PTSD IN VETERANS AND FIRST RESPONDERS: FINDINGS FROM ASL-MRI FOLLOWING AN OPEN-LABEL ETMS STUDY

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eTMS-PTSD-001

ELECTROENCEPHALOGRAM (EEG) PERSONALIZED TRANSCRANIAL MAGNETIC STIMULATION (ETMS) FOR POST-TRAUMATIC STRESS DISORDER (ETMS FOR PTSD)

(NCT06081309)

eTMS-PTSD-001 Stage 2

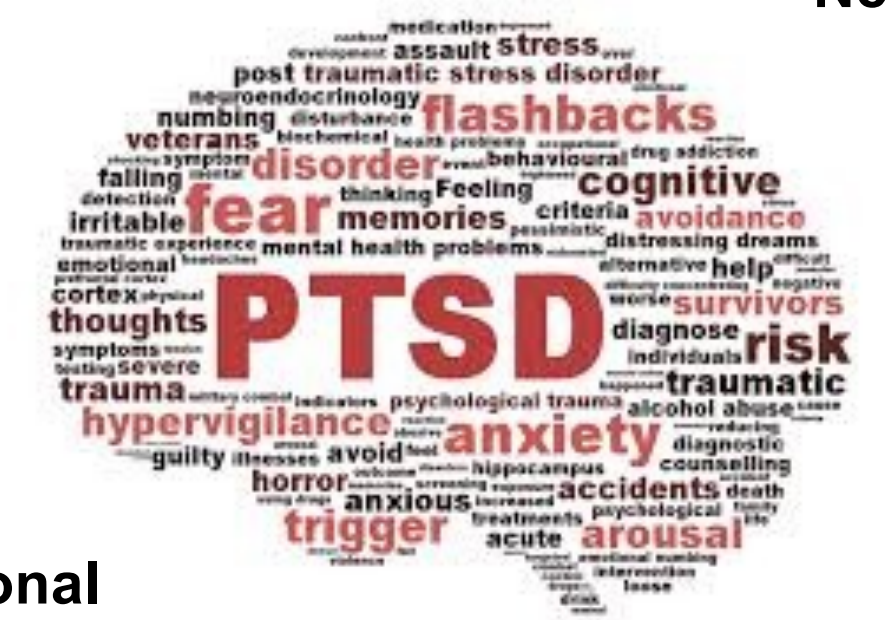
A RANDOMIZED CONTROLLED TRIAL OF ELECTROENCEPHALOGRAM (EEG) PERSONALIZED TRANSCRANIAL MAGNETIC STIMULATION (ETMS) FOR POST-TRAUMATIC STRESS DISORDER (ETMS FOR PTSD)

(NCT06892028)

Trauma exposure

Negative cognitions and mood

Arousal and reactivity



Intrusive memories

Avoidance

Sleep issues

Emotional Numbness

Flashbacks

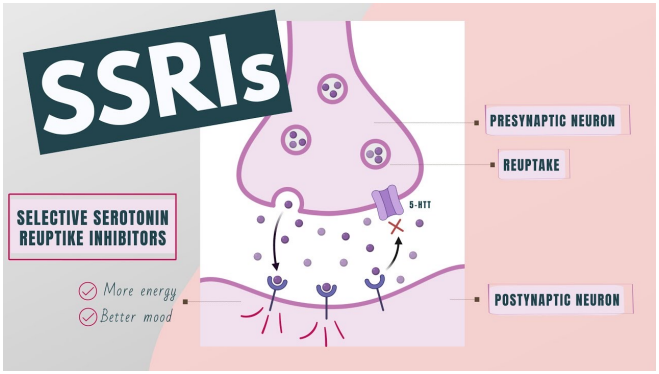
(Taylor et al., 1998)

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

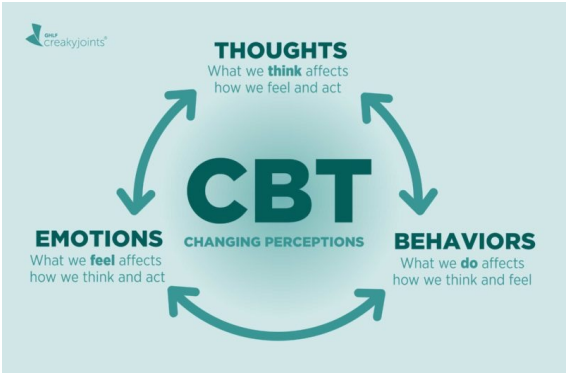
Current PTSD treatments:

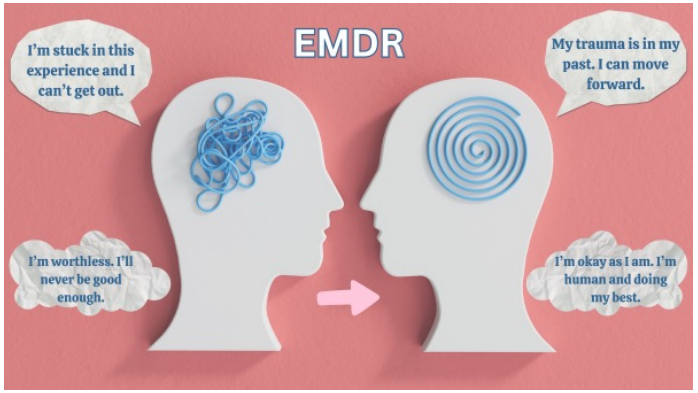
Medications

- Anti-depressants (SSRIs)
- Anti-anxiety



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=0CBYQjRxqFwoTCJCkulj-y5ADFQAAAAAdAAAAABAE

