MUSC Health
Medical University of South Carolina

BRAIN & BEHAVIOR
RESEARCH FOUNDATION

NIH
National Institute of Mental Health
K23 Award: 5K23MH123931

Fulfilling the Promise of Noninvasive Brain Stimulation as a Precision Medicine Tool

Christopher T. Sege, Thomas Uhde, Bernadette Cortese, Lisa M. McTeague, Mark S. George

For questions or comments please contact Chris Sege at sege@musc.edu

Disclosures

- Contracted research with Attune Neurosciences©, who also provides the ultrasound device for this study

- No other disclosures

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Brain Stimulation as a Precision Medicine Tool

- Clinical applications historically have targeted broad disorder classifications with a "one size fits most" approach
  - Standard brain target; standard course; broad clinical target (e.g., depression)

- Innovations in the BSL and beyond focus on improving **precision and individualization:**
  - Targeting different brain areas for different specific symptoms (e.g., lack of motivation versus rumination)
  - Syncing stimulation to significant brain events
  - Pairing stimulation with tasks and exercises to target specific processes/ behaviors

The American Journal of Psychiatry

FULL ACCESS | Articles | Published Online: 12 March 2020

Distinct Symptom-Specific Treatment Targets for Circuit-Based Neuromodulation

DARPA

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimula

Sonication of the anterior thalamus with MRI-Guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: A double-blind, sham-controlled study

Bashar W. Badran [a,*], Kevin A. Caulfield [a], Sasha Stomberg-Firestein [a], Philipp M. Summers [a], Logan T. Dowdle [b], Matt Savoca [a], Xingbao Li [a], Christopher W. Austelle [a], E. Baron Short [a], Jeffrey J. Borckardt [a], Norman Spivak [c], Alexander Bystritsky [d], Mark S. George [a,e]

My Work: Can we Pair Brain Stimulation with Emotional Coping Practice to Help with Relearning of Fear Behaviors?

Outline

The Clinical Context: The Anxiety Spectrum

- Fight/ flight/ freeze as a treatment target
- Limits of current fight/ flight/ freeze treatment

The Treatment Tools: Brain Stimulation

- The goal of enhancing brain plasticity
- rTMS and LIFU stimulation approaches

Our Current Work: Targeting Fight-or-Flight with Brain Stim

- Measuring fight/ flight (escape/ avoid bias)
- Modulating fight/ flight (escape/ avoid bias)

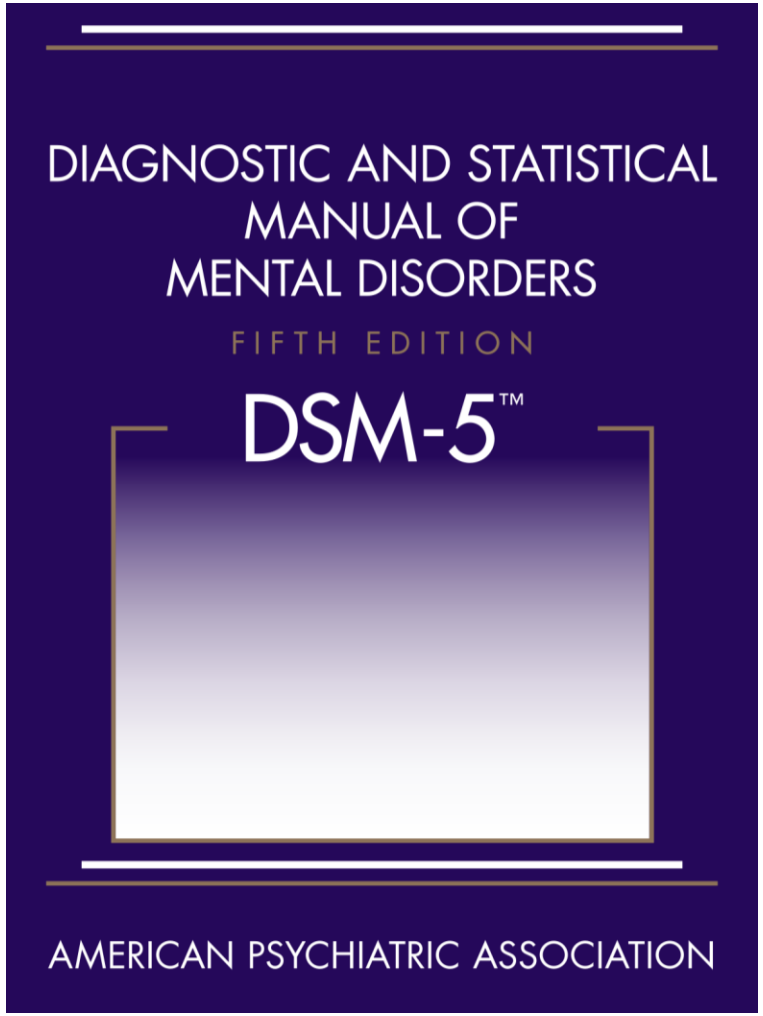
Our Future Work: Toward Treating Behaviors, not Disorders

- Pairing brain stim with behavior
- Other possibilities (cognition and reward)

Anxiety as a Clinical Area

Treating maladaptive "fight-flight-freeze" responding

The Anxiety Spectrum and its Treatment



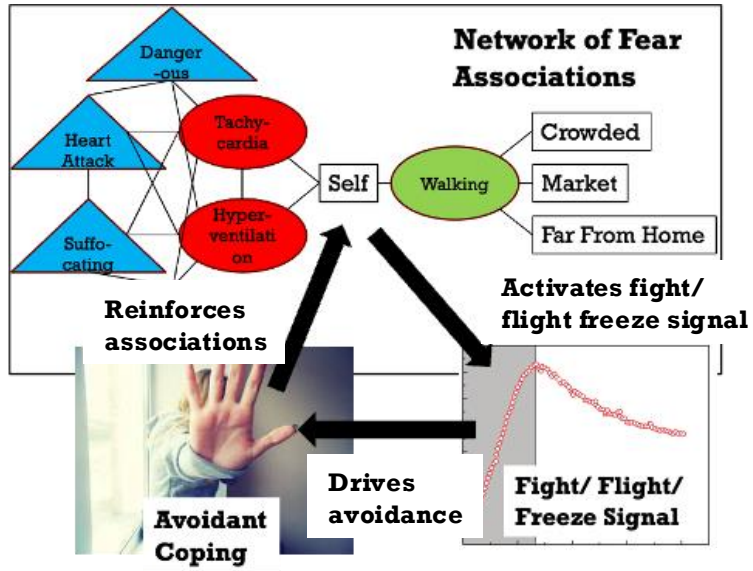
- **Anxiety Disorders**
  - Generalized Anxiety Disorder (GAD)
  - Panic Disorder
  - Agoraphobia
  - Social Anxiety Disorder (SAD)
  - Specific Phobia
  - Anxiety Disorder NOS
- **Related Disorders**
  - Obsessive-Compulsive Disorders
  - Trauma-/ Stressor-Related Disorders

The Anxiety Spectrum and its Treatment

Common Mechanism: Disrupted Operation of a **Fight/ Flight/ Freeze Brain System**

Common triggers of fight/ flight disruption across diagnoses can include:

- Physiology itself ("anxiety sensitivity;" Naragon-Gainey, 2010)
- Situational uncertainty ("intolerance of uncertainty;" Boswell et al., 2014)
- Distorted perception of control (Mineka & Zinbarg, 2006)



A fight/ flight/ freeze activation -> avoidance cycle drives impairment and is a core treatment target (Foa et al., 2006)

Cognitive behavioral treatments are effective for many – but many others cannot complete, do not benefit, or relapse (Taylor et al., 2012; Bentley et al., 2021)

Emotional Processing of Fear: Exposure to Corrective Information

Psychological Bulletin 1986, Vol. 99, No. 1, 20-35

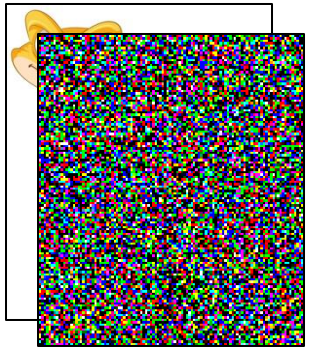
Edna B. Foa and Michael J. Kozak
Temple University

