Neurostimulation for Neuropsychiatric Disorders II
Matthew Sherwood

Disclosures

- No Conflicts of Interest
- eTMS – for investigational use only, breakthrough status with Wave Neuroscience for PTSD
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ACCELERATED ELECTROENCEPHALOGRAM (EEG) GUIDED TRANSCRANIAL MAGNETIC STIMULATION (ETMS) FOR POST-TRAUMATIC STRESS DISORDER (PTSD) IN VETERANS AND FIRST RESPONDERS

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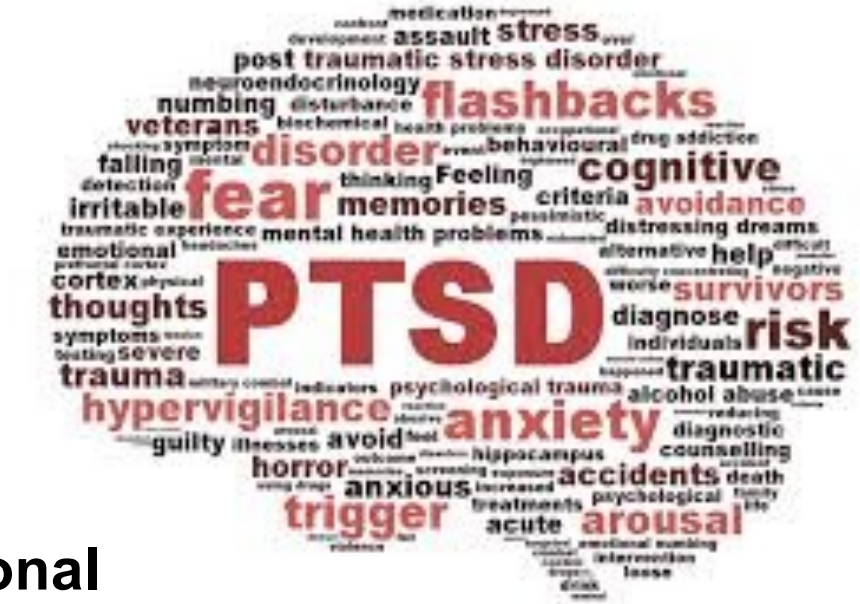
eTMS-PTSD-001
Electroencephalogram (EEG) Personalized Transcranial Magnetic Stimulation (eTMS) for Post-Traumatic Stress Disorder (eTMS for PTSD)

Clinical Trial Registry NCT06081309
FDA Protocol #G230168

Trauma exposure

Negative cognitions and mood

Arousal and reactivity



Intrusive memories

Avoidance

Sleep issues

Emotional Numbness

Flashbacks

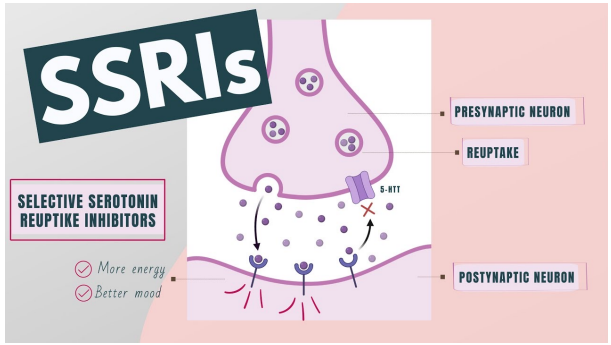
https://www.aspirehealthcorp.com/2019/02/post-traumatic-stress-disorder-ptsd/

(Taylor et al., 1998)

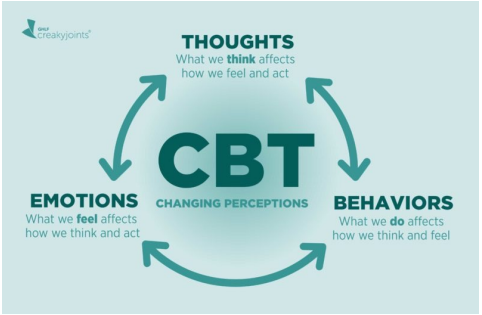
Current PTSD treatments:

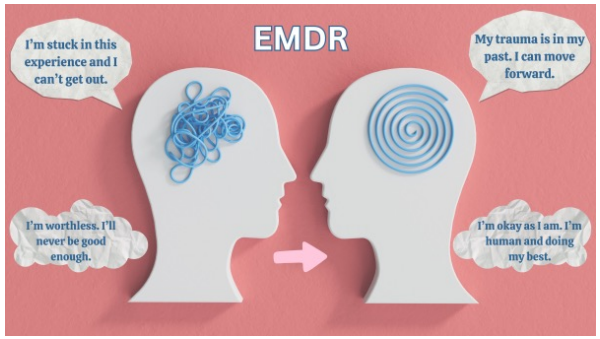
Pharmaceuticals

- Anti-depressants (SSRIs)
- Anti-anxiety



Psychotherapy



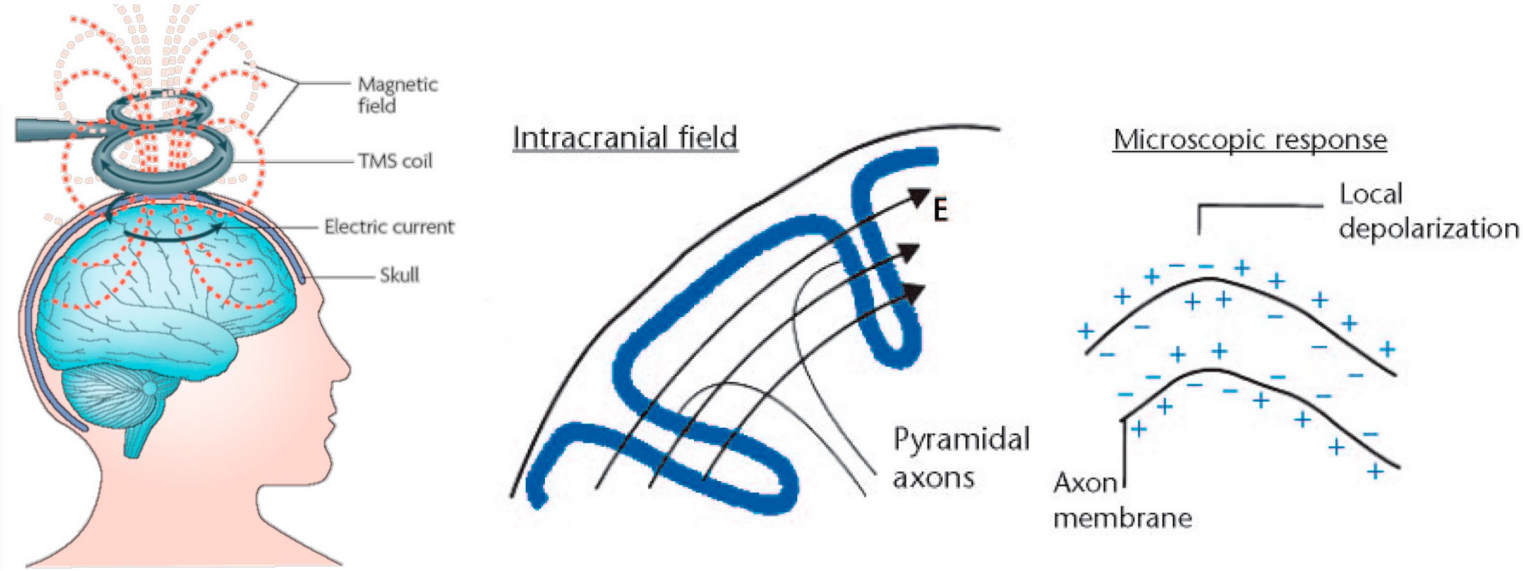


Outcomes are not as high as we would prefer

- Pharmacotherapy treats co-morbid symptoms not the root cause
- Reports of 30-50% of people do not optimally respond to to psychotherapy