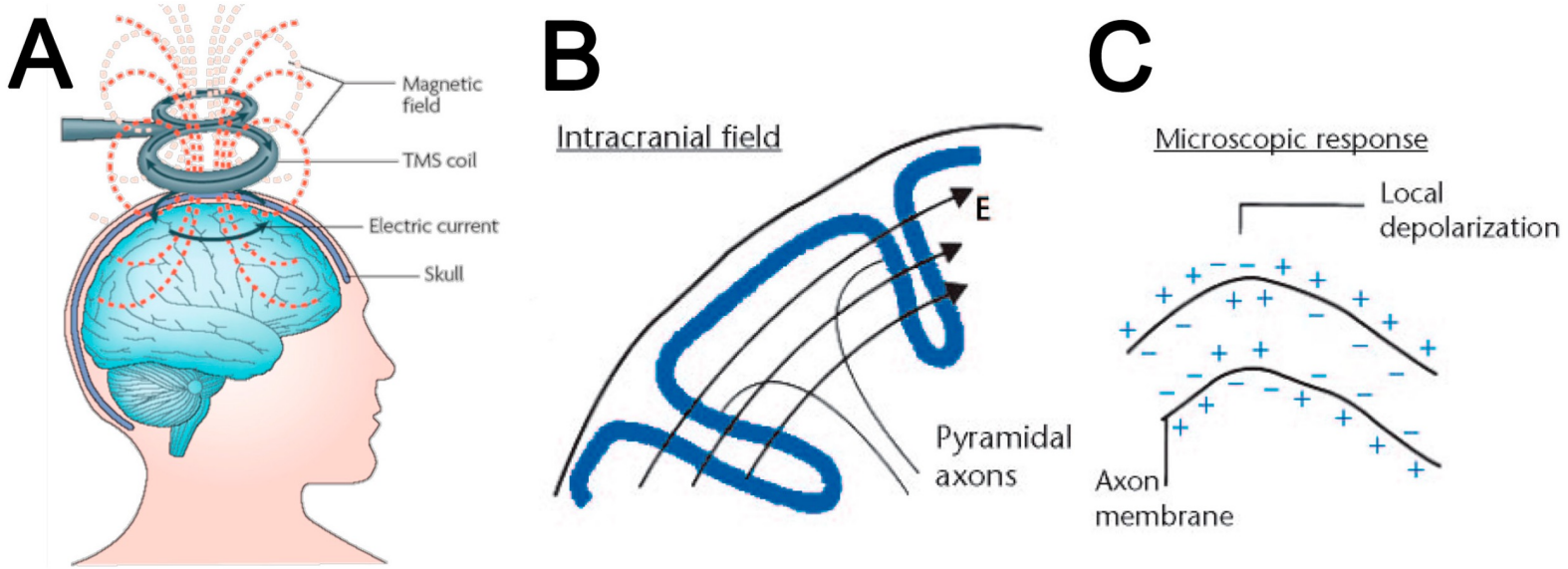
Current PTSD treatments:

Outcomes are not as high as we would prefer

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

https://psycnet.apa.org/fulltext/2024-93459-001.html

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).

https://www.mdpi.com/1422-0067/24/22/16456

How does TMS apply to PTSD?

rTMS is NOT FDA approved for PTSD, but it is approved for MDD.

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

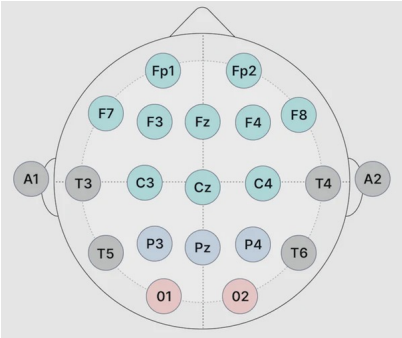
- Alpha oscillations support the default mode network (DMN) – a network dominating during rest
- Disruption of the DMN may underpin hypervigilance and sensory disinhibition symptoms in PTSD

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

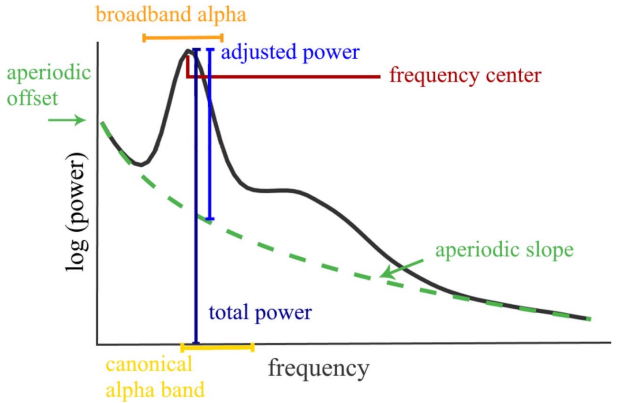
What is electroencephalogram TMS (eTMS)?

1. Collect EEG



Standard 10-20 system

2. Compute Individual Alpha



3. Conduct rTMS

rTMS machine and treatment chair

Butterfly figure-8 coil

Stage 1 Open Label Trial

Baseline: **Determine eligibility**

PCL-5 total score > 1

20 eTMS Treatments

16 participants completed 1 treatment per day
(must be completed within 35 total days)

14 participants completed 2 treatments per day
(must be completed within 21 total days)

1 Follow-Up Visit

No less than 2 hours after last treatment and within the treatment window

	Enrollment		Randomized Study Treatment in Clinic		Follow-Up (F) Evaluations		
Procedures	**SC**	**BL**	**Day 1**	**Days 2 through 35**	**(F1)**	**(F2)**	**(F3)**
Acceptable windows	RD-28 to RD-2	RD-28 to RD-1	RD+1	RD+2 to RD+35	RD+20 to RD+35	RD+71 to RD+77	RD+176 to RD+196
Phone Screen	X						
Informed Consent	X						
MMSE, TMSs		X					
Demographics		X					
DHQ, BPI		X			X		
LEC-5, OSU-TBI-ID		X					
Medical History/Physical, CGI		X			X	X	X
Braincheck		X	X		X		
VR-36, PCL-5		X			X	X	X
PHQ-SADS, AUDIT, DAST-10, OCS, PSQI		X			X		
CSSRS		X			X	X	X
Concomitant Treatments, Medications, Illicit Drug and Alcohol Use		X	X	X	X	X	X
SEQ/AEs		X	X	X	X	X	X
EEG		X			X		
MT			X				
eTMS: (Active/Sham)			X	X			