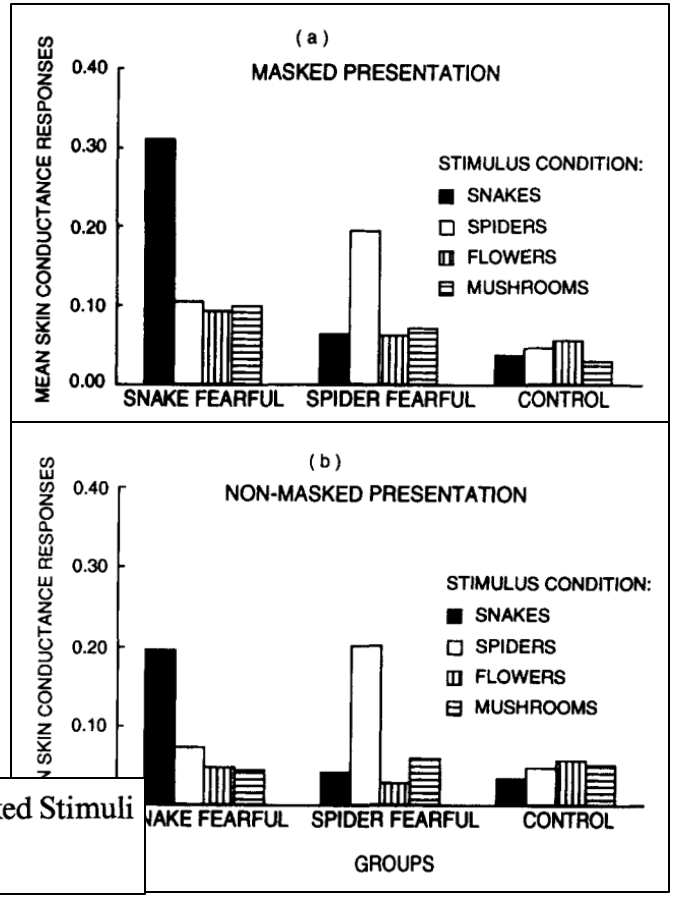
"Some form of exposure to feared situations is common to psychotherapies for anxiety…and is an effective treatment.

"…information must be integrated for emotional processing of a fear structure."

The Anxiety Spectrum and its Treatment

A key Challenge - The "Automaticity" of Fight/Flight/Freeze





"Unconscious Anxiety": Phobic Responses to Masked Stimuli

Arne Öhman and Joaquim J. F. Soares

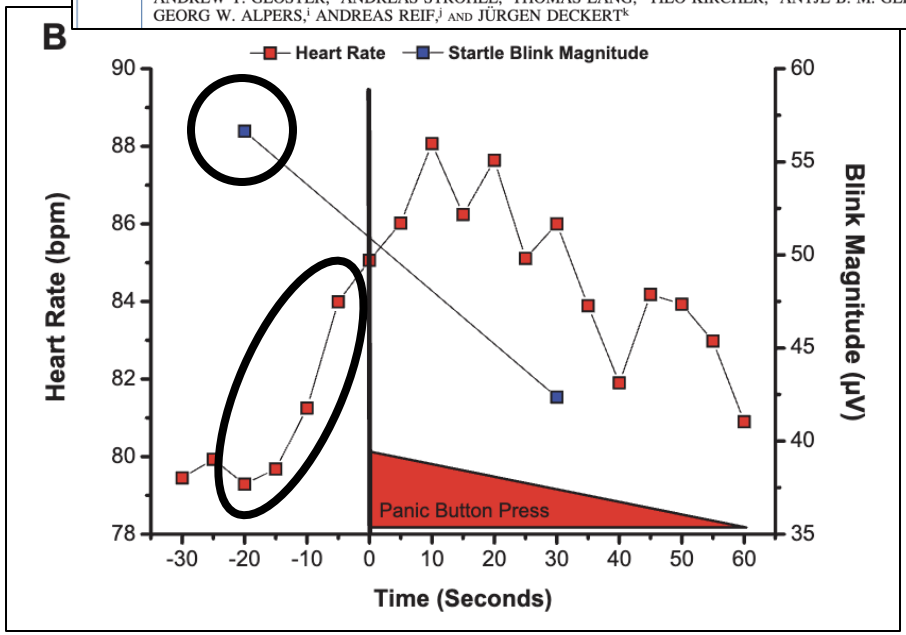
Psychophysiology, *53* (2016), 312–322. Wiley Periodicals, Inc. Printed in the USA.

DOI: 10.1111/psyp.12553

2016

Panic disorder with agoraphobia from a behavioral neuroscience perspective: Applying the research principles formulated by the Research Domain Criteria (RDoC) initiative

ALFONS O. HAMM,[a*] JAN RICHTER,[a*] CHRISTIANE PANÉ-FARRÉ,[a] DORTE WESTPHAL,[b] HANS-ULRICH WITTCHEN,[b] ANNA N. VOSSBECK-ELSEBUSCH,[c] ALEXANDER L. GERLACH,[d] ANDREW T. GLOSTER,[e] ANDREAS STRÖHLE,[f] THOMAS LANG,[g] TILO KIRCHER,[h] ANTJE B. M. GERDES,[i] GEORG W. ALPERS,[i] ANDREAS REIF,[j] AND JÜRGEN DECKERT[k]



The Anxiety Spectrum and its Treatment

A key Challenge - The "Automaticity" of Fight/Flight/Freeze

Received: 16 October 2017 | Revised: 13 December 2017 | Accepted: 28 December 2017
DOI: 10.1002/da.22720

RESEARCH ARTICLE

WILEY

Behavioral avoidance predicts treatment outcome with exposure and response prevention for obsessive–compulsive disorder

Michael G. Wheaton PhD[1,2,3] | Marina Gershkovich PhD[2,3] | Thea Gallagher Ps
Edna B. Foa PhD[4] | H. Blair Simpson MD, PhD[2,3]

Results: More than half (69%) of the full sample had moderate or severe avoidance b
at baseline. In EX/RP, controlling for baseline severity, pretreatment avoidance predict
treatment YBOCS symptoms ($\beta = 0.45$, $P < .01$). Avoidant individuals were less likely to
remission with EX/RP (odds ratio = 0.04, 95% confidence interval [CI] range 0.01–0.28, P
Baseline avoidance was also associated with degree of patient adherence to between
EX/RP assignments, which mediated the relationship between baseline avoidance and EX
comes ($P < .05$). Baseline avoidance did not predict outcomes or wellness among patients r
risperidone or placebo.

Behaviour Research and Therapy 73 (2015) 96–103
Contents lists available at ScienceDirect
Behaviour Research and Therapy
journal homepage: www.elsevier.com/locate/brat

Avoidant decision-making in social anxiety disorder: A laboratory task linked to in vivo anxiety and treatment outcome

Andre Pittig [a, b, *], Georg W. Alpers [a], Andrea N. Niles [c], Michelle G. Craske [c]

Journal of Obsessive-Compulsive and Related Disorders 41 (2024) 100871
Contents lists available at ScienceDirect
Journal of Obsessive-Compulsive and Related Disorders
journal homepage: www.elsevier.com/locate/jocrd

Behavioral avoidance as a factor in concentrated exposure and response prevention for obsessive-compulsive disorder

Michael G. Wheaton [a,*], Kristen Hagen [b,c], Thröstur Björgvinsson [d,e], Gerd Kvale [b,f],

Highlights

- We studied OCD-related avoidance before and after concentrated ERP.
- Patients with more severe avoidance had equivalent short-term outcomes but worse long term outcomes.
- Avoidance improved with concentrated ERP but rebounded during follow-up.
- Worsening avoidance predicted subsequent worsening in global OCD severity.

Clinical Psychology Review 42 (2015) 179–192
Contents lists available at ScienceDirect
Clinical Psychology Review

A systematic review of predictors and moderators of improvement in cognitive-behavioral therapy for panic disorder and agoraphobia

Eliora Porter *, Dianne L. Chambless

HIGHLIGHTS

- Agoraphobic avoidance predicted less improvement from pre- to post-treatment.
- Functional impairment and low expectancy for change predicted less improvement.
- Comorbid depression and medication use consistently did not predict improvement.
- Few studies examined moderators of improvement in CBT vs. other treatments.

