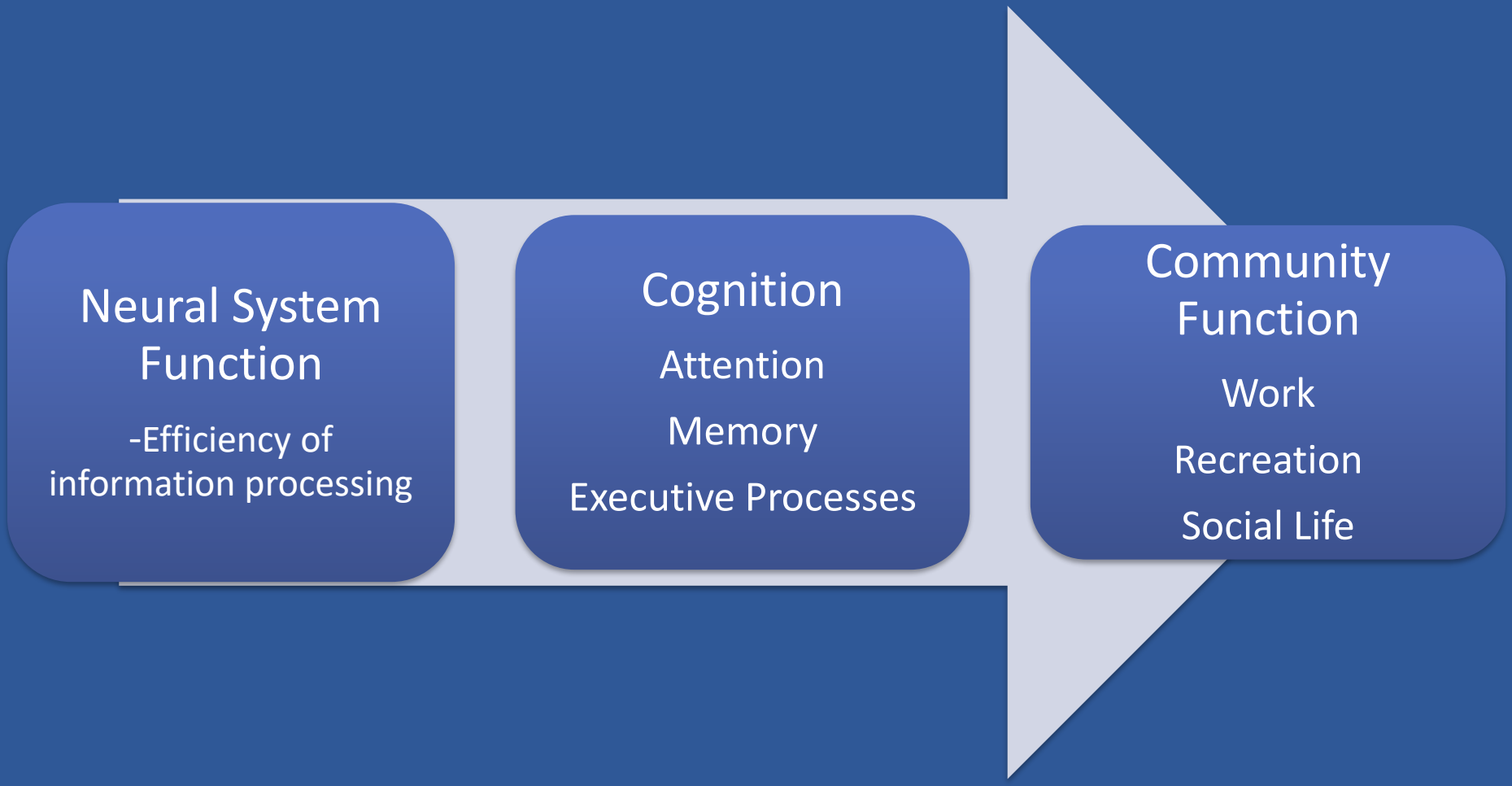
# Presentation Overview

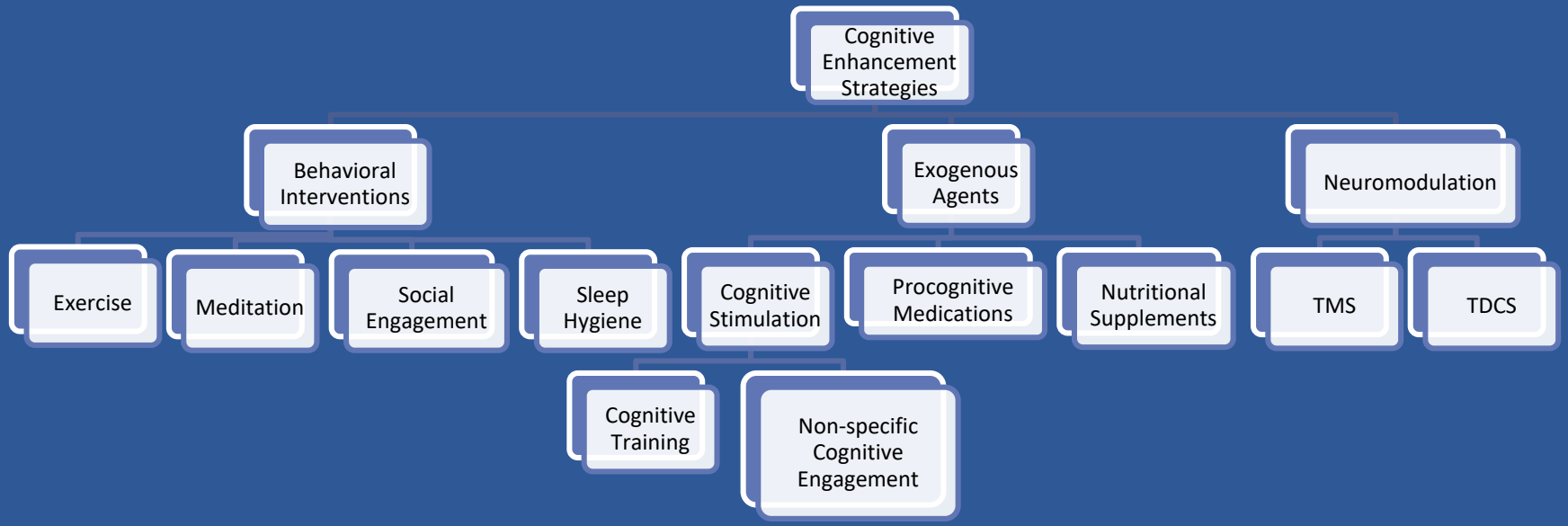
- Cognition as an Intervention Target
- Cognitive Training and the Current State of Intervention Development
- Behavioral and Neural Evidence of Target Engagement with Working Memory Training
- Next Phase of Cognitive Training Studies - Enhancement with TDCS
- Current Applications to Mild Traumatic Brain Injury