Stage 1 Open Label Trial

Demographics

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*

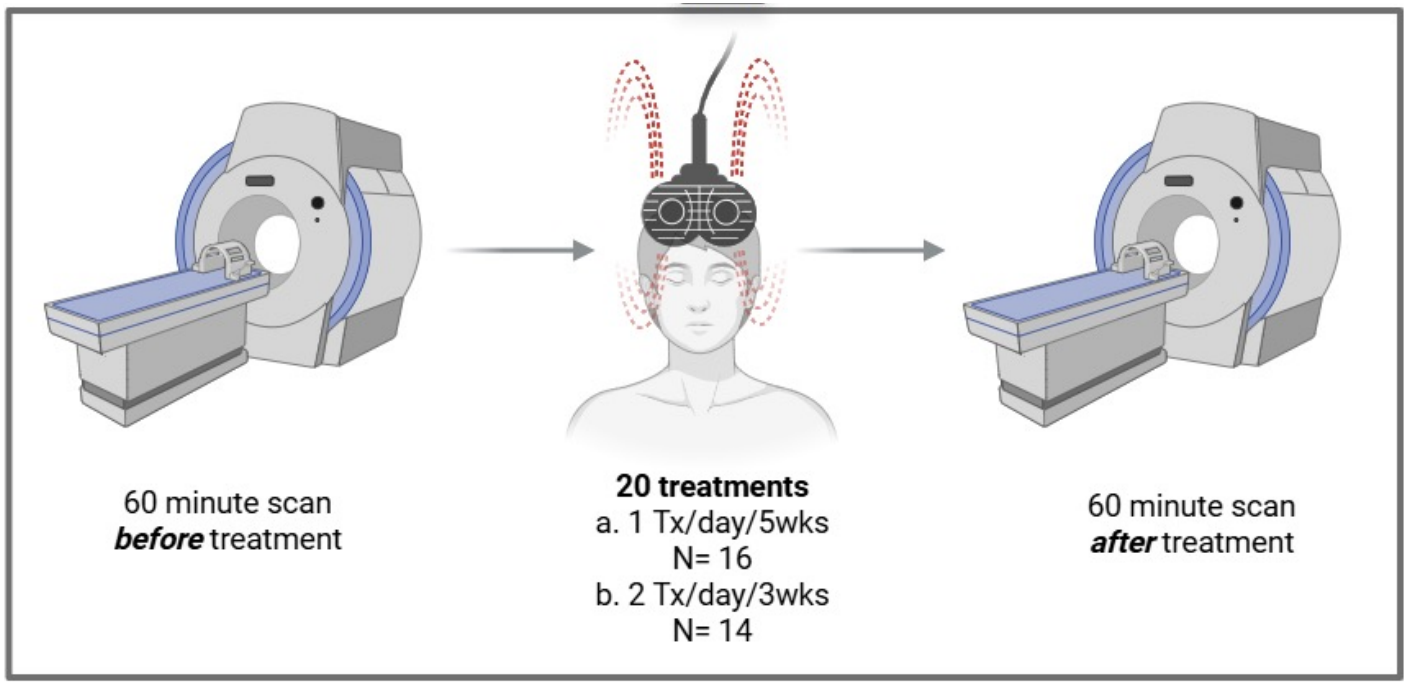
Adverse Events

14/30 reported at least 1 AE
26 Mild, 3 Moderate, 2 Severe
17/31 Not related to treatment, 5/31 suspected relationship, 9/31 definitely related
Observed AEs were: headache (20), irritability (2), short-term sadness (1), local site pain (1)

Primary Outcome: PCL-5 (26 completers)

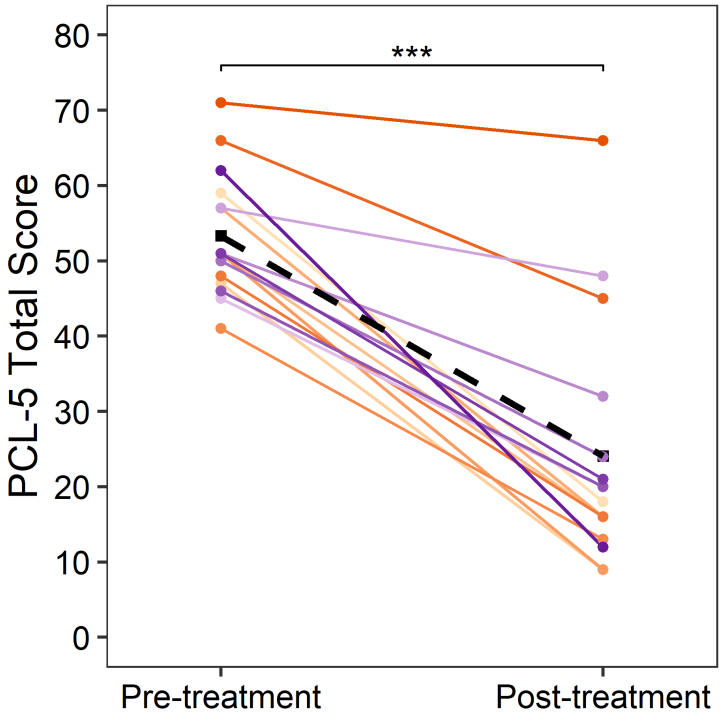
Baseline mean	52.2 +/- 8.9
Follow-up mean	22.9 +/- 14.0
Mean Change	**29.3 +/- 13.1**

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).

Behavioral Results



	Pre-treatment		Post-treatment		Mixed-Model ANOVA		
Variable	M	SD	M	SD	F(df)	p	η^2
1x	54.56	9.59	23.11	19.36			
2x	51.71	5.99	25.29	11.64			
Interaction: Group x Time					0.66(1,14)	0.43	0.045
Main Effect: Group					0.003(1,14)	0.955	0

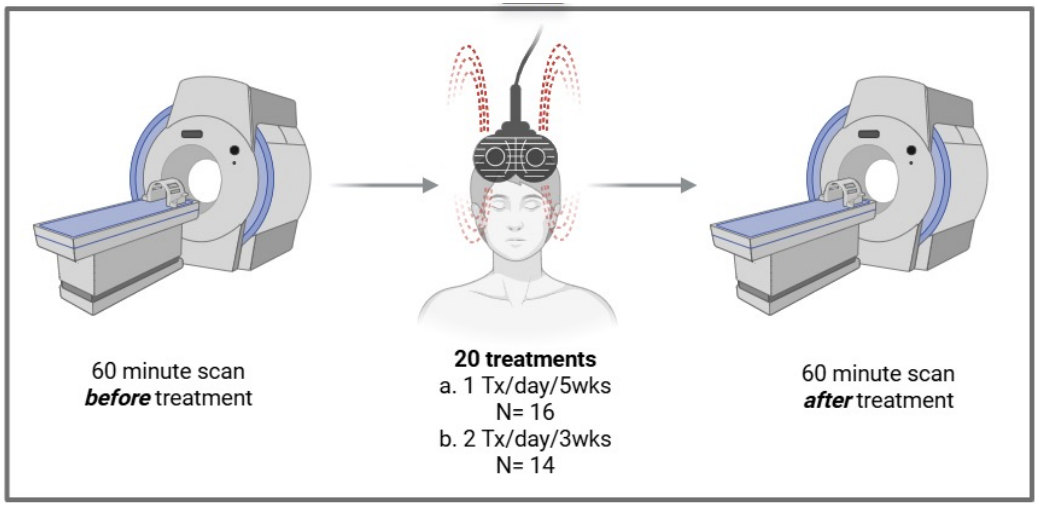
No significant difference between the 1x and 2x protocol.