https://mindfulmovementscounseling.com/healing-trauma-how-emdr-therapy-is-the-real-deal/
https://creakyjoints.org/living-with-arthritis/mental-health/cognitive-behavioral-therapy-for-arthritis/
https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.youtube.com%2Fwatch%3Fv%3DSwsWkTWJMTw&psig=AOvVaw1ov_tZhRWOSunK2bFb9XqD&ust=1761915618302000&source=images&cd=vfe&opi=89978449&ved=0CBYQjRxqFwoTCICkuli-y5ADFQAAAAAdAAAAABAE

What is Transcranial Magnetic Stimulation (TMS)?

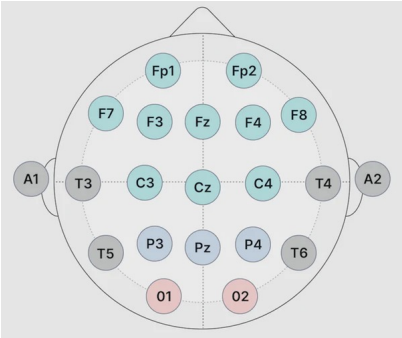


Neurons are depolarized by the electric field that accompanies the magnetic field which passes through the skull and scalp.

This magnetic field is “pulsed” to produce repeated depolarization, referred to as repetitive TMS (rTMS).

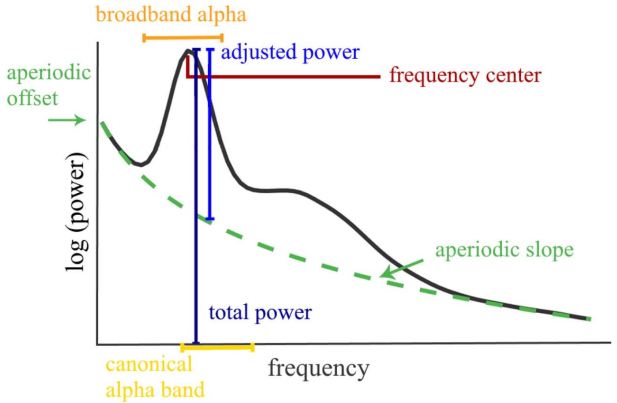
What is electroencephalogram TMS (eTMS)?

1. Collect EEG



Standard 10-20 system

2. Compute Individual Alpha



3. Conduct rTMS @ 80% MT

rTMS machine and treatment chair

Butterfly figure-8 coil

How does TMS apply to PTSD?

eTMS is NOT FDA approved for any indication, it's use is strictly off-label

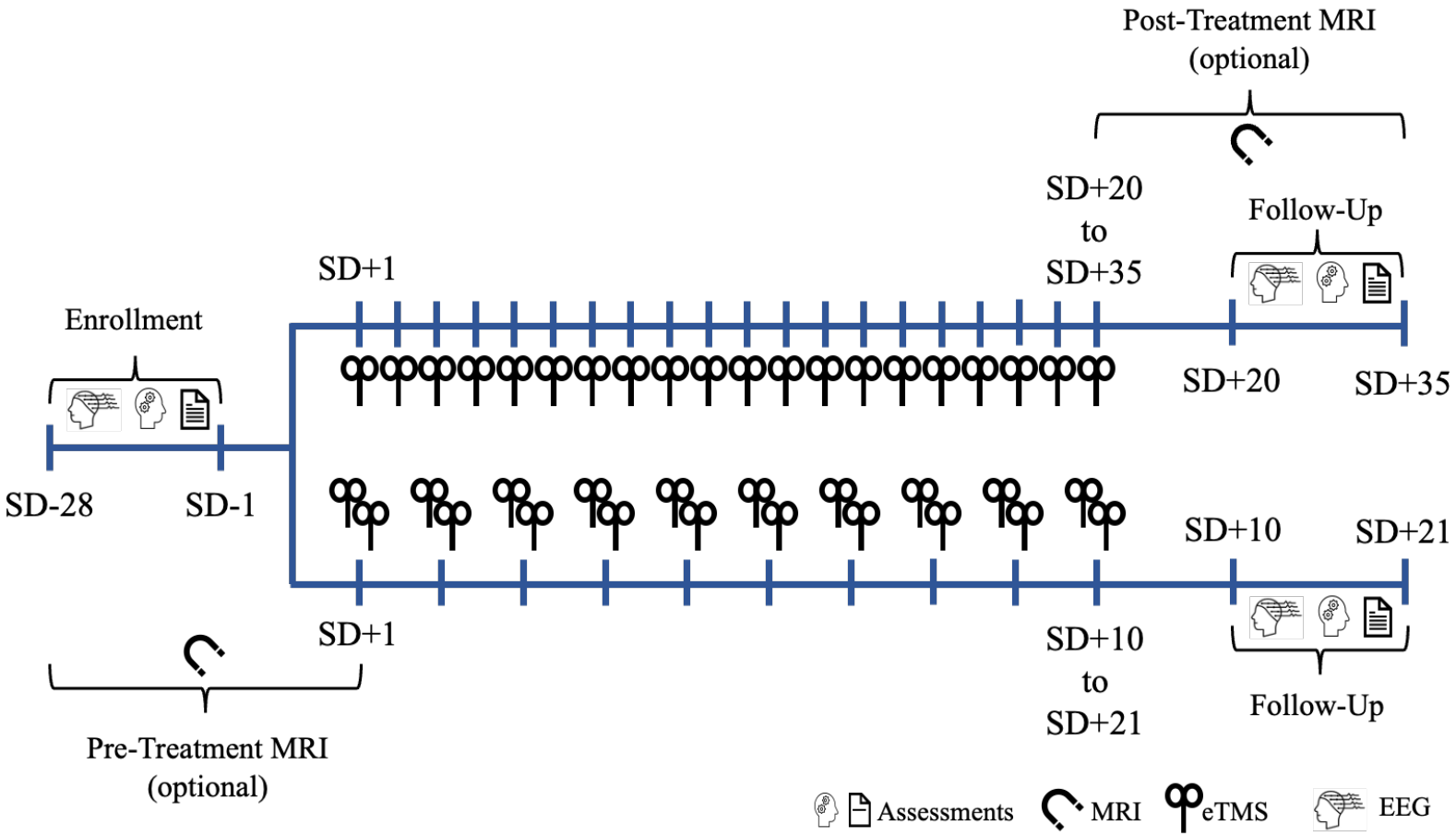
Synchronous neural activity, particularly alpha oscillations, have been observed in PTSD.