# Targeting Cognition




Keshavan, et al., 2014

# Approaches to Cognitive Enhancement




Keshavan, et al., 2014

# What is Cognitive Remediation?

- **"A behavioral training-based intervention that aims to improve cognitive processes** (attention, memory, executive function, social cognition, or metacognition) **with the ultimate goal of durability and generalization."**
  - Cognitive Remediation Experts Workgroup 2010
- **"An intervention targeting cognitive deficits using scientific principles of learning with the ultimate goal of improving functional outcomes."**
  - Cognitive Remediation Experts Workgroup 2012

# What Does Cognitive Remediation Look Like?

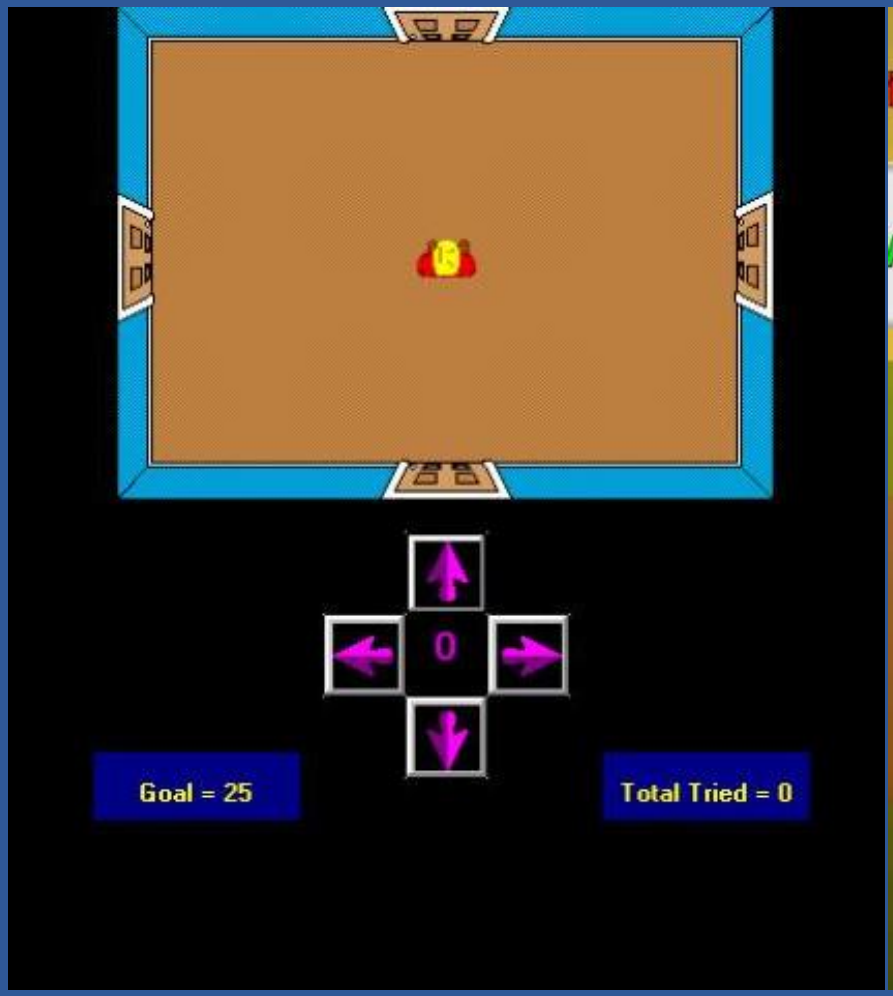
- Training can be offered individually or in small groups
- Participants attend a “Learning Center” and have their own work station
- Training is computerized
- Participants complete 4-6 activities in a 60 minute session
- Training is offered at least twice a week

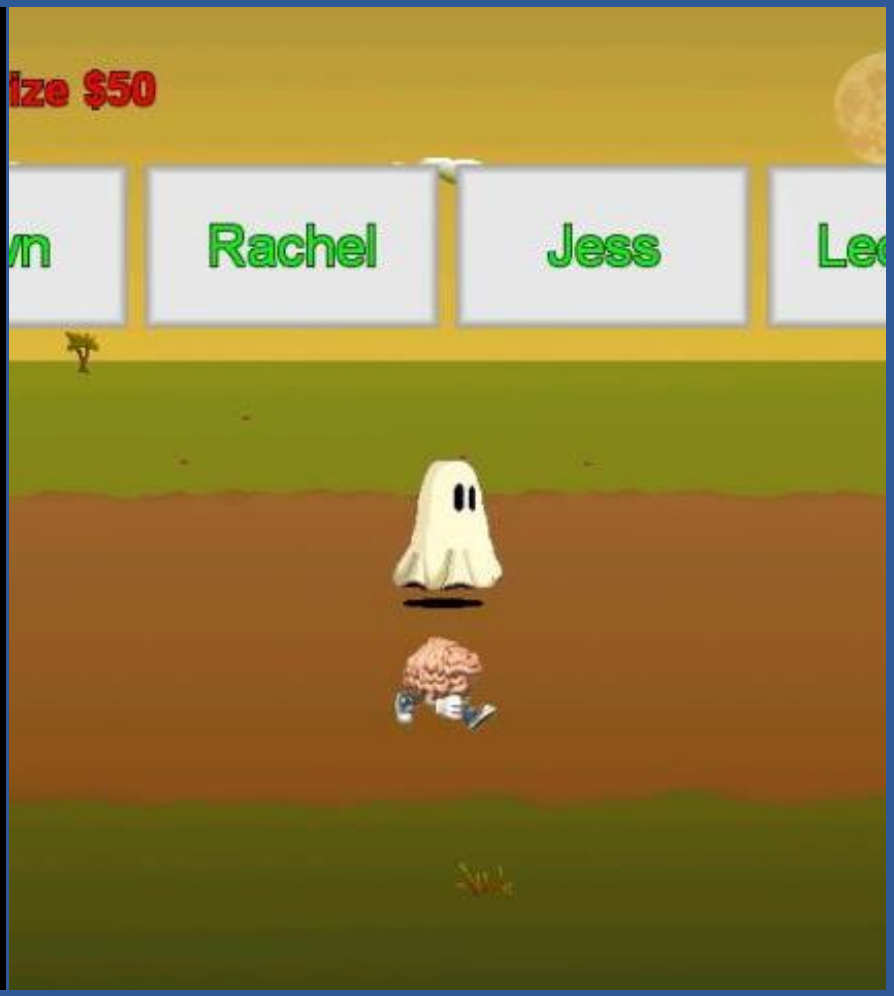
# What Does Cognitive Remediation Look Like?