Psychological Trauma:
Theory, Research, Practice, and Policy
TRAUMA PSYCHOLOGY
In the public domain
ISSN: 1942-9681
2020, Vol. 12, No. 4, 405–412
http://dx.doi.org/10.1037/tra0000484

Predicting Treatment Dropout Among Veterans Receiving Prolonged Exposure Therapy

Afsoon Eftekhari, Jill J. Crowley, and Margaret-Anne Mackintosh
National Center for PTSD, Dissemination and Training Division/VA Palo Alto Health Care System, Palo Alto, California

Craig S. Rosen
National Center for PTSD, Dissemination and Training Division/VA Palo Alto Health Care System, Palo Alto, California, and Stanford University School of Medicine

dropout. ***Results:*** In total, 782 patients (30.0%) completed fewer than 8 sessions of PE. Younger veterans were more likely to drop out of PE; odds ratio (OR) per year of age = 0.97, $p < .01$. Controlling for other factors, veterans who focused on childhood trauma were less likely to drop out than those focusing on combat trauma (OR = 0.51, $p < .05$). Dropout was unrelated to symptom course or symptom worsening between sessions. Nevertheless, clinicians attributed dropout to distress or avoidance in 45% of the patients who dropped out, citing other factors in 37% of dropout cases. ***Conclusions:*** Treatment dropout

The Anxiety Spectrum and its Treatment

A key Challenge - The "Automaticity" of Fight/Flight/Freeze

Can we improve treatment by targeting fight/flight processing more directly?

Brain Stimulation Tools for Targeting Fight/ Flight/ Freeze

Increasing neural flexibility to improve fear response relearning

Non-Invasive Neuromodulation Overview

- Use of superficial (electrical, magnetic, or mechanical) transmitters to influence central (brain) or peripheral (para/sympathetic) nerve activity without any surgery

- A variety of technologies available with different mechanisms of action

Central	Peripheral
Transcranial magnetic stimulation (TMS)	Transauricular vagus nerve stimulation (taVNS)
Transcranial direct current stim. (tDCS)	Trigeminal nerve stimulation (TNS)
Transcranial alternating current stim. (tACS).	Transcutaneous electrical nerve stimulation (TENS)
Electroconvulsive therapy (ECT)	
Low-intensity focused ultrasound (LIFU)	

Non-Invasive Neuromodulation Overview

- Use of <u>superficial</u> (electrical, magnetic, or mechanical) transmitters to influence central (brain) or peripheral (para/sympathetic) nerve activity without any surgery

In therapeutic applications, the common goal is PLASTICITY

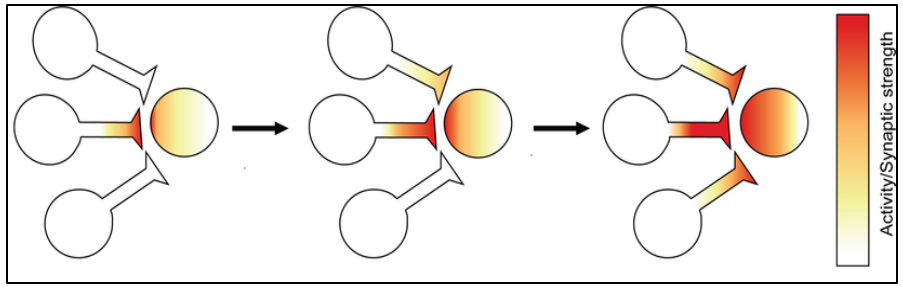
Formation of new connections by repeated firing

Remodeling of neurons in a way that makes it easier to form new connections

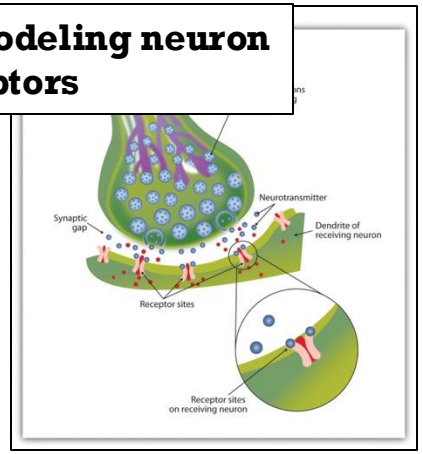
This is the basis of relearning and behavior change

<u>Mechanisms of Plasticity</u>

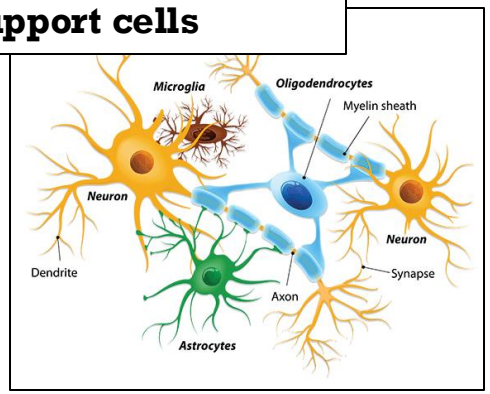
Forming new connections by firing (Hebbian learning)



Remodeling neuron receptors

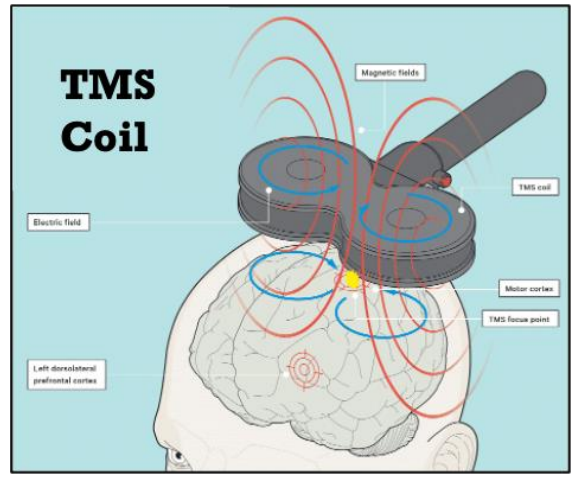


Influencing neuron support cells



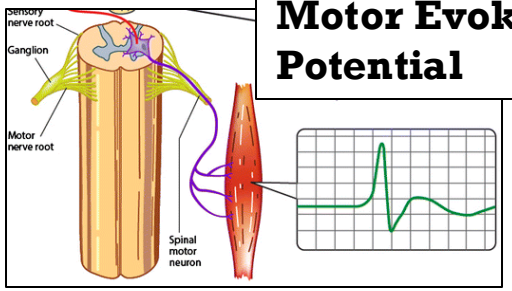
Transcranial Magnetic Stimulation (TMS): The Major Player

The technology – a figure-eight or H-shaped superficial electromagnet that sends a weak (1.5 to 2T) magnetic pulse into the cortex



Different delivery patterns = different effects

- Single pulse = acute neuronal firing
- Repeated-pulse session (repetitive TMS) = short-lived changes in neuronal firing propensities
- Multi-session course = more durable neuronal changes support new, more active connections



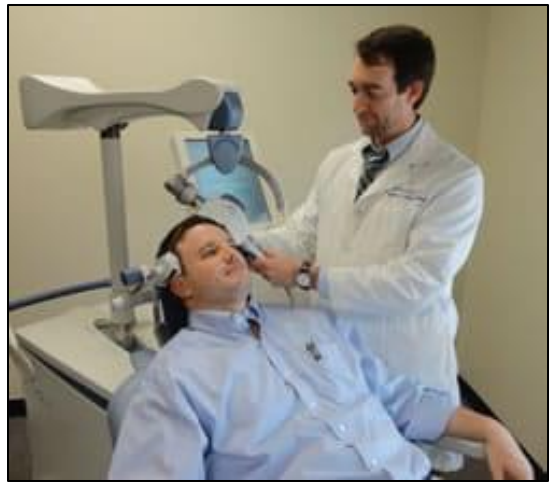
Motor Evoked Potential

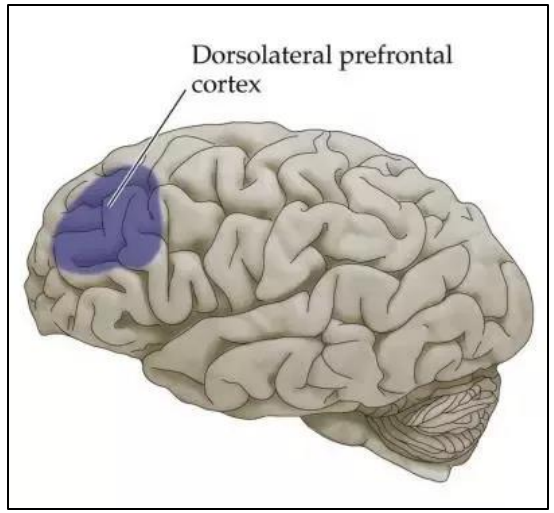
Immediate effect can be directly measurable (motor thresholding)