- Alpha oscillations support the default mode network (DMN) – a network dominating during rest
- Disruption of the DMN may underpin hypervigilance and sensory disinhibition symptoms in PTSD

The frequency of TMS may be adjusted to selectively target alpha oscillations to promote alpha synchronicity

https://pmc.ncbi.nlm.nih.gov/articles/PMC7405069/#:~:text=Significance%20Statement,network%2Dbased%20neural%20oscillatory%20interventions.
https://psychcentral.com/depression/treatment-of-depression-with-rtms

Methods



Assessments

- PCL-5*
- Braincheck*
- BPI*
- Audit*
- CGI*
- C-SSRS*
- DAST-10*
- DHQ*
- LEC-5
- MMSE
- OCS*
- Psych & Med History
- Concomitant Meds*
- OSU-TBI-ID
- PHQ-SADS*
- PSQI*
- VR-36*

*conducted at pre- and post-treatment

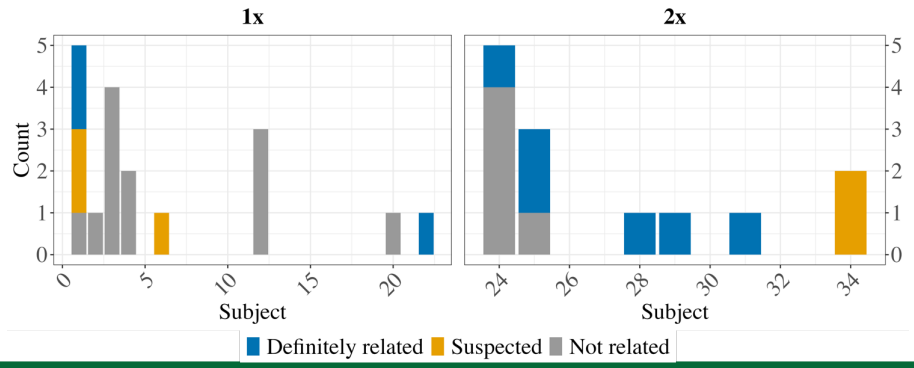
Demographics and eTMS Tolerance

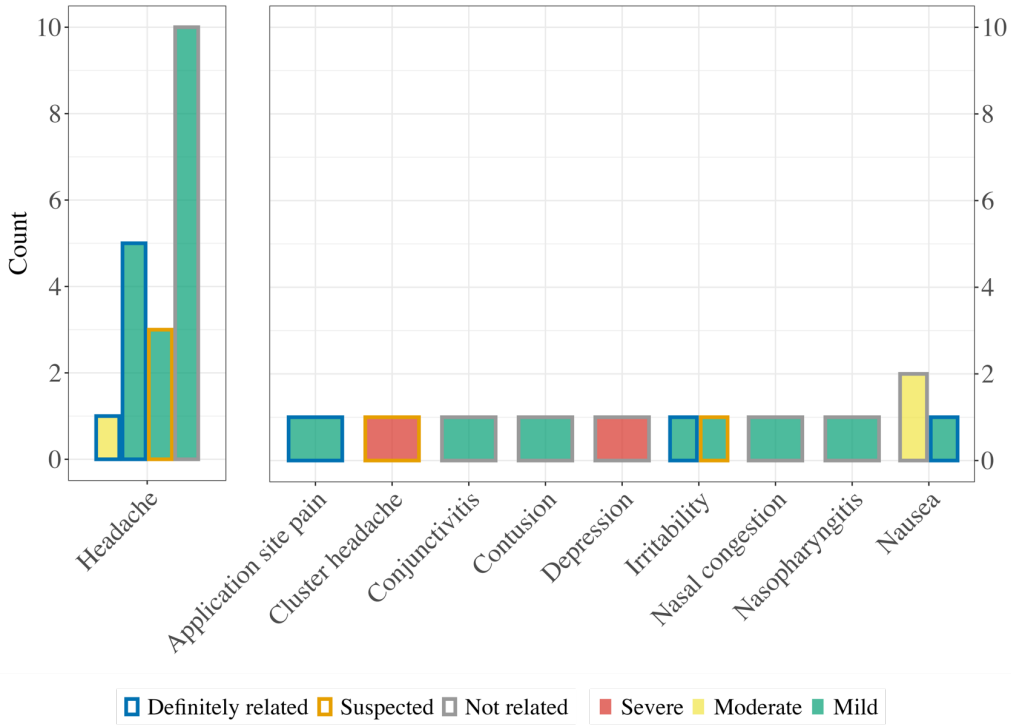
Demographics (ITT group)

- Mean Age: 42.7 years
- 6 Female, 24 Male
- 2 Hispanic/Latino, 28 Not Hispanic/Latino
- 1 American Indian or Alaska Native, 25 White, 3 more than one race, 1 unknown/not reported
- 22 Military (retiree or Veteran), 4 Firefighters, 6 Police Officers*

Adverse Events (ITT group)

- 31 Total AEs reported
- 14/30 participants reported >=1 AE





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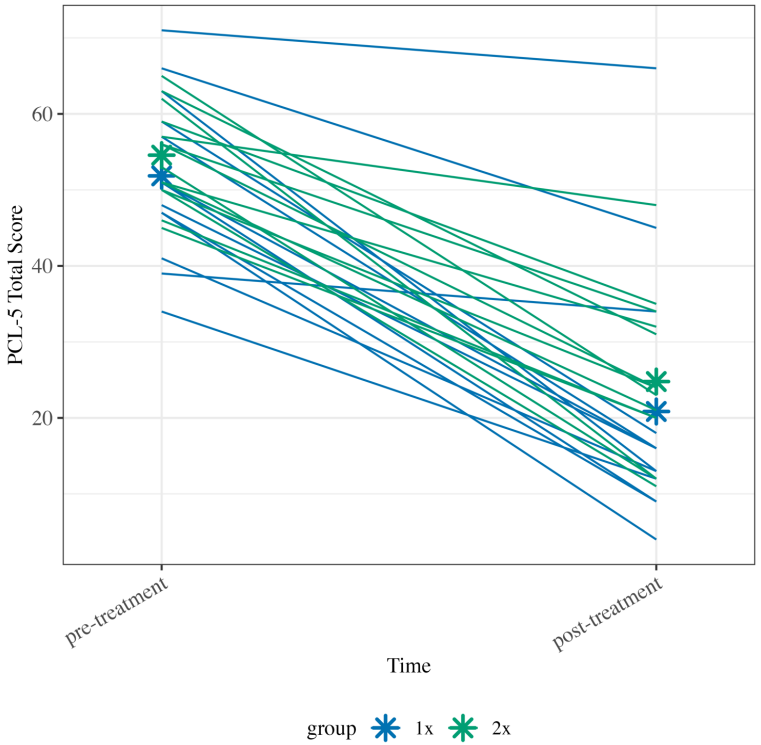
Behavioral Results



	Summary Statistics			Linear Mixed-Effects Model		
Variable	Mean Pre-Treatment	Mean Post-Treatment	SE	F(df)	p	η^2
1x	51.8	20.8	3.28			
2x	54.6	24.8	3.16			
Main Effect: Time				159.4(1,25)	< 0.001	0.864
Main Effect: Group				0.746(1,25)	0.396	0.029
Interaction: Group x Time				0.064(1,25)	0.803	0.003