- CogRehab Psychological Services Software, Bracy, 1995

# What Does Cognitive Remediation Look Like?

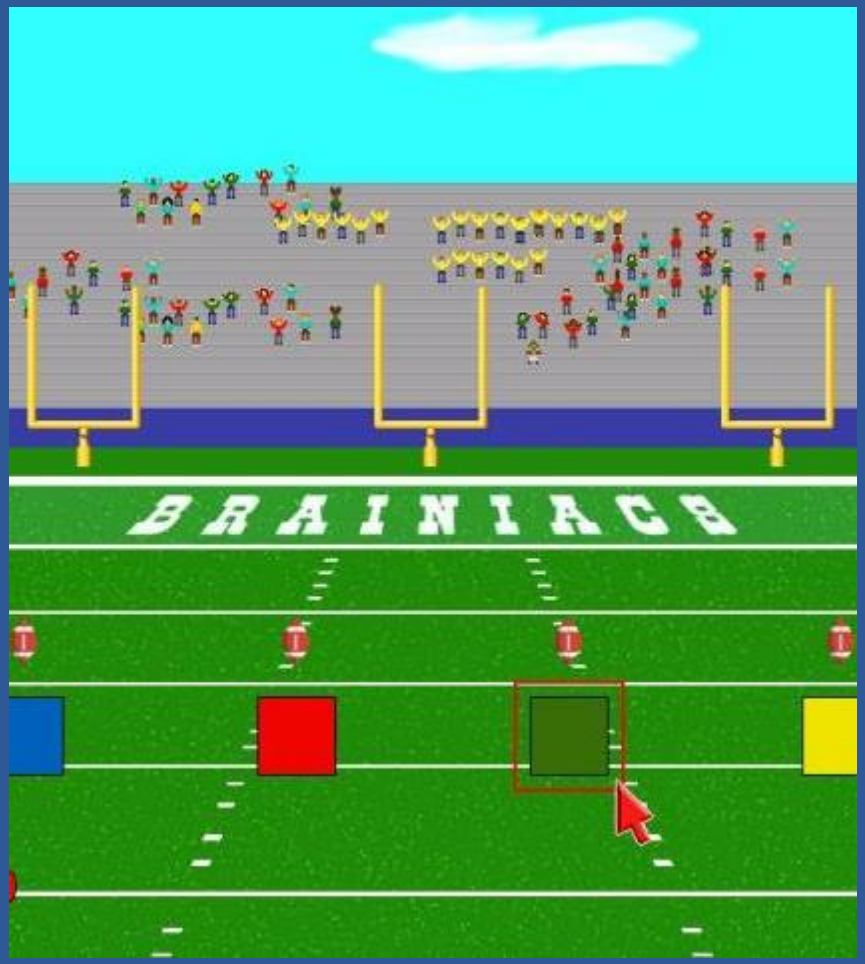



- CogRehab PSS, Bracy, 1995

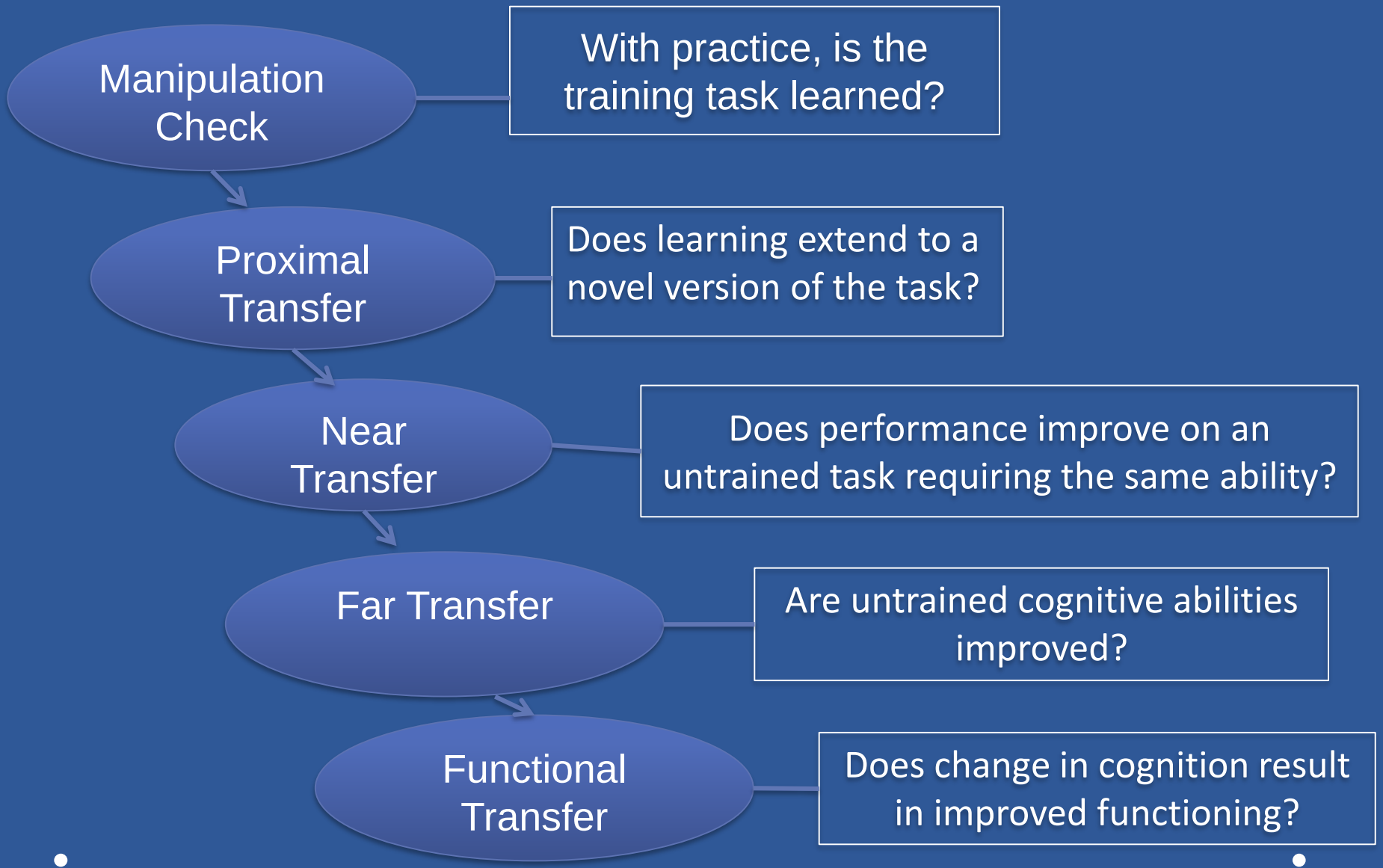
Capitan's Log BrainTrain, 2009 •

# What Does Cognitive Remediation Look Like?


- Capitan's Log BrainTrain, 2009

# How is Cognitive Change Assessed?



# What Is the Impact on Cognition in Schizophrenia?

- **Cognition is a modifiable intervention target; however effect of intensive cognitive training is modest**
  - d = .41 (.09-.54), 26 studies (McGurk et al., 2007)
  - d = .45 (.15 - .65), 40 studies (Wykes et al., 2011)
- **Methodological Challenges**
  - Clinical Trial Assessment Measure, Trial Quality score = 57.4 (Wykes et al., 2011)
  - Multiple approaches and combinations of interventions
- **Improvement on training tasks doesn't always generalize to untrained measures of the cognitive domain** (Dickinson et al., 2010; Keefe et al. 2012; Murthy et al., 2012; Rass et al., 2012)