Transcranial Magnetic Stimulation (TMS): The Major Player

Clinical applications

- First standard course of TMS for major depressive disorder FDA approved in 2008
  - Neural target – dlPFC
  - Rapid TMS ”pulses” at a rate of 10/ second
  - A single treatment session delivers 3,000 pulses over ~38 minutes
  - A treatment course is one session of rTMS/ day over 25 days





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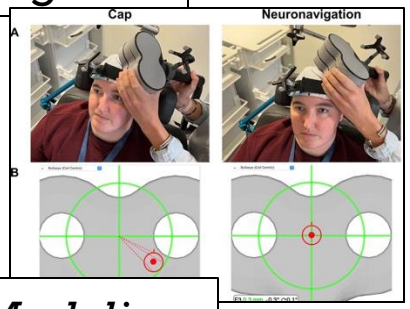
Continued Innovations

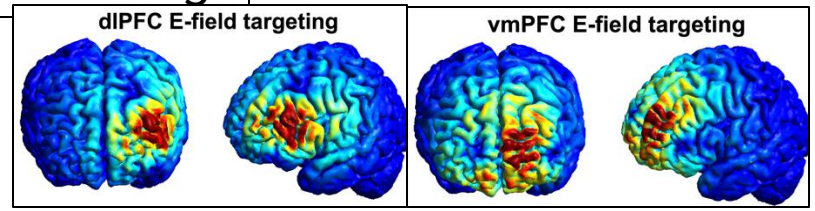
Neuronavigation



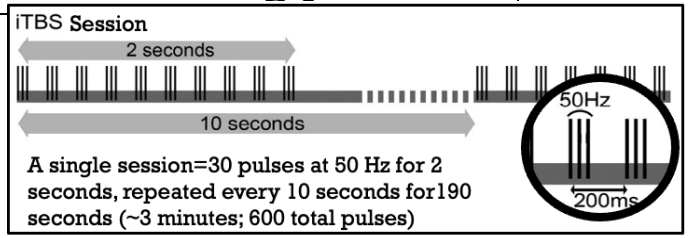
Rogue Research Inc.

Brainsight® TMS

E-Field Modeling



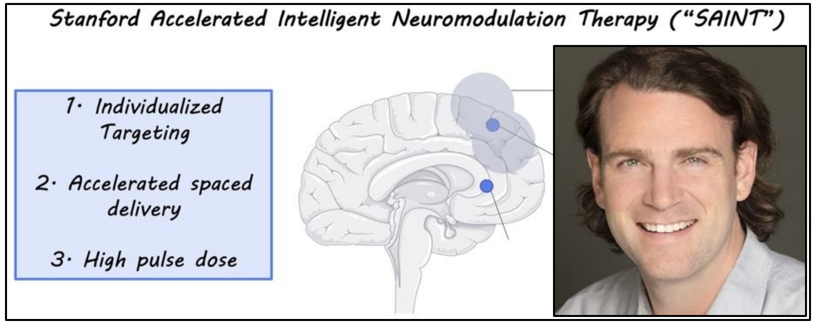
Bio-rhythm-based firing patterns



Transcranial Magnetic Stimulation (TMS): The Major Player

Clinical applications

- Most recent step forward in depression TMS: SAINT TMS (FDA cleared in 2023)

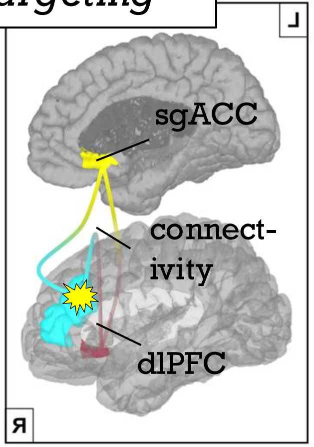


Other recent developments

- rTMS paired with behavioral procedures
  - OCD (w/ situational exposure; 2017)
  - Smoking cessation (w/ cue exposure; 2020)
- Anxiety w/ Major Depression (since 2021)

All covered as second-/ third-line options

Sub-circuit targeting



Accelerated delivery

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

Transcranial Magnetic Stimulation (TMS): The Major Player

Clinical applications

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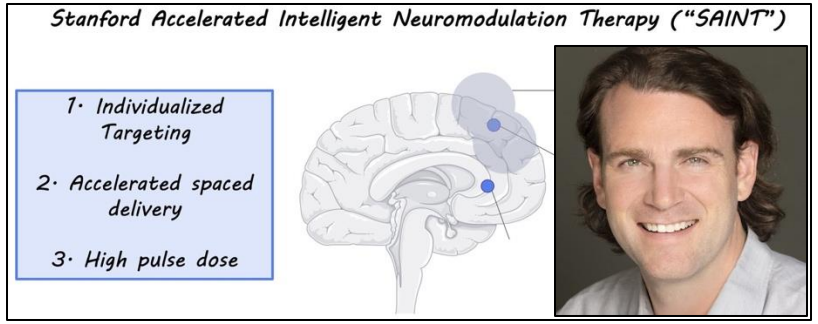

Other recent developments

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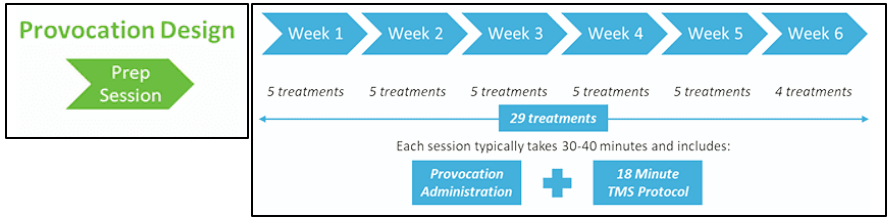
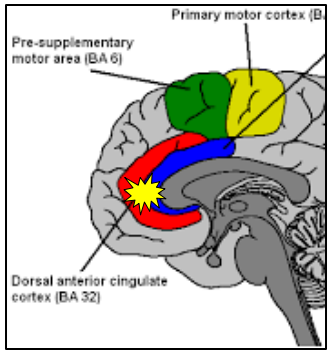
Behavioral Pairing



Deep Cortex Coils



All covered as second-/ third-line options

TMS Considerations

- Very safe and very minimal side effects
  - But it is usually contraindicated for people who are at risk for seizures
- No negative effects on cognition (e.g., memory, attention) – and in fact, a lot of research suggests benefits!

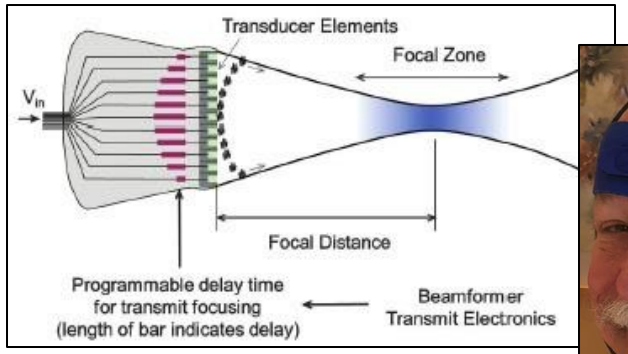
As a research and treatment tool, main that still could limit TMS are:

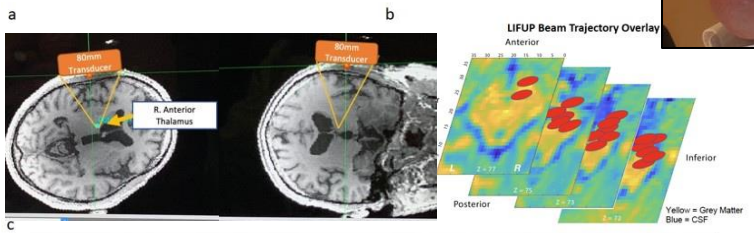
1. It cannot reach below the surface level of the brain (the cortex), and
2. The stimulated area is a bit broad (in brain terms) – especially deeper in the cortex

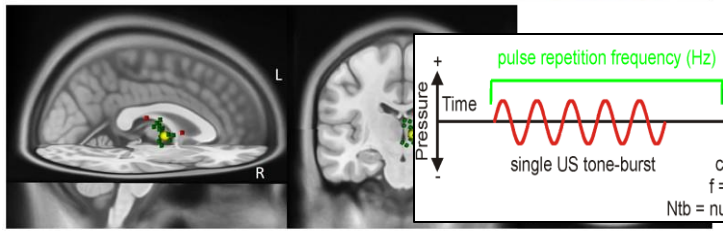
Low-Intensity Focused Ultrasound (LIFU): The Next Generation?