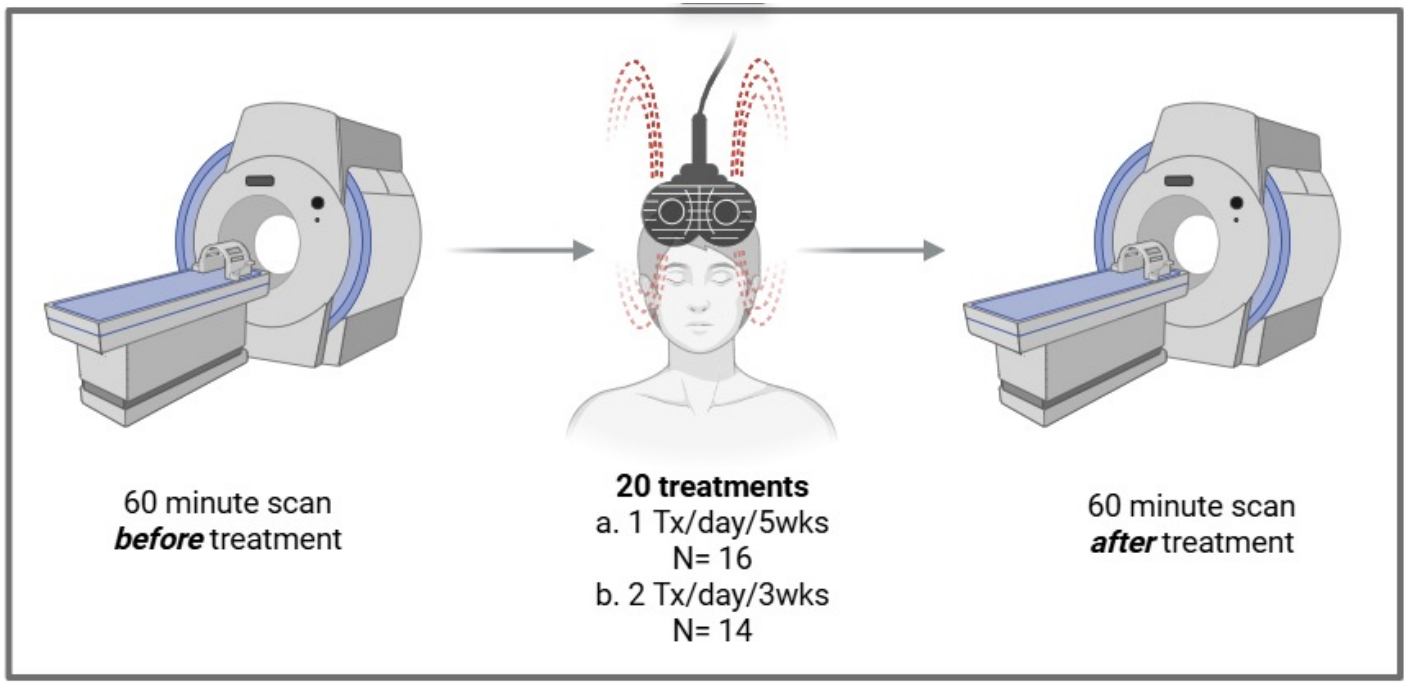
No significant difference between the 1x and 2x protocol.

	Summary Statistics			Pairwise Comparison	
	Mean Difference	SE	95% CI	t(df)	Sig (two-tailed)
PCL-5 Total Score	-30.393	2.407	[25.44, 35.35]	-12.625(25)	<.0001

Significant decrease in PCL-5 total score (PTSD symptomology).
Decrease on average of >30 points (>10 is clinically significant).

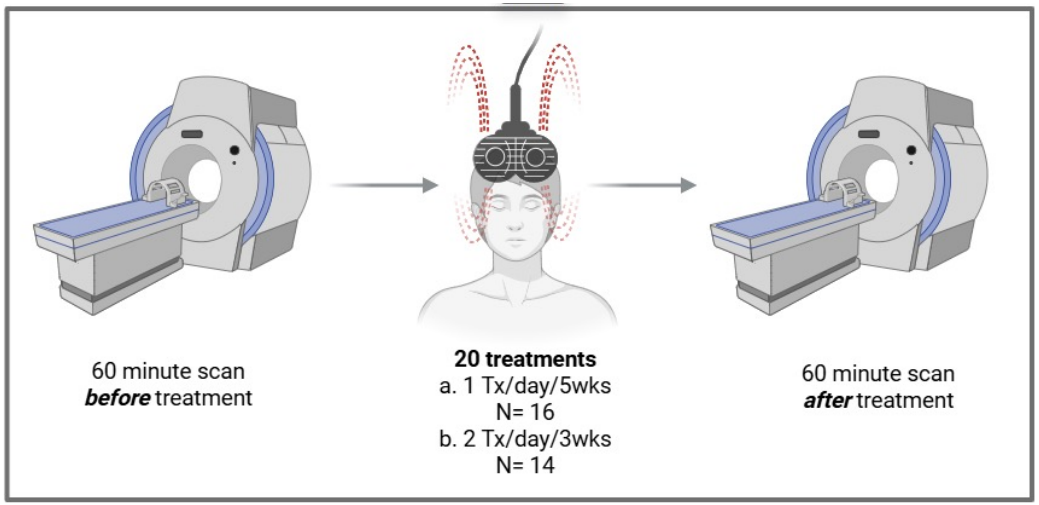
Participants (PP group):
One group (n=13) received 20 treatments once per day (1x)
One group (n=14) received 20 treatments twice per day (2x)

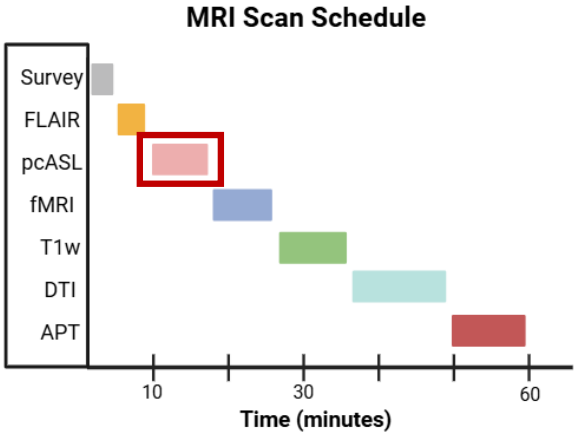
Stage 1 Concurrent MRI study



Participants: **16 of 26 completers first responders and/or veterans** that consented for the eTMS pilot clinical trial also consented to the separate **MRI study**. All participants were aged 25-62 (mean age= 40.6, 5 females).

Stage 1 Concurrent MRI study





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Participants completed 60-minute scans **pre- and post-eTMS treatment.**

What is Arterial Spin Labeling (ASL)?