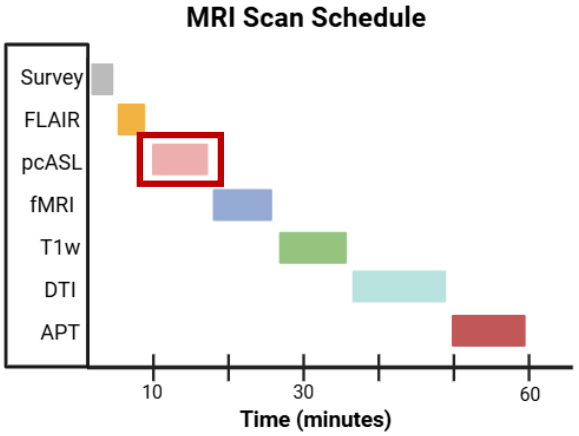
	Pre-Treatment		Post-Treatment		Post- Minus Pre-Treatment		Paired t-test	
	M	SD	M	SD	M	SD	t(df)	Sig(one-tailed)
PCL-5 Total Score	53.31	8.10	24.06	15.98	-29.25	12.11	-9.66(15)	<.001

Significant decrease in PCL-5 total score (PTSD symptomology). Decrease on average of 24 points (>10 is clinically significant).

Participants: One group (n=9) received 20 treatments once per day, the other (n=7) received 20 treatments twice per day.

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).

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

What is Arterial Spin Labeling (ASL)?

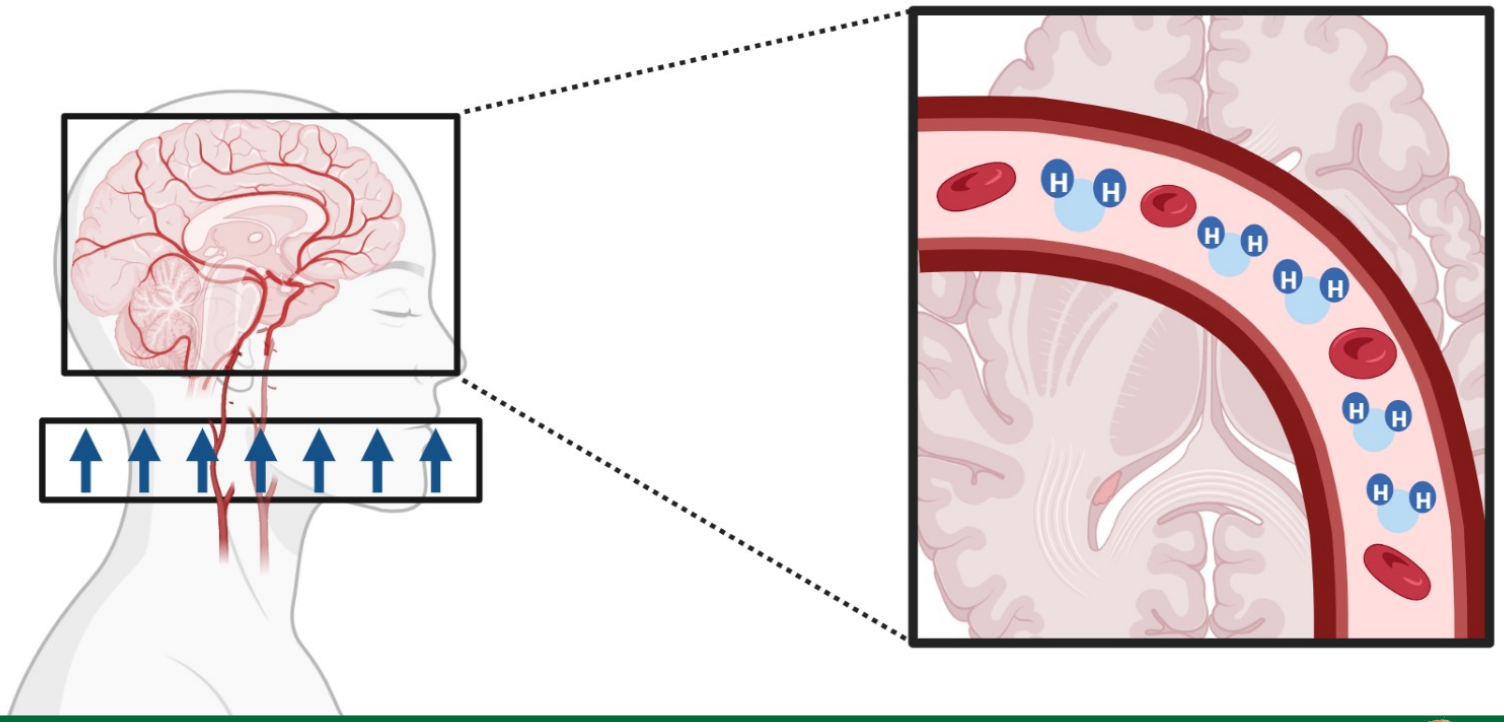
MRI technique that uses *inflowing arterial blood* as an endogenous contrast agent