The technology – a mechanoelectrical transducer array generates ultrasound waves that travel through bone and tissue to a targeted depth

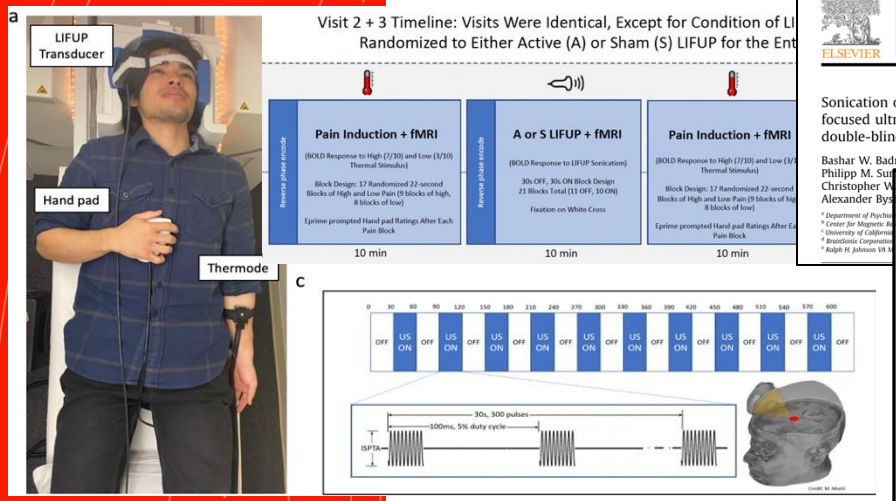
- Thought to change neuron firing capacity by mechanical effect on the membrane
- Overcomes depth and focality limitations of TMS
- Like rTMS, LIFU can be patterned to produce different effects
  - But optimal parameters are still very much being worked out

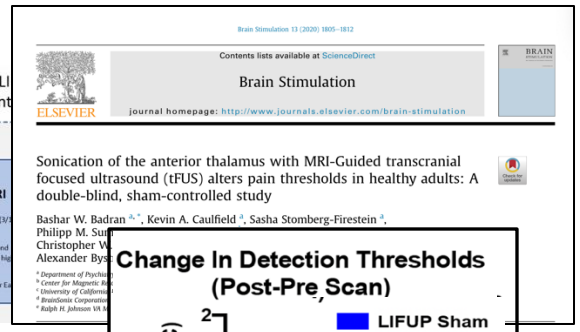


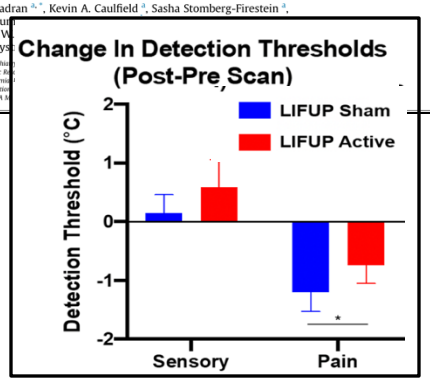


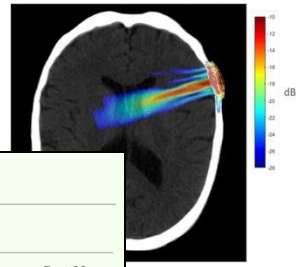


Low-Intensity Focused Ultrasound (LIFU): The Next Generation?









Global Affect scores for Experiment 1.

	Global Affect			
	Baseline	Post-10	Post-20	Post-30
tFUS-Active				
Mean	67.22	71.97	75.36*	75.49*
SD	13.74	12.05	11.71	10.99
Placebo				
Mean	70.79	67.70	70.28	71.16
SD	13.16	16.00	13.60	11.99

- New technology (2002) with no clinic indications yet…
- …but the pre-clinical work is coming fast and furious
- Demonstrated effects on
  - TMS-evoked motor potential threshold
  - Basic sensory processing responses
  - Sensory (e.g., pain) perception
  - Subjective emotion (e.g., depressive symptoms)

LIFU Considerations

- Like TMS, all research to date suggests LIFU is very safe with very minimal side effects
- Ability to reach anywhere with precision could allow us to stimulate more important areas for diagnoses beyond depression

But as a research and treatment tool, the main considerations are that:

1. An immediate, direct response to a LIFU pulse (like the motor twitch for TMS) is not yet apparent…
2. …and with great depth and focality but a beam that can't be seen, it can be a challenge to show that we're successfully stimulating in the most effective way

BRAIN & BEHAVIOR RESEARCH FOUNDATION

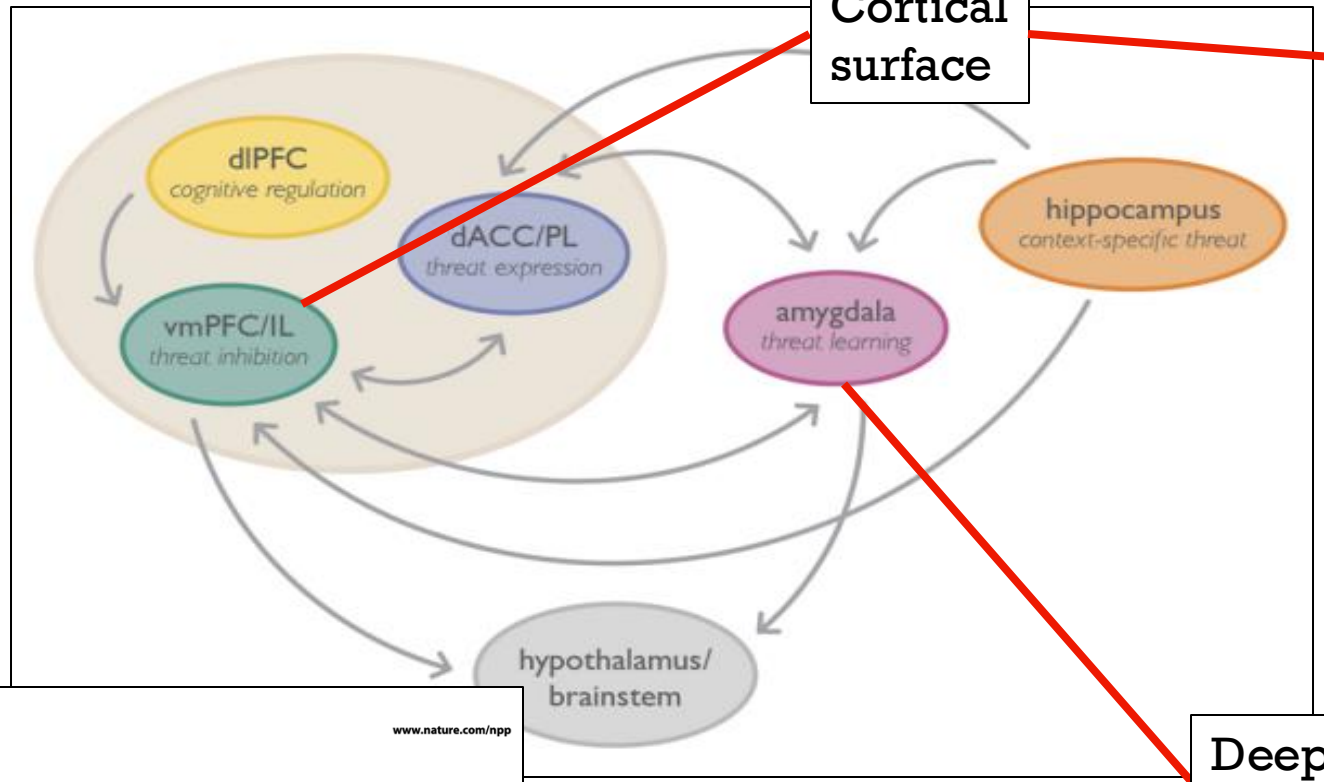
Current Work: Can TMS or LIFU be used to Target Fight/ Flight Circuitry

What's the best approach to relearning a more adaptive fight-or-flight approach?