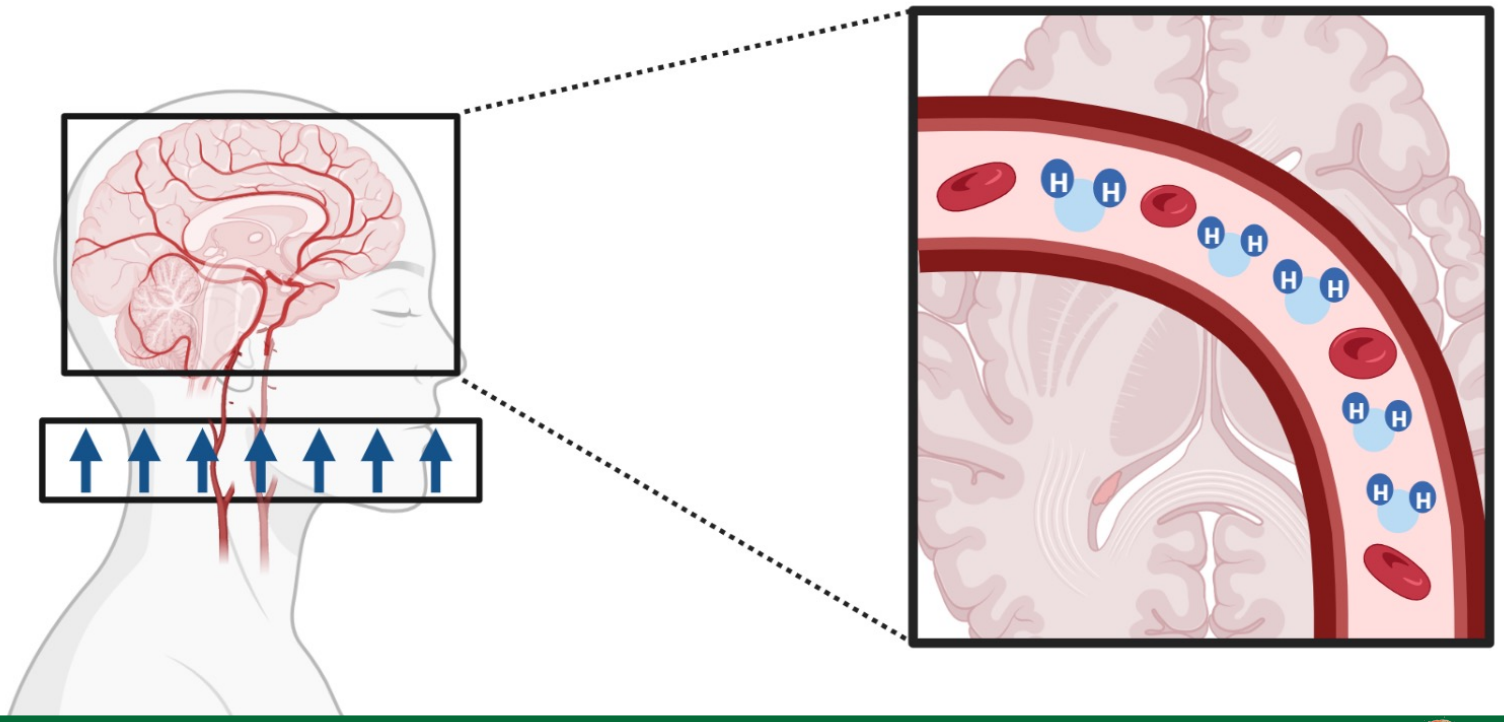
MRI technique that uses *inflowing arterial blood* as an endogenous contrast agent

Produces a quantitative map of cerebral perfusion (referred to as cerebral blood flow)

3D pseudocontinuous ASL (pcASL) is the clinical standard established in the literature[1]

[1]Alsop et al. (2015). doi: 10.1002/mrm.25197

How does ASL work?



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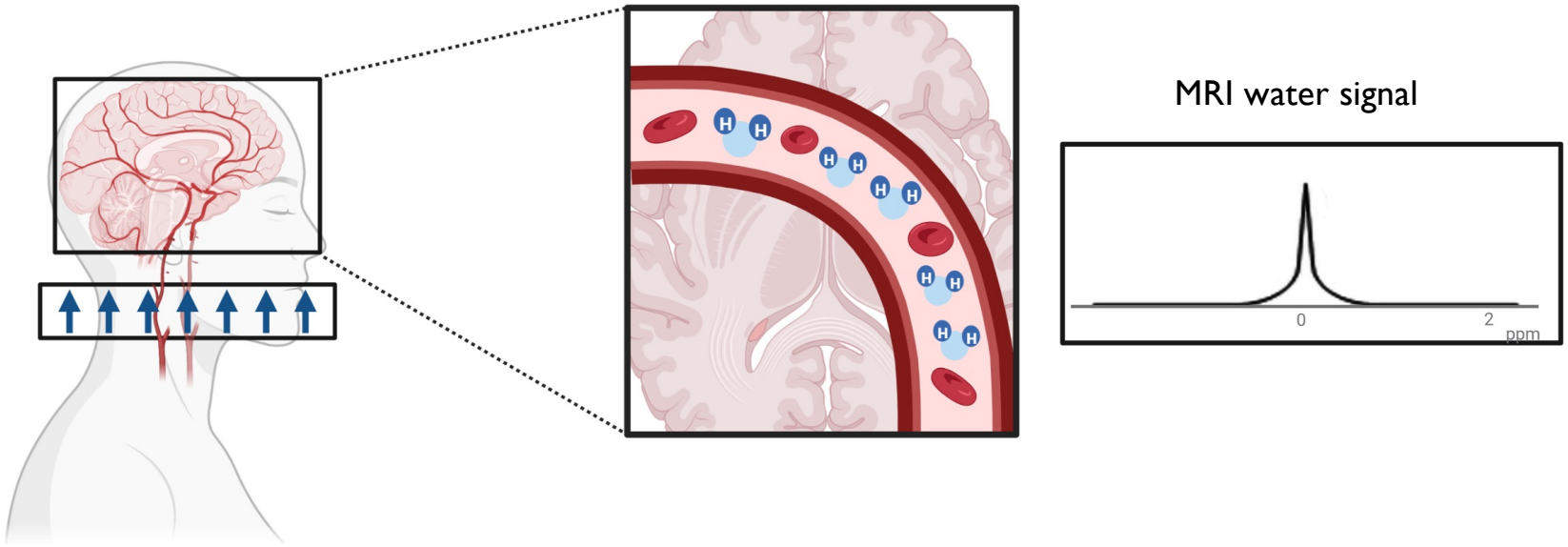

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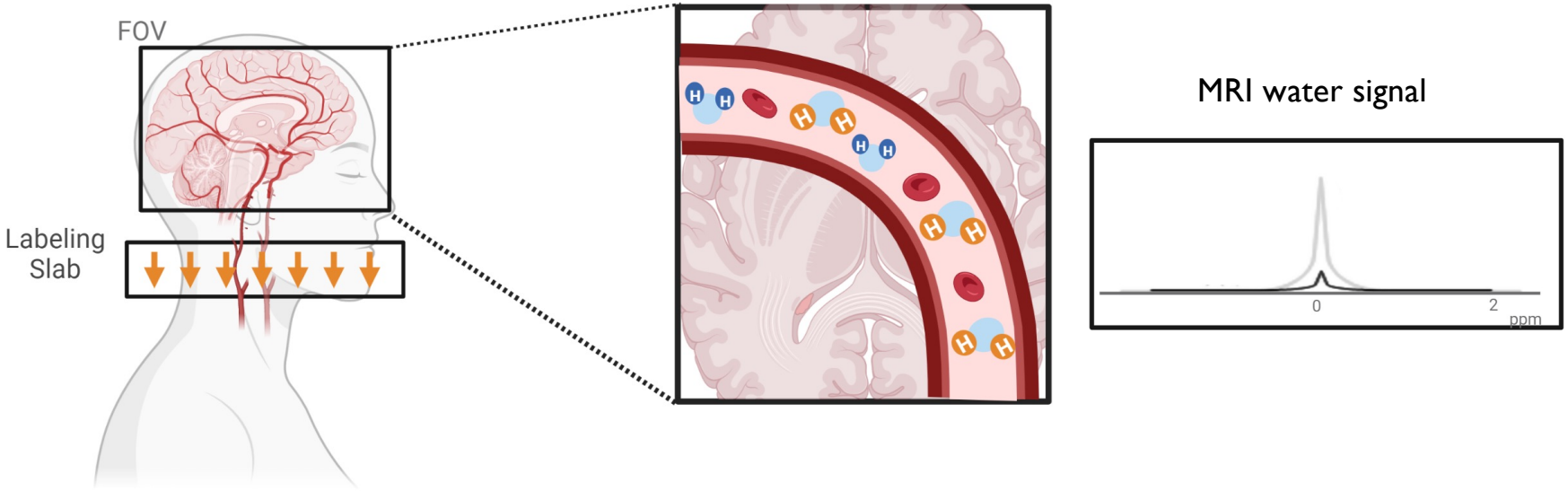