# Targeted Cognitive Training

- **Understanding of neural systems guides the design of training protocols** (Vinogradov et al., 2012)
  - Approach assumes that the intervention mechanism is restorative
  - Training is designed to capitalize on neural plasticity, the brain's ability to alter it's structure, function, and connectivity in response to environmental demands
  - Training places demands on the neural structures that support a cognitive function with repeated practice of focused cognitive tasks
  - Goals are to enhance cognitive performance and to strengthen or repair the neural circuitry that supports the cognitive ability

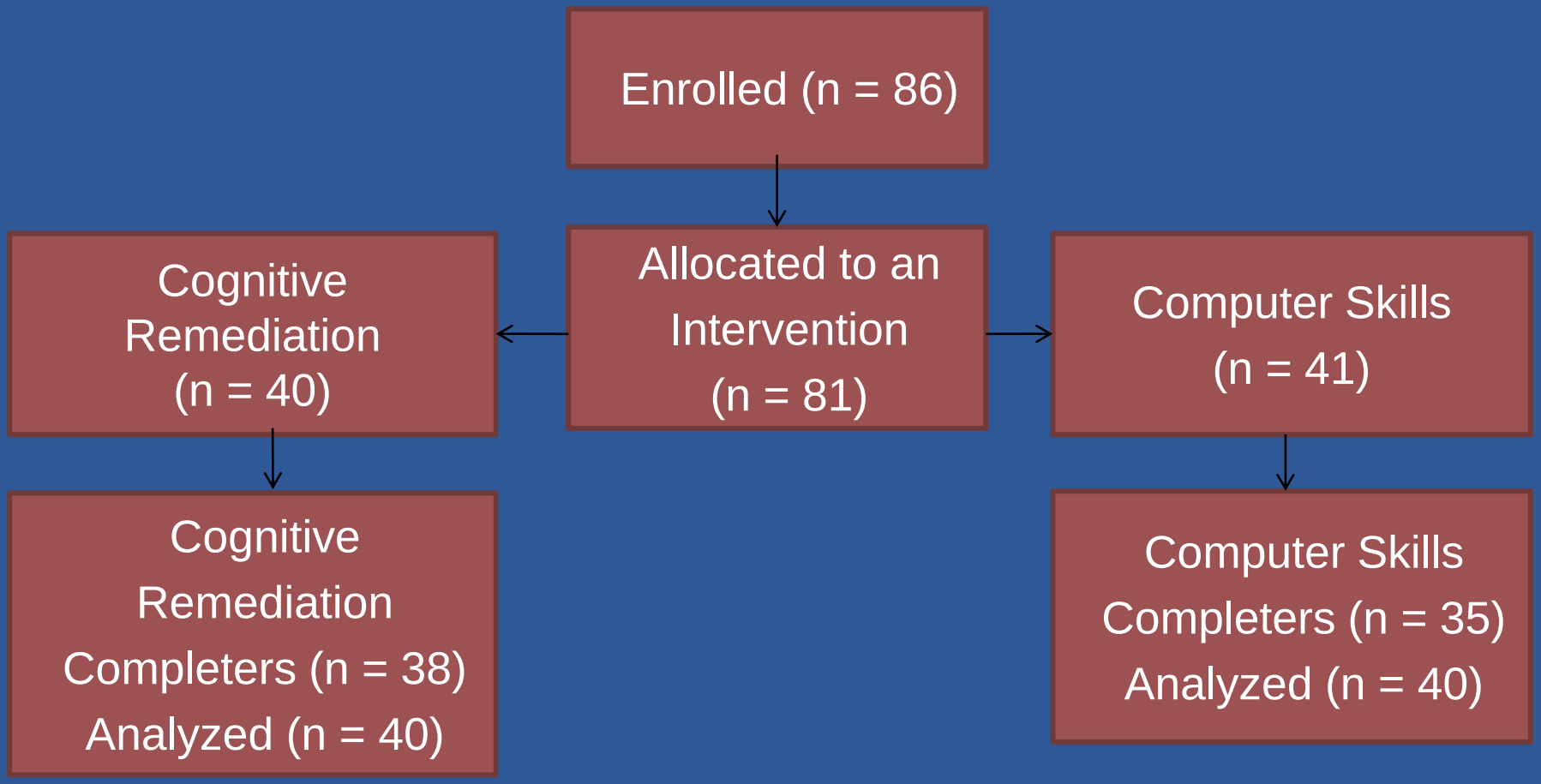
# Working Memory and the Prefrontal Cortex

- **Working memory is the ability to temporarily maintain information so that it can be referenced, manipulated or acted upon**

- **Poor working memory is associated with:**
  - Alterations in activation in the prefrontal cortex (Minzenberg et al., 2010)
  - Disruptions in connectivity between the prefrontal cortex and the thalamus (Giraldo-Chica et al., 2017)

- **Neural network supporting working memory is relatively well understood, enabling targeted intervention**

# Working Memory Training RCT




**Hypothesis:** A training protocol that engages the prefrontal cortex will be effective in enhancing working memory and related cognitive functions.