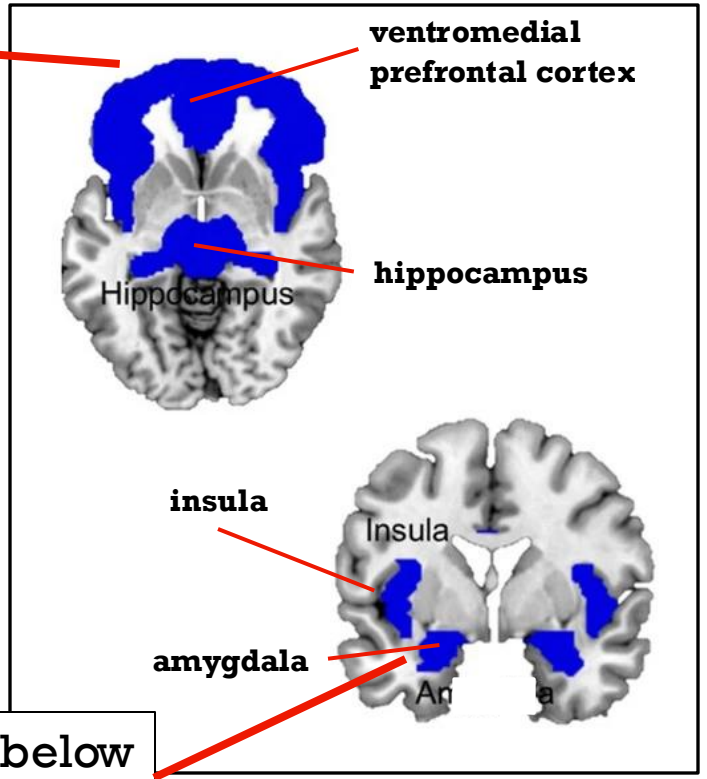
National Institute of Mental Health
K23 Award: 5K23MH123931

Fight-Flight-Freeze Circuitry

Threat Response Network



Key Brain Regions



Cortical surface

Deep below cortex

American College of Neuropsychopharmacology

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REVIEW ARTICLE OPEN

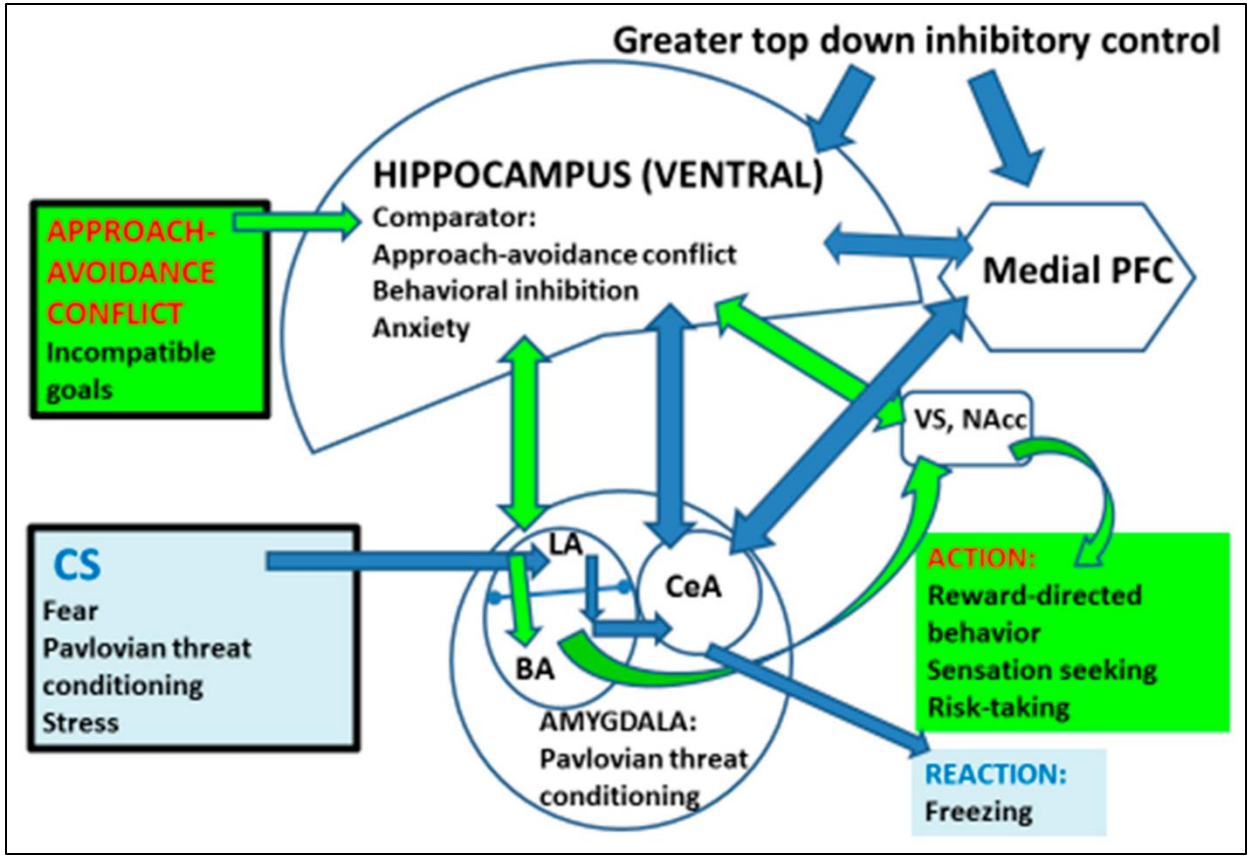
Check for updates

Prefrontal cortex, amygdala, and threat processing: implications for PTSD

M. Alexandra Kredlow[1,3], Robert J. Fenster[2,3], Emma S. Laurent[1], Kerry J. Ressler[2] and Elizabeth A. Phelps[1]

Fight-Flight-Freeze Circuitry

Threat response network regions interact to select the best response for specific threat contexts