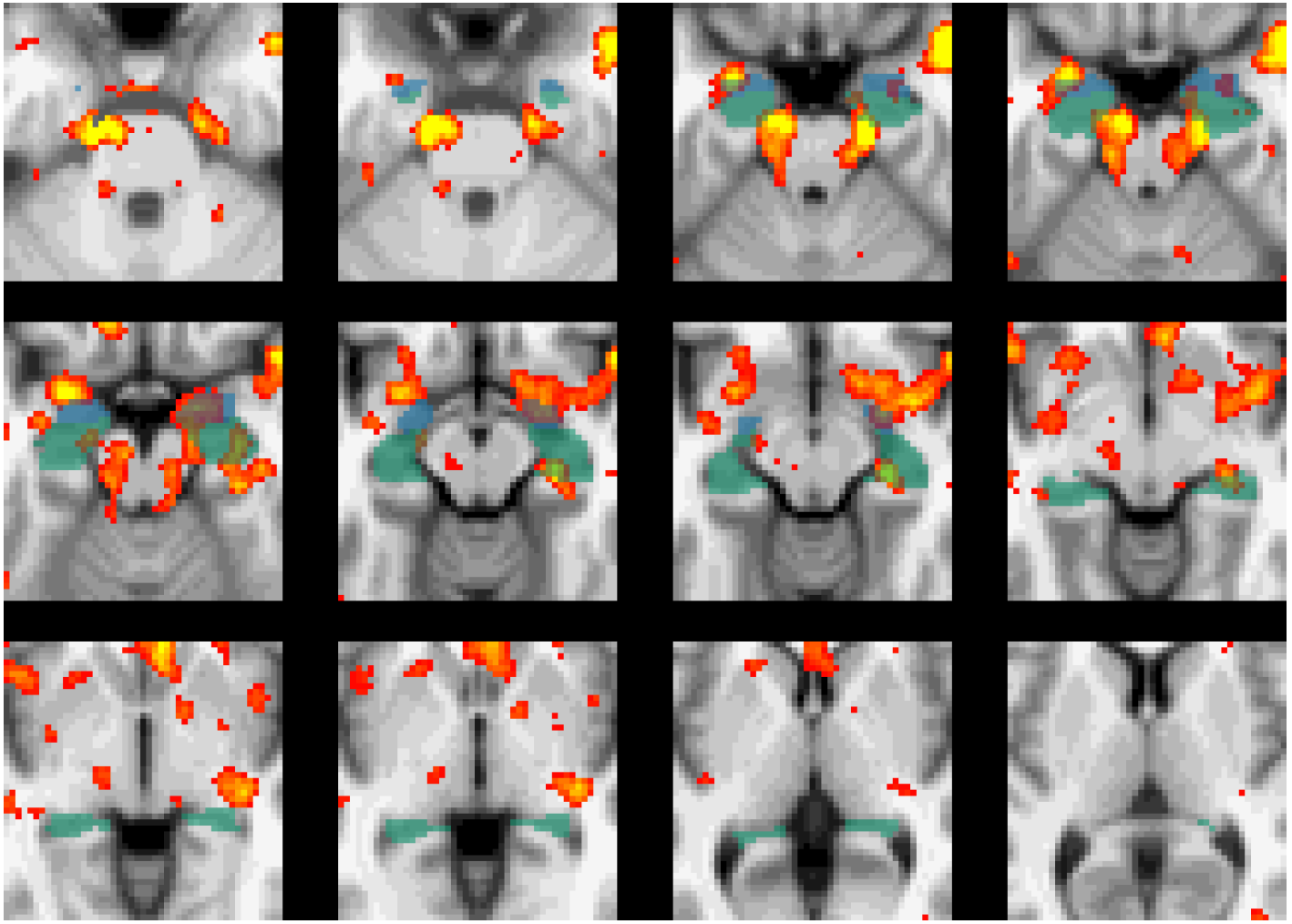
How does ASL work?

$$(SI_{control} - SI_{label})$$

$$CBF = \frac{6000 \cdot \lambda \cdot (SI_{control} - SI_{label}) \cdot e^{\frac{PLD}{T_{1,blood}}}}{2 \cdot \alpha \cdot T_{1,blood} \cdot SI_{PD} \cdot (1 - e^{-\frac{\tau}{T_{1,blood}}})} [ml/100g/min]$$

ASL Results

Subsample
16 Participants
- 9 from 1x
- 7 from 2x



rCBF Changes by Region: post - pre-treatment

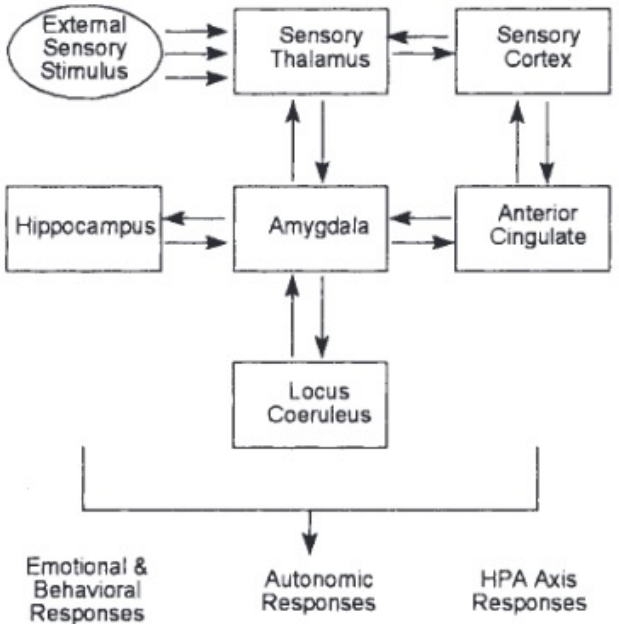
ROI	Hemisphere	rCBF
Superior Temporal Gyrus	Bilateral	increase
Transverse Temporal Gyrus	R	increase
Insula	Bilateral	increase
Medial/Rostral Cingulate	R	increase
Frontal Limbic Area	R	increase
Putamen	Bilateral	increase
Amygdala	L	increase
Hippocampus	L	increase
Anterior Cingulate	Bilateral	increase