# Working Memory Training RCT

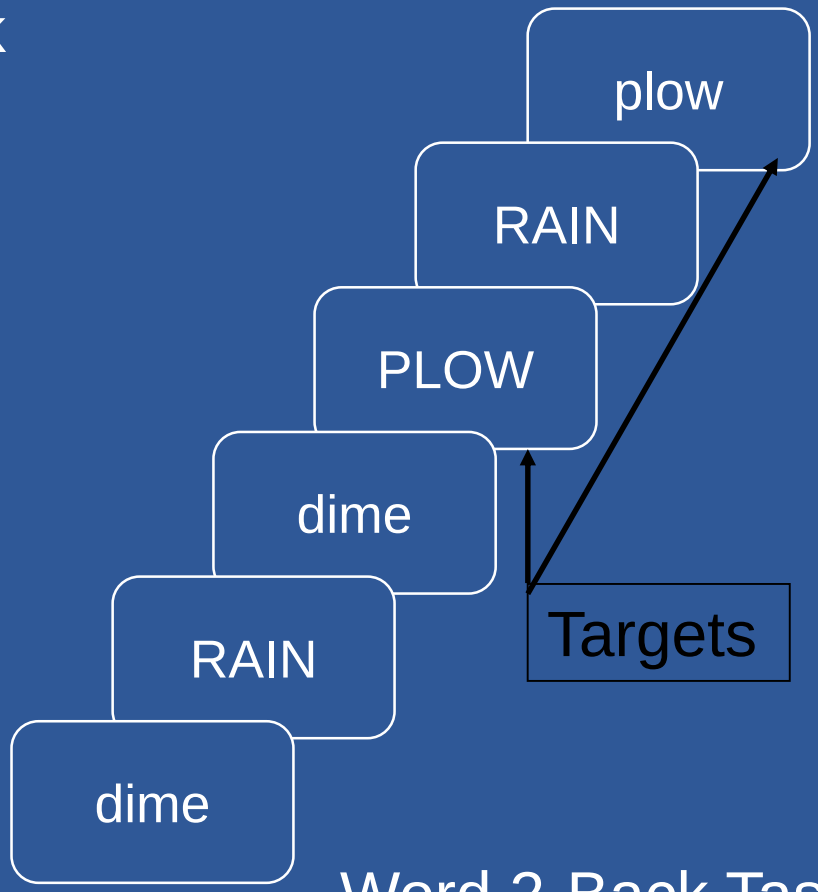
- **Double-blind study with an active placebo control, computer skills training**
- **Conditions matched on:**
  - Session Number and Time
    - 3 60-minute sessions weekly for a total of 48 sessions
  - Attention from Instructors
    - Same Masters and Bachelor-level instructors taught both courses to groups of 3-6 participants
  - Exposure to Computers
  - Opportunity to Learn a Skill

# Study Sample Characteristics

| | Cognitive Remediation (n = 40) | | Computer Skills (n = 40) | | |
|---|---|---|---|---|---|
| Characteristic | M | SD | M | SD | *p* |
| Age | 45.83 | 9.08 | 47.05 | 10.16 | .57 |
| Education (Yrs) | 13.15 | 1.83 | 13.33 | 1.94 | .68 |
| Parental Ed (Yrs) | 12.81 | 3.29 | 13.37 | 2.72 | .42 |
| WTAR Estimated IQ | 103.18 | 10.08 | 102.53 | 9.39 | .77 |
| BPRS Total | 44.47 | 11.11 | 43.70 | 10.81 | .76 |
| CPZ Equivalents | 435.55 | 410.30 | 507.28 | 482.93 | .48 |
| Illness Length (Yrs) | 21.35 | 11.23 | 19.28 | 11.00 | .41 |
| % Completed Training | 95 | | 88 | | .43 |
| Training Hours | 47.38 | 3.95 | 44.23 | 10.97 | .09 |

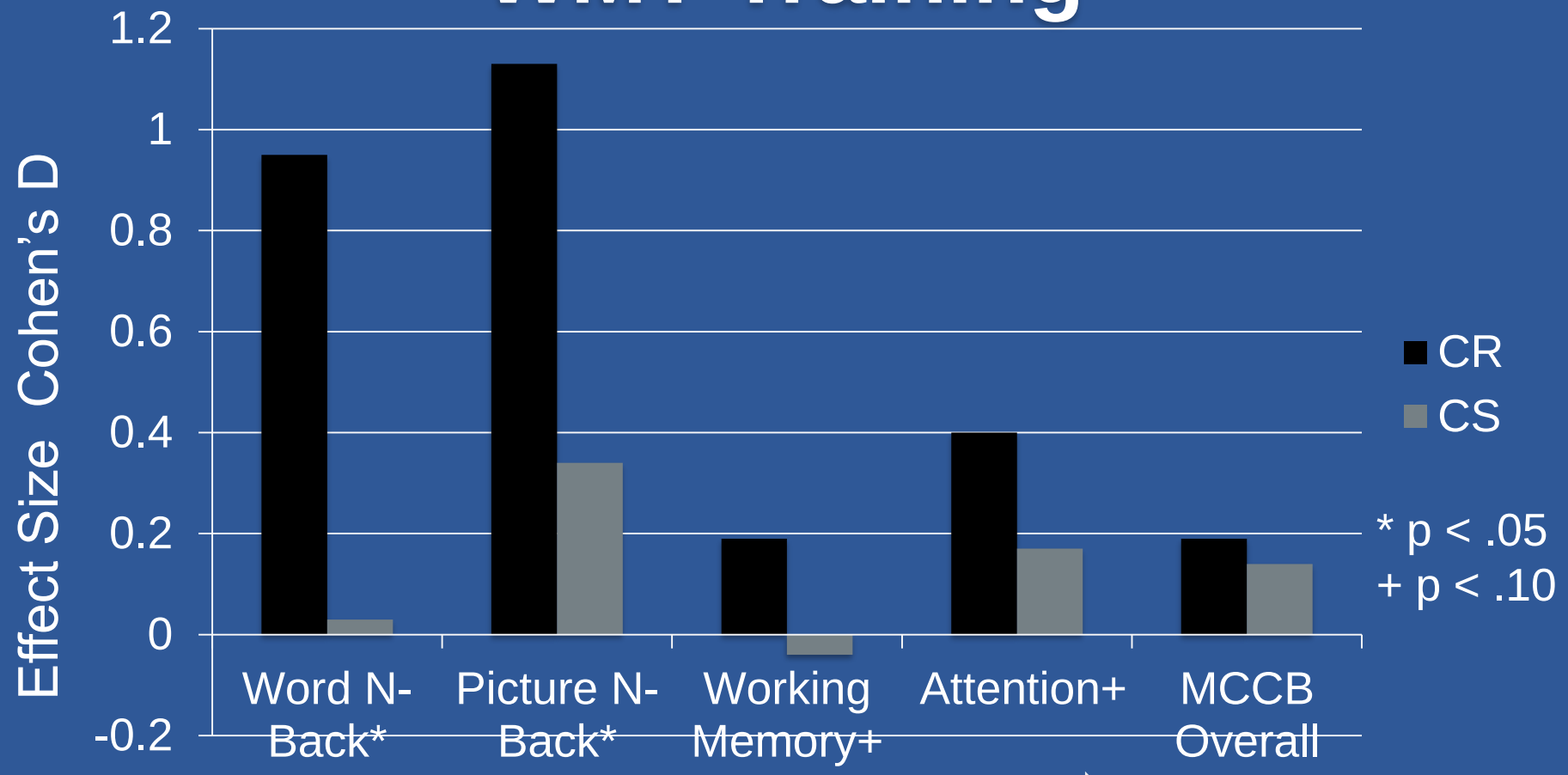
# Outcome Assessment

- **Manipulation Check**
  - Word N-Back, Trained Task
- **Proximal Transfer**
  - Picture N-Back, Untrained Version of  Task
- **Near Transfer**
  - MCCB Attention and Working Memory Tasks
- **Far Transfer**
  - MCCB Overall Composite