brain sciences
MDPI

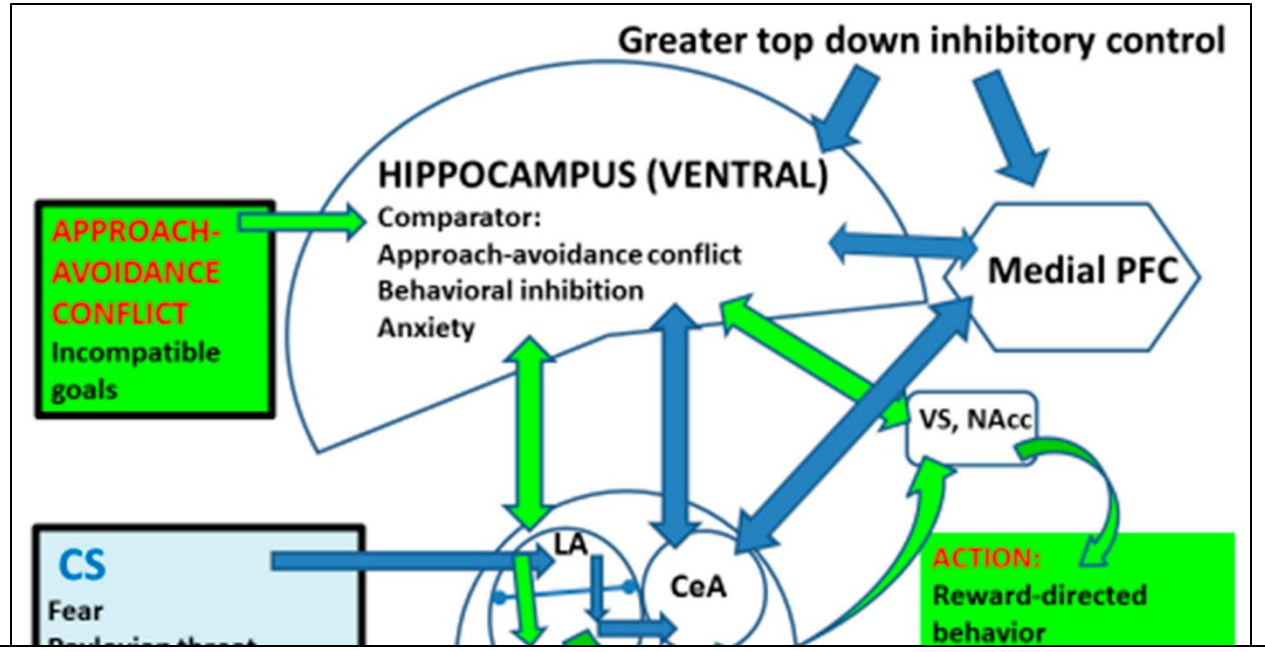
Commentary

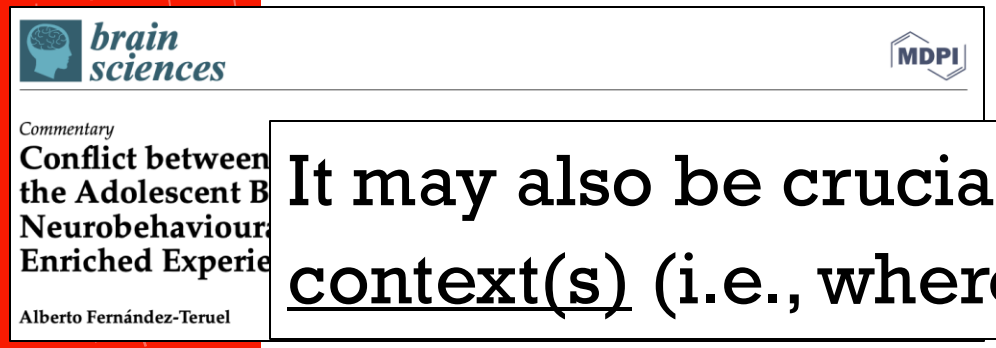
Conflict between Threat Sensitivity and Sensation Seeking in the Adolescent Brain: Role of the Hippocampus, and Neurobehavioural Plasticity Induced by Pleasurable Early Enriched Experience

Alberto Fernández-Teruel

Fight-Flight-Freeze Circuitry

Threat response network regions interact to select the best response for specific threat contexts




brain sciences

MDPI

Commentary

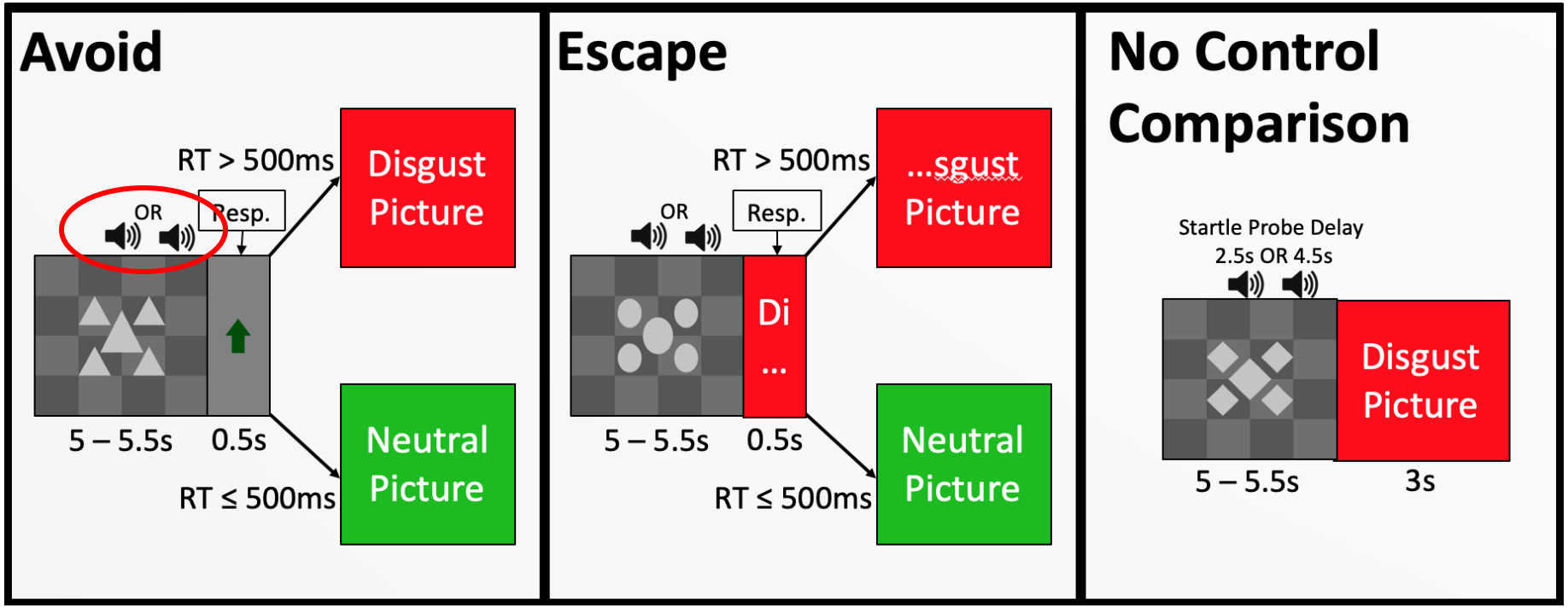
Conflict between
the Adolescent B
Neurobehaviour
Enriched Experie

Alberto Fernández-Teruel

It may also be crucial to stimulate circuitry <u>in the right context(s)</u> (i.e., where it is not working adaptively)

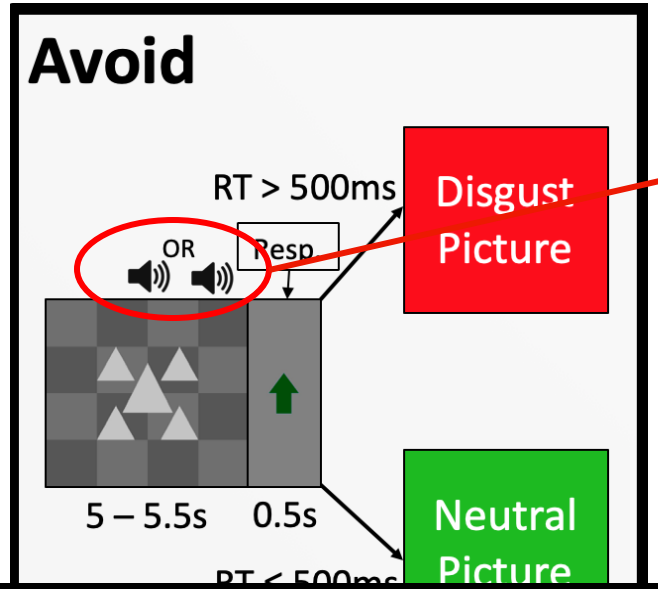
Fight-Flight-Freeze Context: Escape Preparation