- Right hemisphere is involved in emotions and the processing and integration of trauma recall
- Temporal Lobe structures play a critical role in the acquisition and extinction of conditioned fear and in the expression of associated autonomic arousal
- Recent evidence indicates that the insula is involved in emotional processes

PCL and rCBF Correlation: post - pre-treatment

ROI	Hemisphere
Amygdala	L
Anterior Cingulate	R
Insula	R
Hippocampus	L

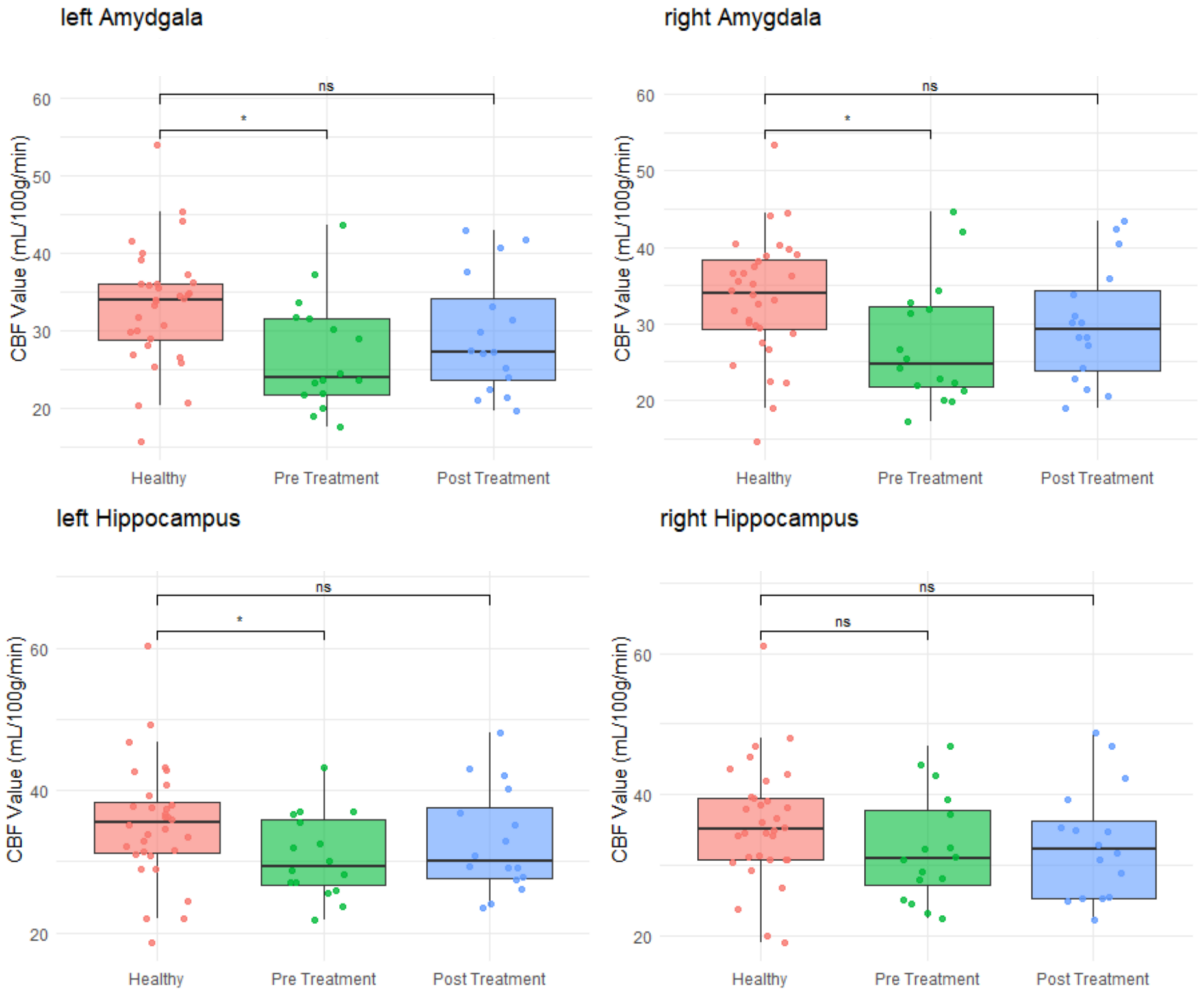
- Hippocampus through the amygdala may be important for internal imagery, including intrusive traumatic memories
- Studies have suggested that the anterior cingulate region has an important executive function in selecting of prioritizing stimuli (i.e., selective attention)
- Nuclei of the amygdala are considered an “essential link” in the neural circuitry involved in fear conditioning



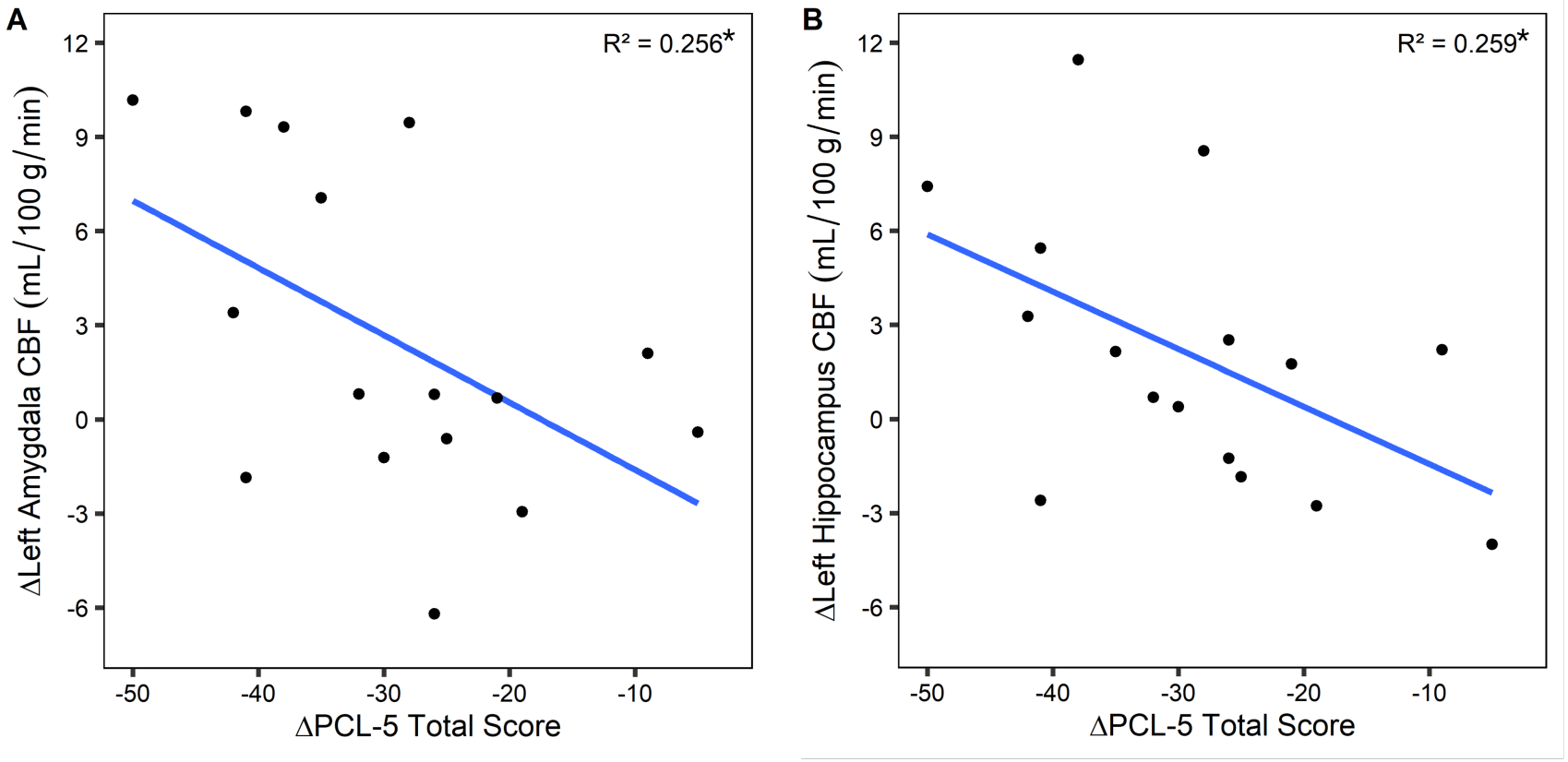
- A “fear circuitry” model of PTSD outlines amygdala and insula are hyperresponsive, thereby increasing fear and anxiety responses