Word 2-Back Task

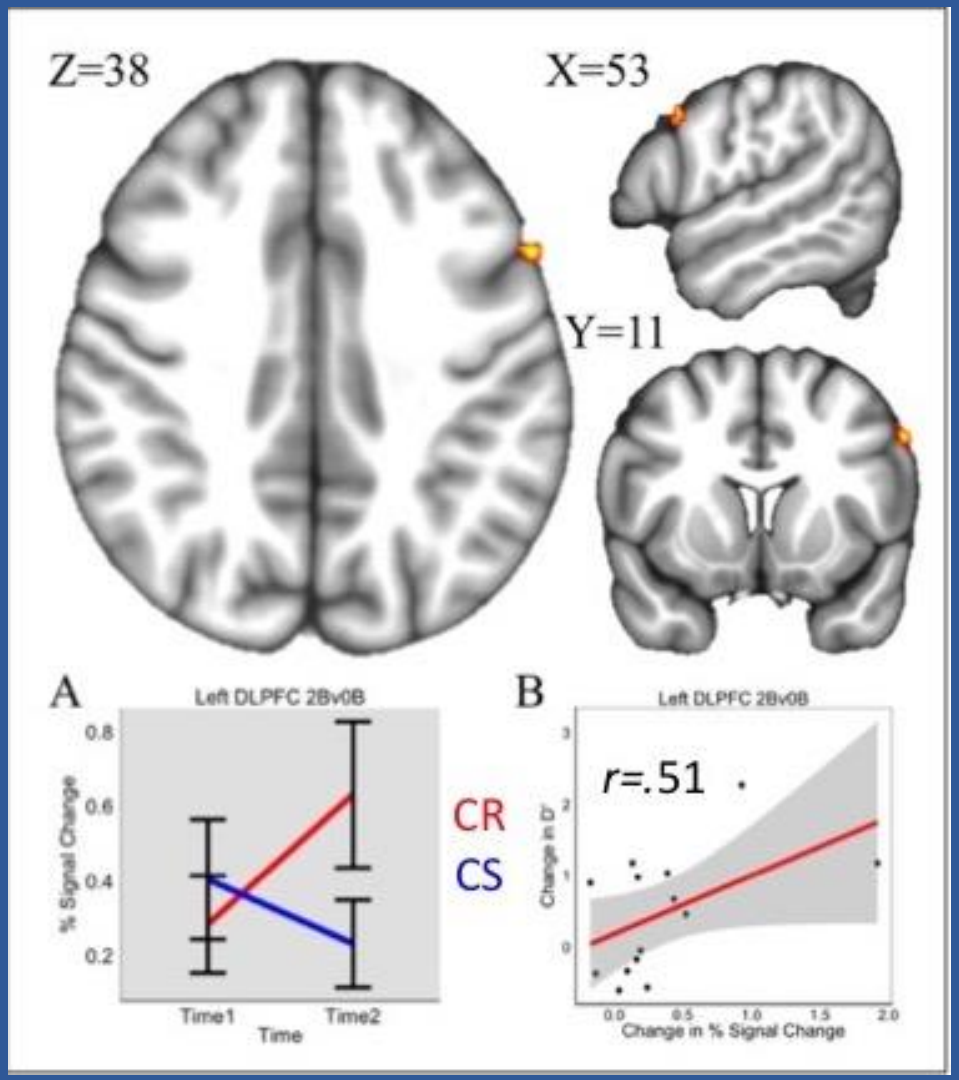
# Magnitude and Generalization of WMT Training




**Proximity to Training Task**

Nienow & MacDonald, *in preparation*

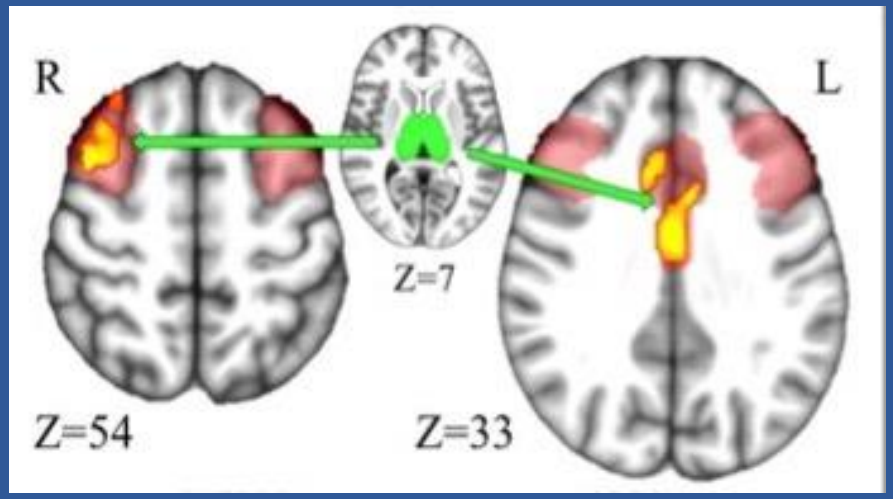
# Evidence of Target Engagement



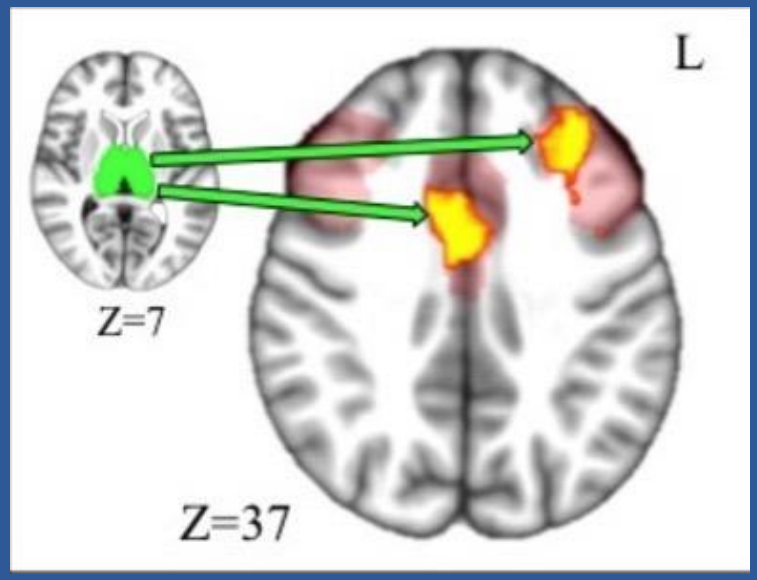

- Change on the Word N-Back task during training was related to near transfer to an untrained attention task, r = .24, p = .05.
- Voxel-wise Group x Time interaction in the left DLPFC ROI.
- Change correlated with improvement in Picture N-Back D' in the CR group, $r = .51$, $p < .05$.
- Neural network supporting working memory is modifiable and associated with intervention-induced change.