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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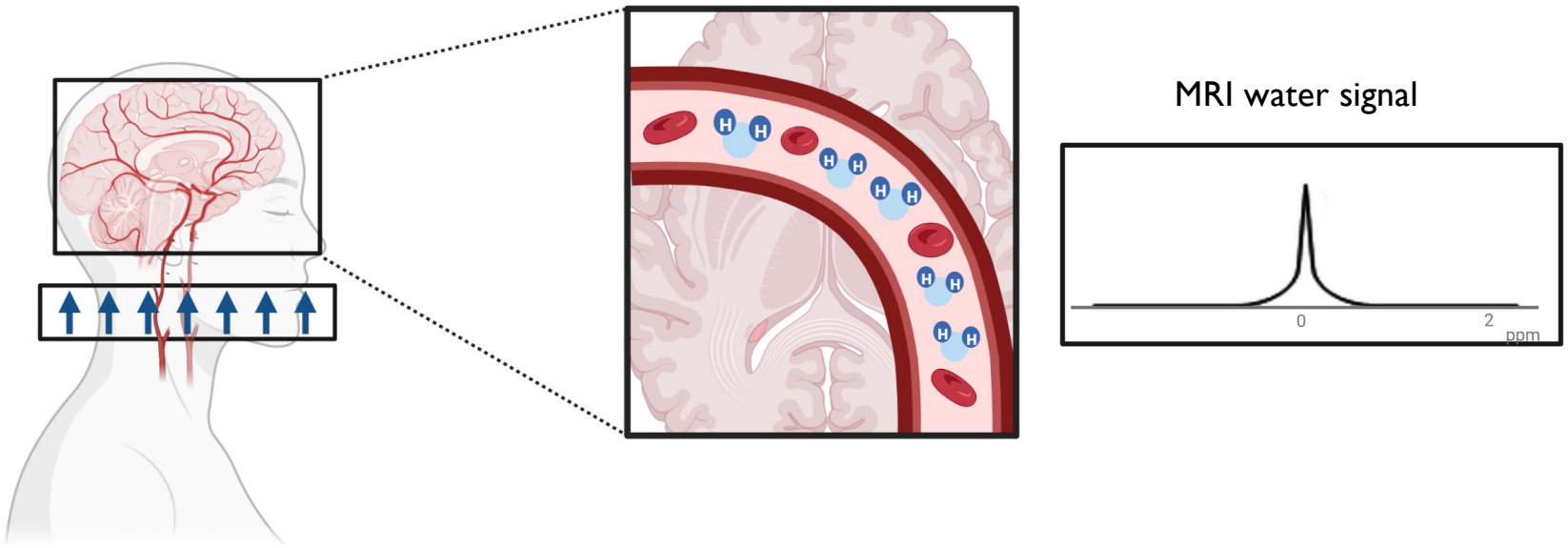

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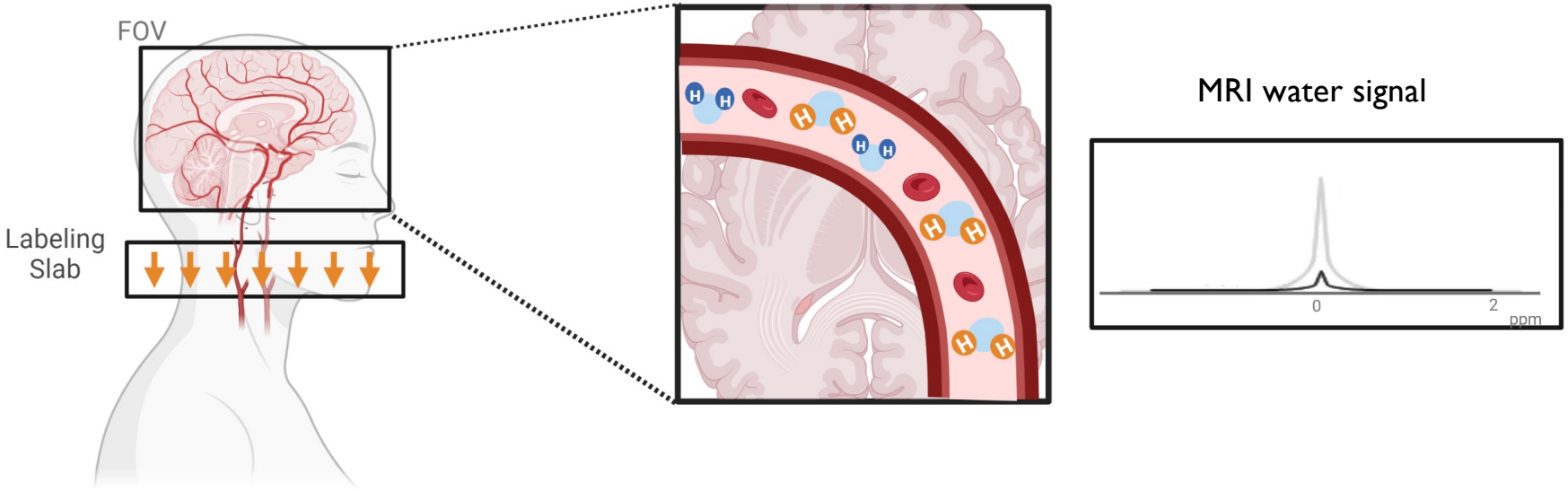
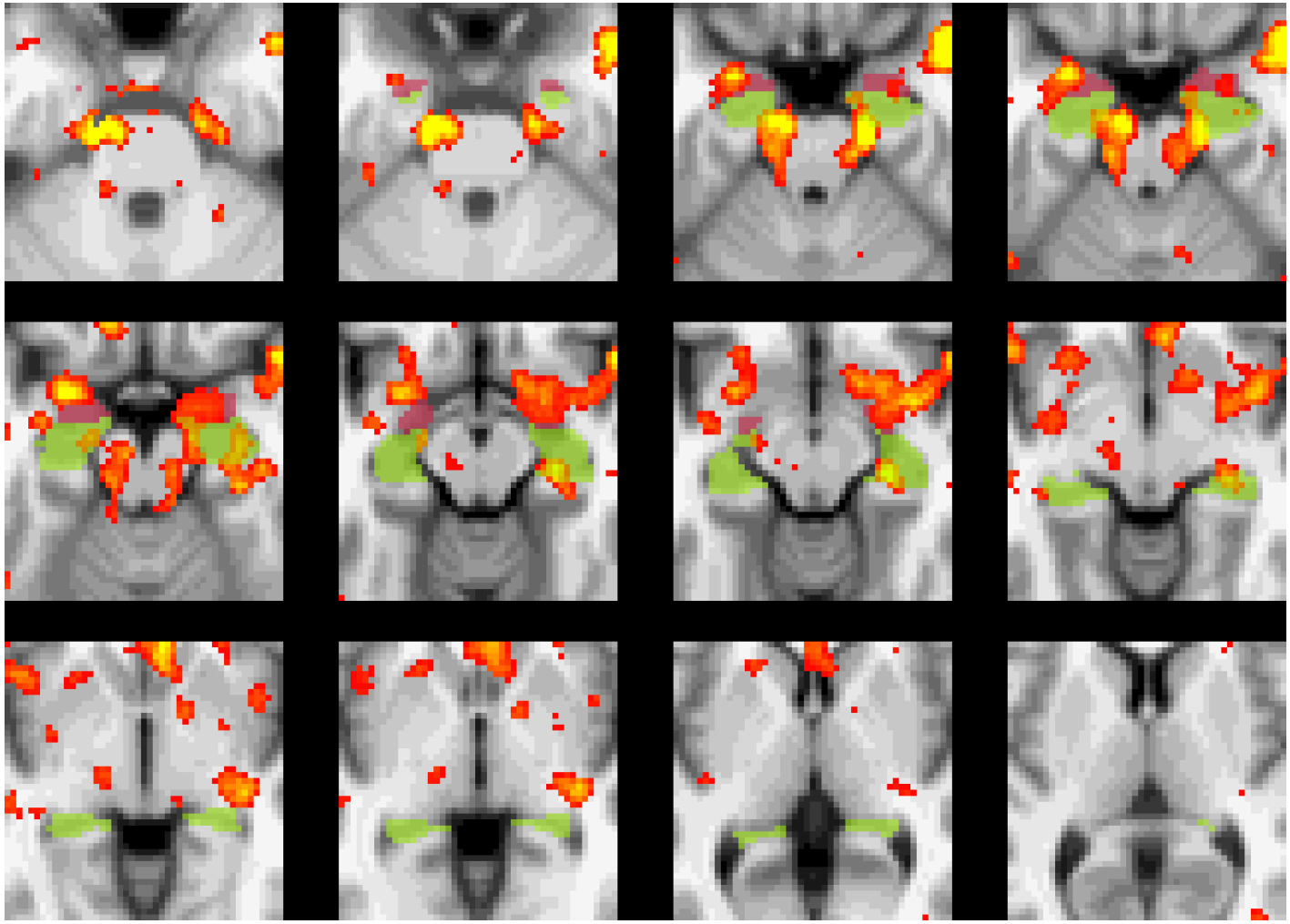