Where is the current research with Perfusion and PTSD?

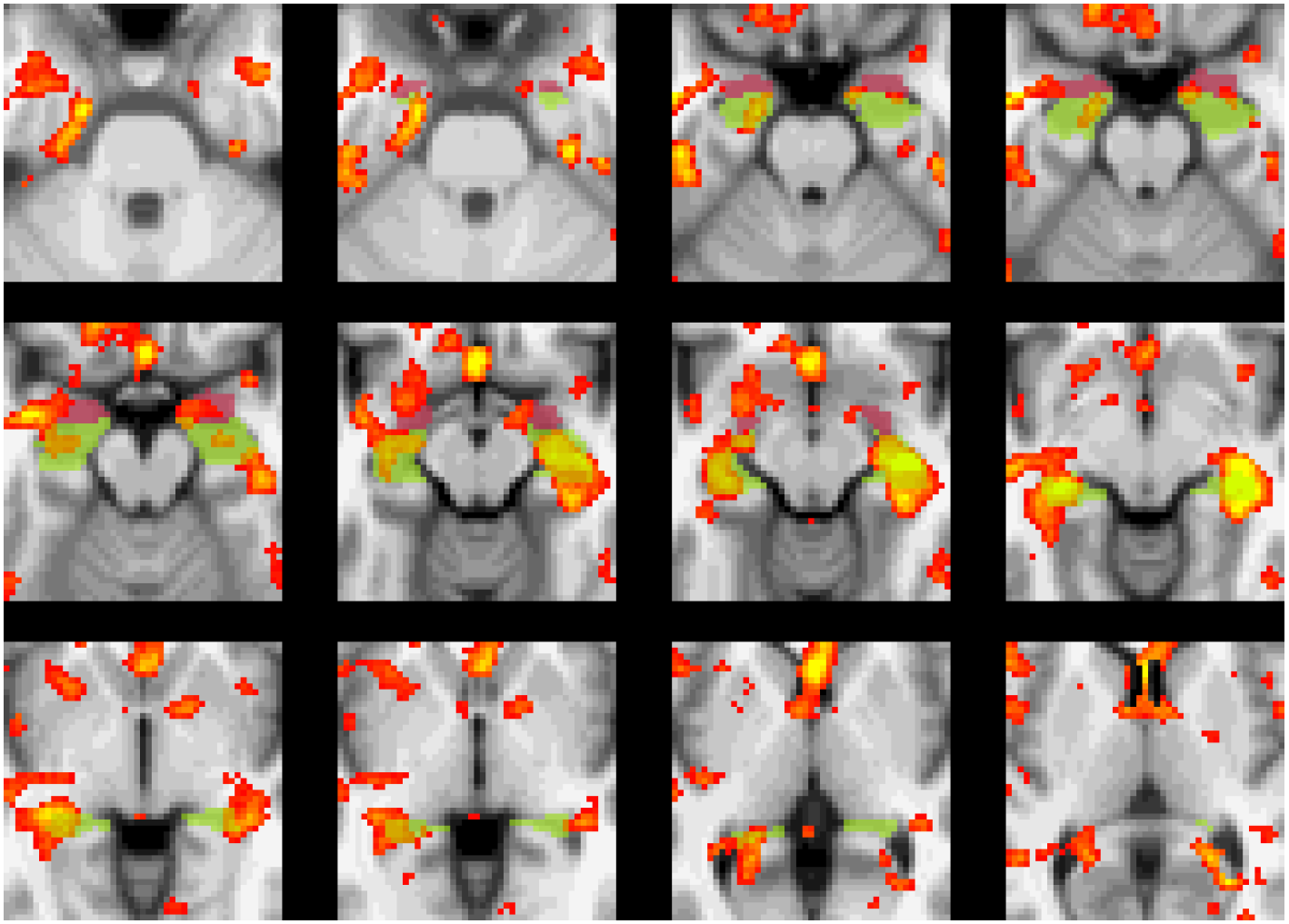
Publication	Aim	Population	Method	Result
Chung et al, 2006[9]	patients without re-exposure would exhibit alterations in regional CBF	Various N= 23	SPECT with Tc-99m- ECD	**Increased** rCBF in limbic regions and decreased rCBF in superior frontal, parietal and temporal regions
Sachinvala et al, 2000[11]	determine whether patients would exhibit alterations in regional CBF	Various N= 17	PET with Tc-99m-HMPAO	**Increase** in rCBF in limbic regions, cingulate, temporal, parietal, caudate/putamen, orbital and hippocampal
Zhe et al, 2016[10]	Determine regional CBF in resting patients with acute PTSD from the coal mine flood	Coal mine collapse survivors in China N= 30	pASL	**Decrease** rCBF in temporal lobe, r precuneus, r insula and r orbital medial frontal
Bonne et al, 2003[12]	Determine regional CBF in acute PTSD from a single event	Civilian traumatic events N= 11	SPECT and MR	**Increased** rCBF in cerebellum, precentral, increased cortisol levels


left Amydgala
right Amygdala
left Hippocampus
right Hippocampus
CBF Value (mL/100g/min)
Healthy
Pre Treatment
Post Treatment
ns
*

ASL Results



Perfusion Increases correlate with decreased PCL-5 scores



Summary

- Personalized, non-pharmacologic and non-invasive treatments are needed to address the complex disruptions caused by PTSD[7]

- Our study demonstrates that 20 sessions of personalized **eTMS** has promise in combating PTSD
  - Significantly lowered PCL-5 scores (>30 points on average)
  - Treatment at 80% motor threshold is well tolerated
  - Follow-on RCT for better evaluation of efficacy

- We know that alterations in **cerebral perfusion** of the amygdala, frontal cortex, limbic systems, and hippocampal cortex contribute to the associated symptomology of PTSD[3]
  - We revealed resting CBF in these regions **increased** following treatment suggesting these areas may be hypo-perfused in those suffering from PTSD
  - These increases were **correlated** with reductions in PTSD symptomology

SCAN FOR FULL SLIDES AND MORE

QUESTIONS?

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Multi-site Phase 2 RCT is underway

- 15 visits/30 eTMS treatments
- 80/110 participants randomized to date
- 70 completers

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