Ramsay, Nienow, Marggraf, & MacDonald, *British Journal of Psychiatry, 2017*

# Evidence of Target Engagement




Increased resting state connectivity was observed between the thalamus and the right MFG, $F(1,24)=13.07$, and the ACC, $F(1,24)=9.59$.

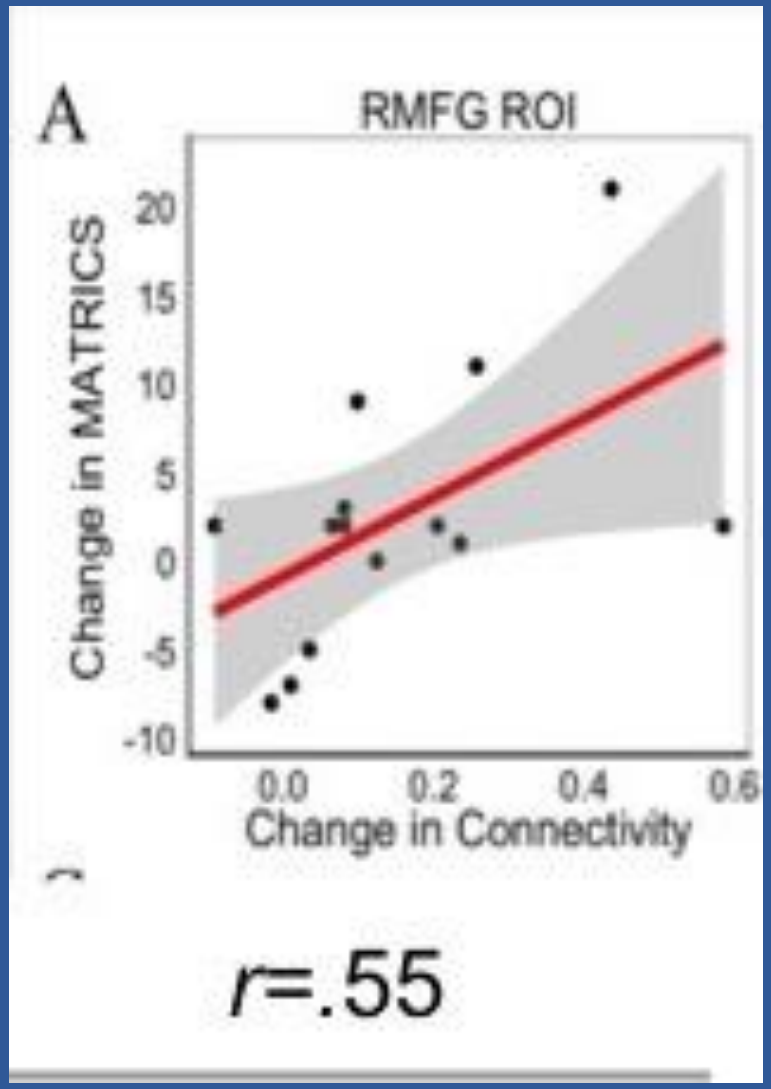



Change in task based connectivity noted between the thalamus and the ACC, $F(1, 24) = 15.89$ and the LMFG, $F(1,24) = 12.28$.

Findings were specific to the CR group, suggesting that repeated exercise with working memory training was able to change how regions of the brain related to each other irrespective of specific task demands.

Ramsay, Nienow, & MacDonald,
*Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2017*

# Evidence of Target Engagement




- Changes in resting state connectivity between the thalamus and the RMFG was positively correlated with change in cognition measured by the the MCCB Battery, $r = .55$, $p = .04$.
- Those with the most increase in thalamocortical connectivity experienced more generalization from training and had greater cognitive improvement.
- Plasticity of the thalamocortical network may support generalization of training to untrained domains.

Ramsay, Nienow, & MacDonald, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2017*

# Can Targeted Cognitive Training Be Made More Effective?

- Transcranial direct current stimulation (tDCS) modulates spontaneous neuronal network activity. It changes the threshold for a neuron to discharge. Thus, altering the likelihood (increasing or decreasing) that a neuron will fire. (Woods et al., 2016)

- The impact of tDCS extends beyond the point of application and impacts the neural network supporting a cognitive function (Meinzer et al., 2012; Zaehle et al., 2011)

- **Hypothesis:** TDCS concurrent with working memory training will facilitate neuroplasticity and produce greater training gains and generalization than sham stimulation.