How does ASL work?

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

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

ASL perfusion increases post-eTMS



rCBF Changes by Region: post - pre-treatment

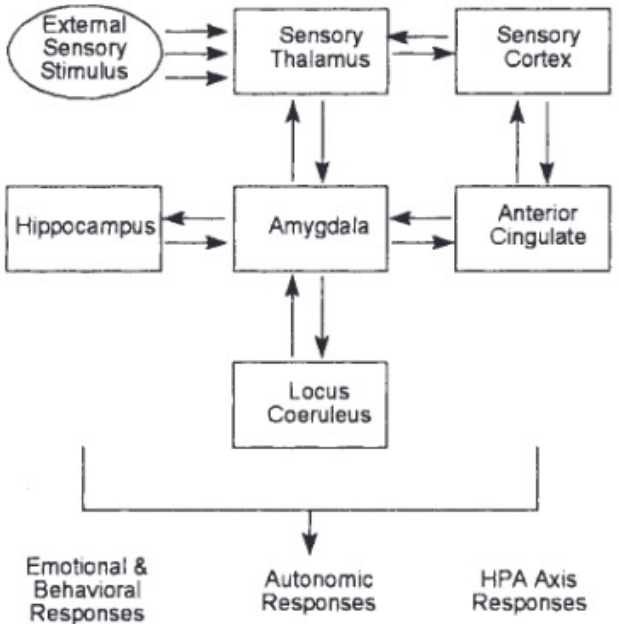
ROI	Hemisphere	rCBF
Superior Temporal Gyrus	Bilateral	increase
Transverse Temporal Gyrus	R	increase
Insula	Bilateral	increase
Medial/Rostral Cingulate	R	increase
Frontal Limbic Area	R	increase
Putamen	Bilateral	increase
Amygdala	L	increase
Hippocampus	L	increase
Anterior Cingulate	Bilateral	increase

- 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

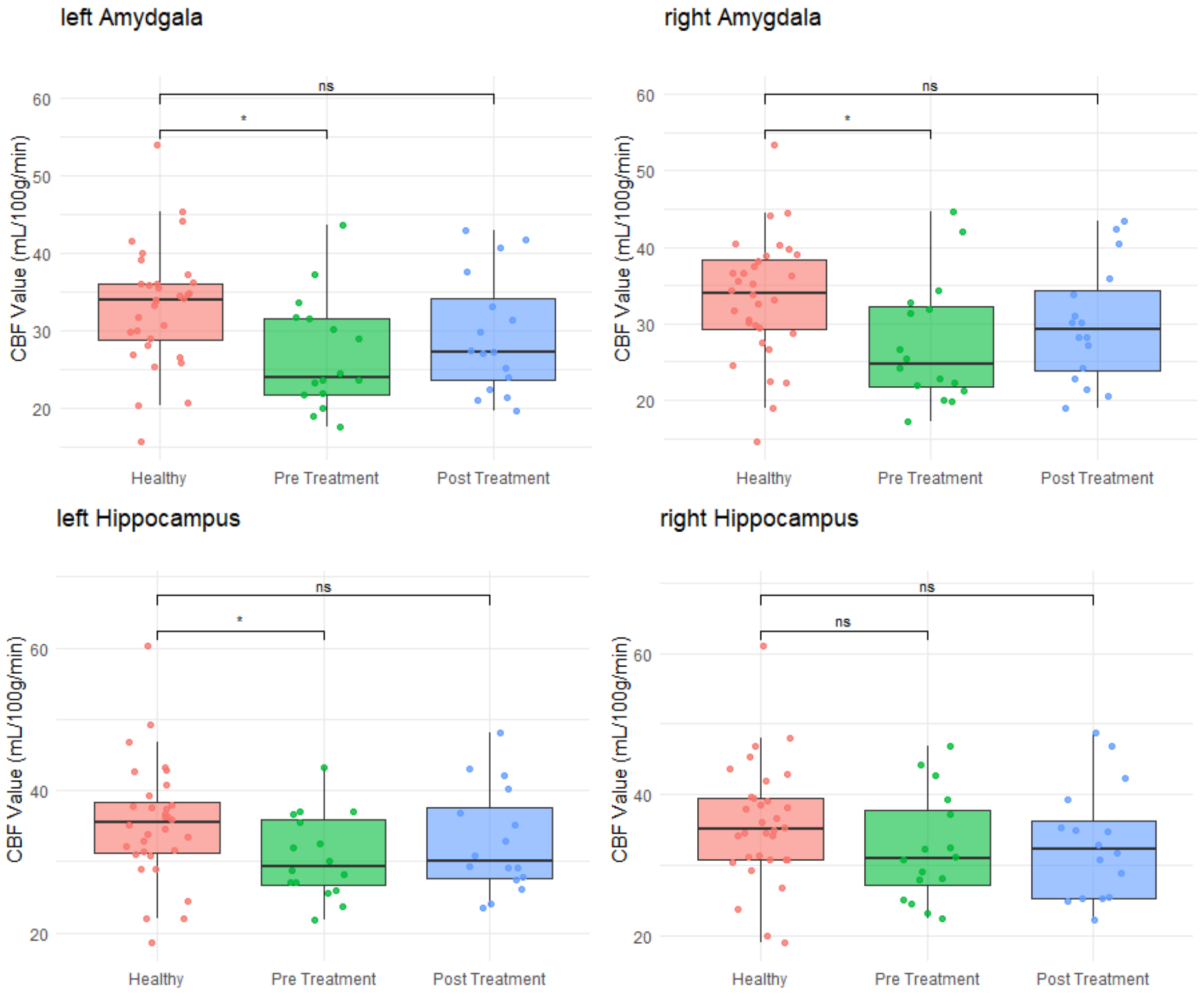
- Hippocampus through the amygdala may be important for internal imagery, including intrusive traumatic memories
- Studies have suggested that the anterior cingulate region has an important executive function in selecting of prioritizing stimuli (i.e., selective attention)
- Nuclei of the amygdala are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