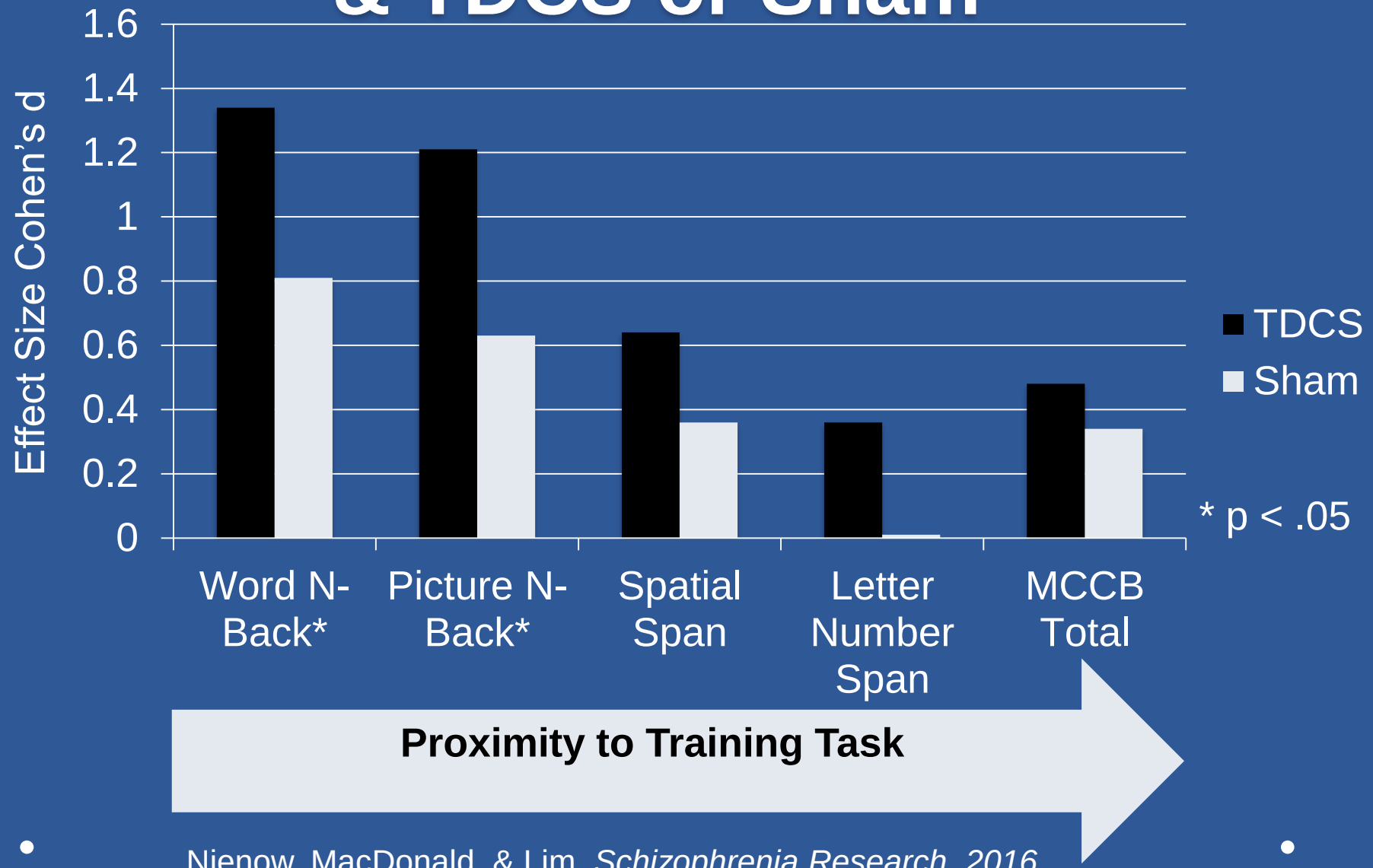
# Proof of Concept Single-Blind Study

- **Working Memory Training**
  - Participants attended 48 hours of working memory training, typically 3 1-hour sessions a week
  - TDCS or sham stimulation was administered twice a week, beginning in week 3, for a total of 28 administrations
- **TDCS Administration**
  - TDCS and sham stimulation was administered with the Soterix Medical, Inc. 1x1 tDCS low intensity stimulator
  - Anodal electrode was placed over F3 and the cathodal electrode placed in the contralateral supraorbital position
  - 1 mA of stimulation was administered concurrent with the first 20 minutes of working memory training

# Study Sample Characteristics

| | TDCS (n = 6) | | Sham (n = 4) | | |
|---|---|---|---|---|---|
| Demographic | M | SD | M | SD | *p* |
| Gender % Male | 50% | | 75% | | |
| Age | 61.50 | 5.99 | 61.00 | 2.83 | .88 |
| Education (Yrs) | 14.17 | 3.25 | 12.5 | 3.42 | .46 |
| Parental Ed (Yrs) | 12.67 | 3.08 | 12.63 | .95 | .98 |
| Baseline Word N-Back | 1.57 | 1.16 | 1.34 | 1.15 | .77 |
| BPRS Total | 38.33 | 8.17 | 48.5 | 15.59 | .21 |
| Age Illness Onset | 25.67 | 7.17 | 28.25 | 7.5 | .60 |
| Illness Length (Yrs) | 36.83 | 9.97 | 32.75 | 6.13 | .50 |
| CPZ Total | 741.50 | 549.26 | 756.25 | 575.32 | .97 |

# Magnitude of Change with Training & TDCS or Sham




Nienow, MacDonald, & Lim, *Schizophrenia Research, 2016*

# Why Target Working Memory in Traumatic Brain Injury?

- Many of the cognitive difficulties associated with TBI, including attention, executive functioning, and memory are predicted by working memory impairment (Serino et al., 2006)
- Working memory is especially vulnerable to disruption by head injury (McAllister et al., 2004; 2006)
- Working memory is among the most impaired cognitive abilities among patients with mild TBI (van der Horn et al. 2015; Xiong et al., 2016)
- Working memory performance is associated with alterations in brain activation and functional connectivity (van der Horn et al. 2015; Xiong et al., 2016)

# What is the Impact of Intervention on Cognition in Mild Traumatic Brain Injury?

- Targeted cognitive training has been found to improve cognitive performance in patients with traumatic brain injury (Bjorkdahl et al., 2013; Kim et al., 2009; Lawton & Huang, 2009; Serino et al., 2007)
- Performance gains have been associated with changes in brain activation, suggesting that the neural system is becoming more efficient (Kim et al., 2009)
- Cognitive training gains are modest (Hallock et al., 2016; Weicker et al., 2016)
- Pilot studies pairing tDCS with working memory training have found improvement in patients with severe traumatic brain injury (Sacco et al., 2016) and stroke (Park et al., 2013)

# Ongoing Study: TDCS as an Intervention for Patients with Traumatic Brain Injury

- Study Aims
  - Aim 1: To assess magnitude of response to repeated anodal tDCS applied to the left DLPFC in mild TBI patients. A double-blind, sham-controlled, pilot study is being conducted with 24 mild TBI patients randomized to tDCS or sham. They will complete 24 training sessions.
  - Aim 2: To identify biomarkers of treatment response. Electroencephalogram (EEG) assessments will be conducted immediately before and after the first training session as well as post-intervention to measure the immediate impact of tDCS on brain activity as well as the impact of repeated tDCS administration.
  - Aim 3. To assess participant perception of TDCS acceptability.

# Summary and Conclusions

- Cognitive remediation is an intervention that is still being developed. Our understanding of treatment mechanisms and best practices is quite limited.
- Working memory training is one example of a training approach that is designed to target a neural system.
- Results suggest that patients learned the training tasks but magnitude of transfer to untrained tasks was small, limiting current utility of the training.
- Despite limited generalization of training behaviorally, neuroimaging revealed that their were regional changes in activation and connectivity that appear to reflect recovery of function.
- Pilot study findings suggest that pairing tDCS with working memory training produces a more effective learning experience for patients with schizophrenia.
- Ongoing study is examining whether this pairing shows promise as a cognitively enhancing intervention for mild traumatic brain injury.

# Collaborators

Angus MacDonald

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Casey Gilmore

Greg Lamberty

Paul Thuras

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# Thank you for your attention!

# Questions?