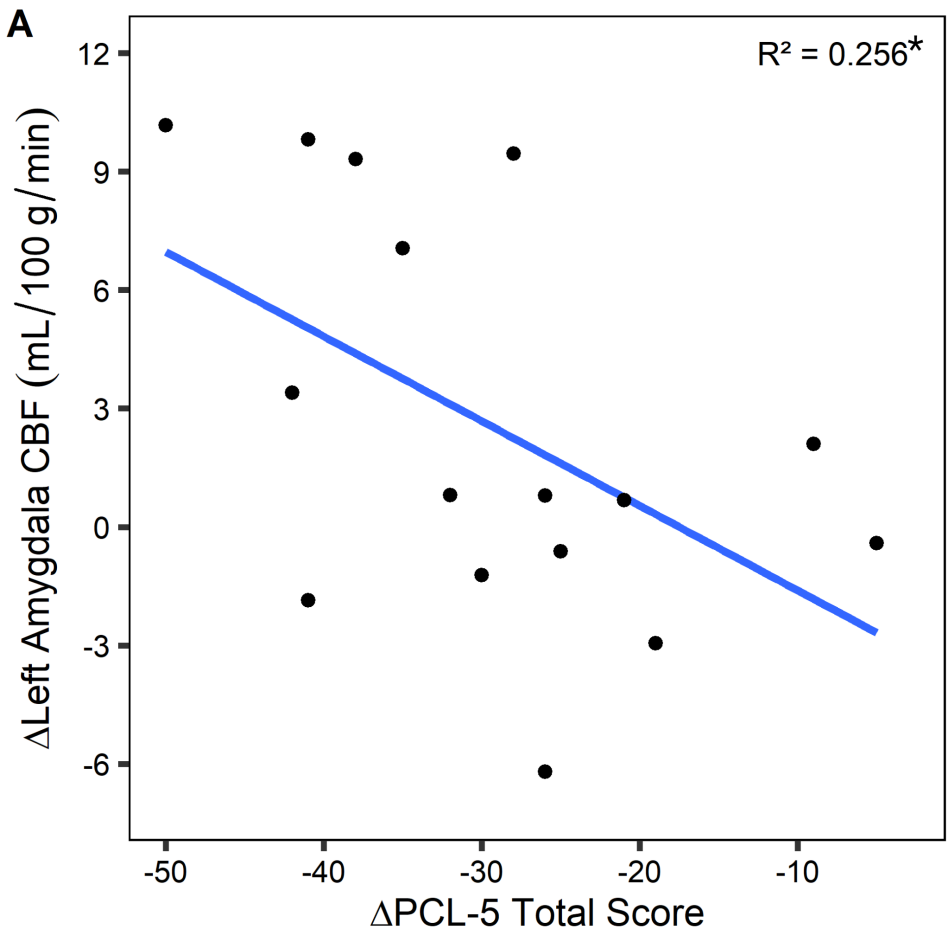


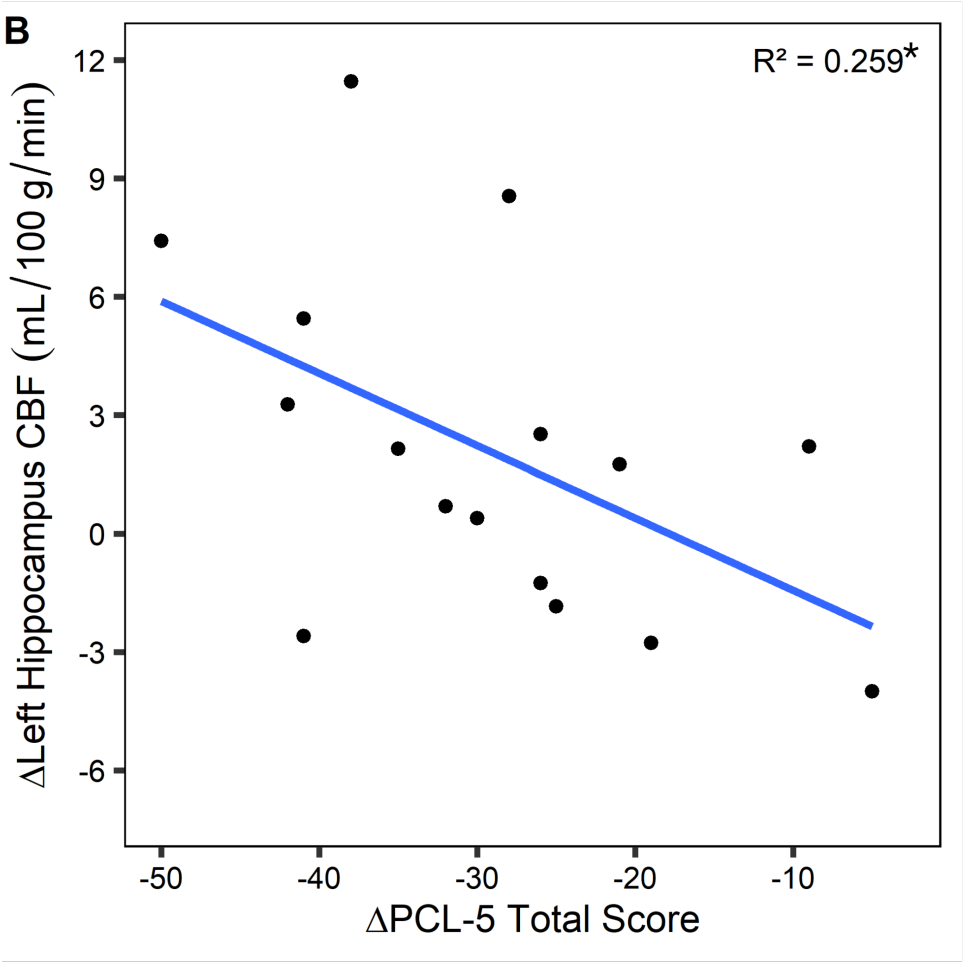
- A “fear circuitry” model of PTSD outlines amygdala and insula are hyperresponsive, thereby increasing fear and anxiety responses

Where is the current research with Perfusion and PTSD?

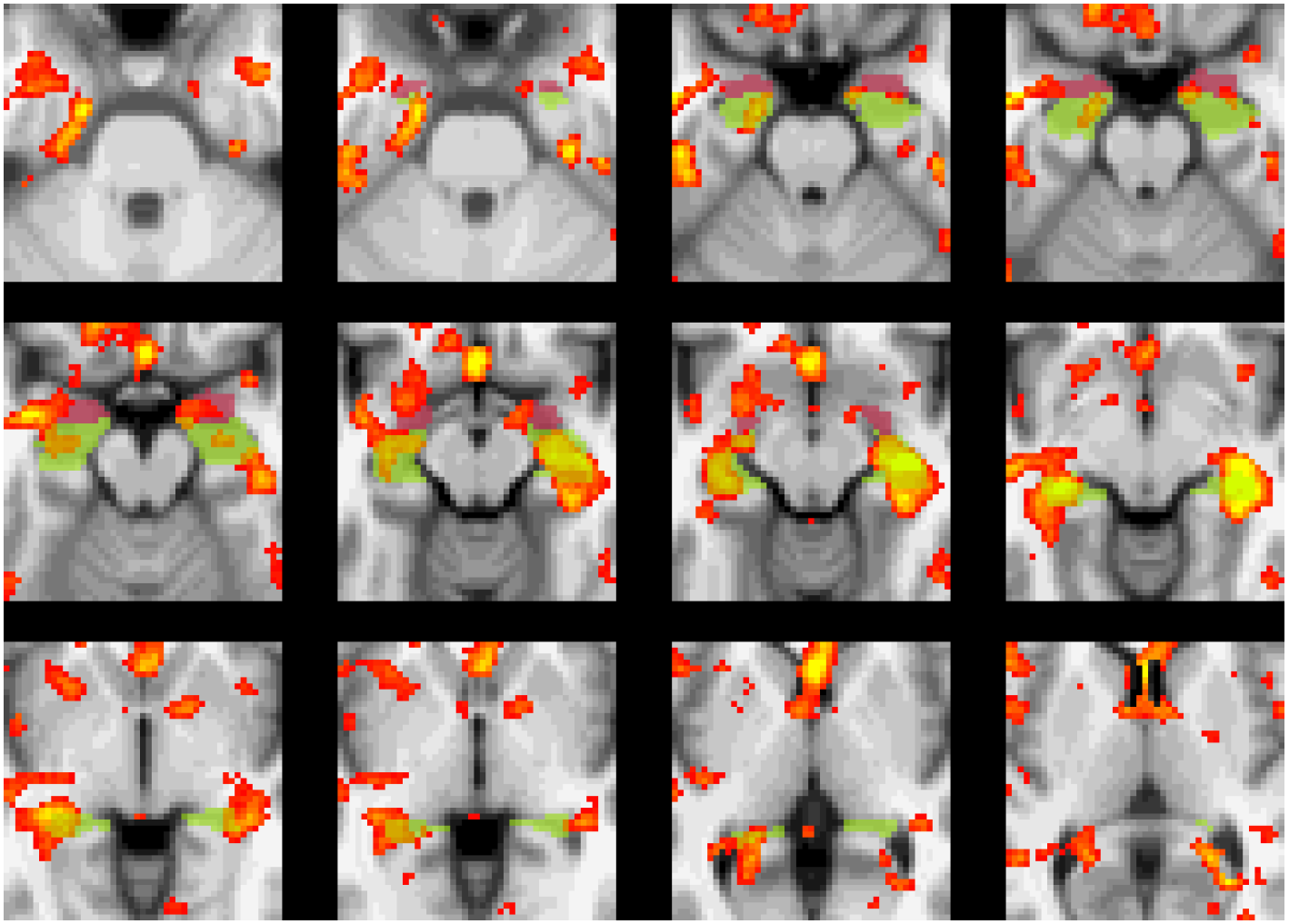
Publication	Aim	Population	Method	Result
Chung et al, 2006[9]	patients without re-exposure would exhibit alterations in regional CBF	Various N= 23	SPECT with Tc-99m- ECD	**Increased** rCBF in limbic regions and decreased rCBF in superior frontal, parietal and temporal regions
Sachinvala et al, 2000[11]	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
*


A
R² = 0.256*
ΔLeft Amygdala CBF (mL/100 g/min)
12
9
6
3
0
-3
-6
-50
-40
-30
-20
-10
ΔPCL-5 Total Score


B
R² = 0.259*
ΔLeft Hippocampus CBF (mL/100 g/min)
12
9
6
3
0
-3
-6
-50
-40
-30
-20
-10
ΔPCL-5 Total Score

Perfusion Increases correlate with decreased PCL-5 scores



Discussion

- Personalized, non-pharmacologic and non-invasive treatments are needed to address the complex disruptions caused by PTSD[7]
- **eTMS** is a personalized non-invasive approach that has shown promise in combating PTSD
- Alterations in **cerebral perfusion** of the amygdala, frontal cortex, limbic systems, and hippocampal cortex contribute to the associated symptomology of PTSD[3]
- This study is the first of its kind to utilize **resting pcASL** to monitor the disruption of neurophysiology associated with PTSD
- This study revealed, for the first time, **resting CBF is diminished** below healthy levels in individuals suffering from PTSD **in regions involved in emotion and attention regulation**[2,3]
- We identified **20 sessions of personalized eTMS** increases resting CBF in these regions, and such **changes were correlated with a decrease in PTSD symptomology** measured via the **PCL-5**

QUESTIONS?

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