- Threat Coping Preparation task

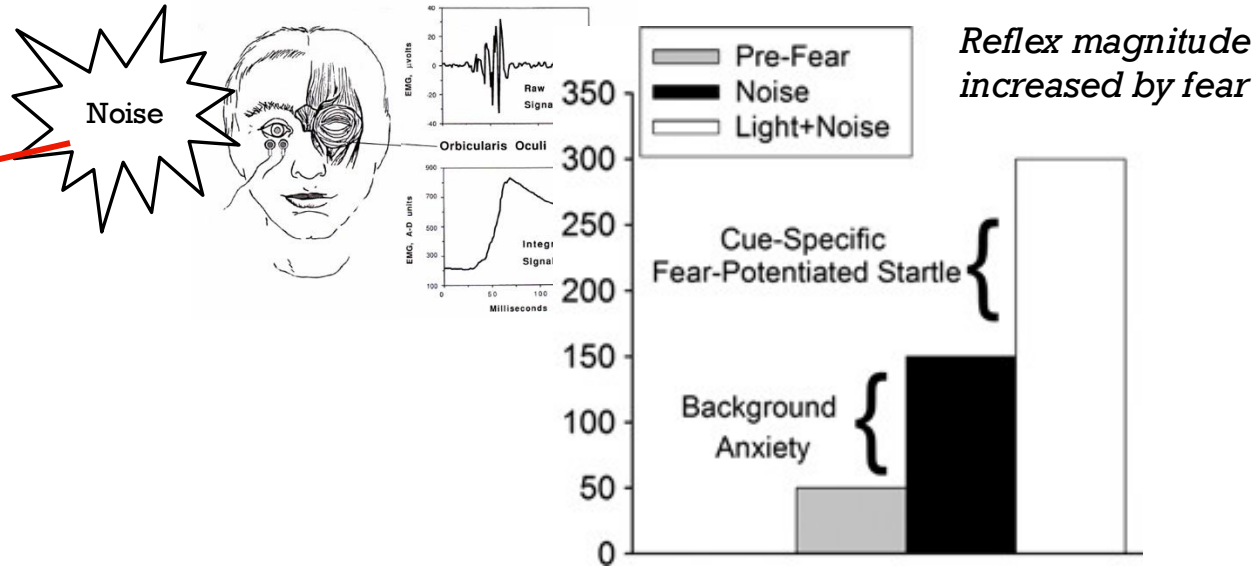


Fight-Flight-Freeze Context: Escape Preparation

- Threat Coping Preparation task



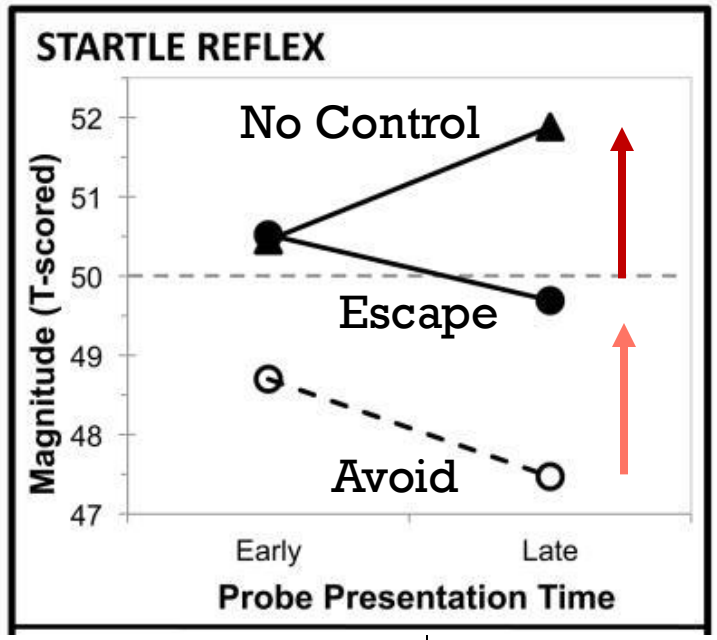
- Startle Reflex Modulation index

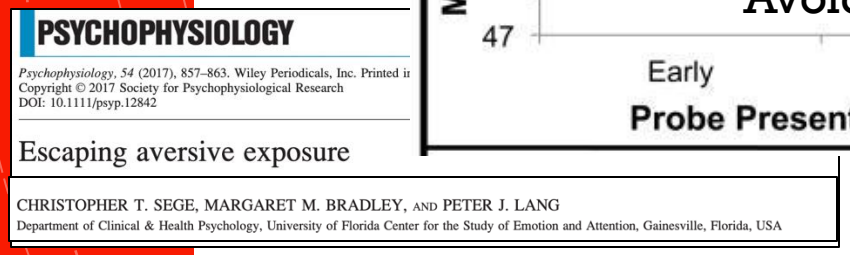


Measures regulation of a fight/ flight (incl. reflex) response preparation system while awaiting increasingly uncontrollable threats

Fight-Flight-Freeze Context: Escape Preparation

- Increasing fight/ flight activation with decreasing control…




PSYCHOPHYSIOLOGY

Psychophysiology, 54 (2017), 857–863. Wiley Periodicals, Inc. Printed i
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DOI: 10.1111/psyp.12842

Escaping aversive exposure

CHRISTOPHER T. SEGE, MARGARET M. BRADLEY, AND PETER J. LANG
Department of Clinical & Health Psychology, University of Florida Center for the Study of Emotion and Attention, Gainesville, Florida, USA

- … and with individual anxiousness *during **escape** preparation specifically*


Behaviour Research and Therapy 104 (2018) 63–68

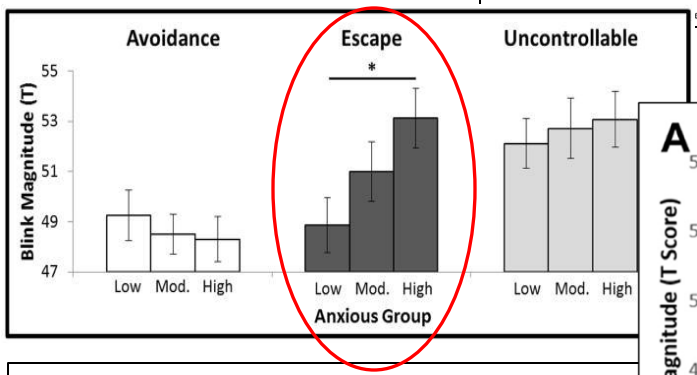
Contents lists available at ScienceDirect

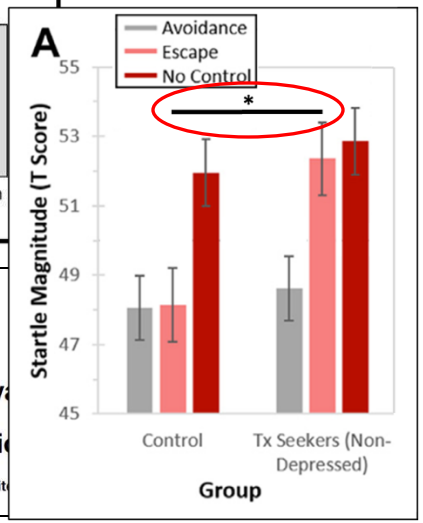
Behaviour Research and Therapy

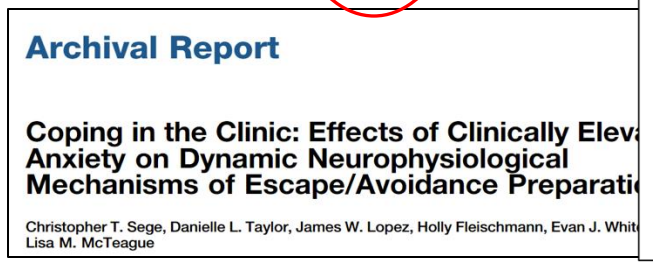
journal homepage: www.elsevier.com/locate/brat

Avoidance and escape: Defensive reactivity and trait anxiety

ey, Peter J. Lang





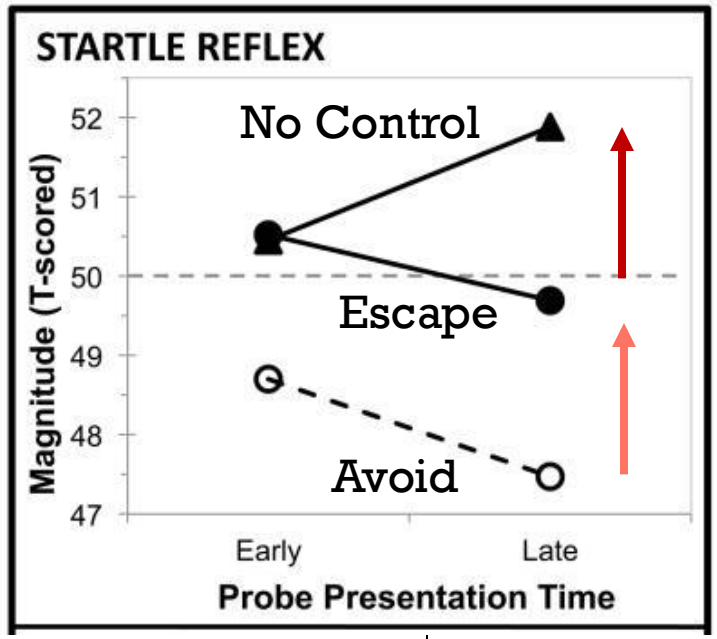

Archival Report

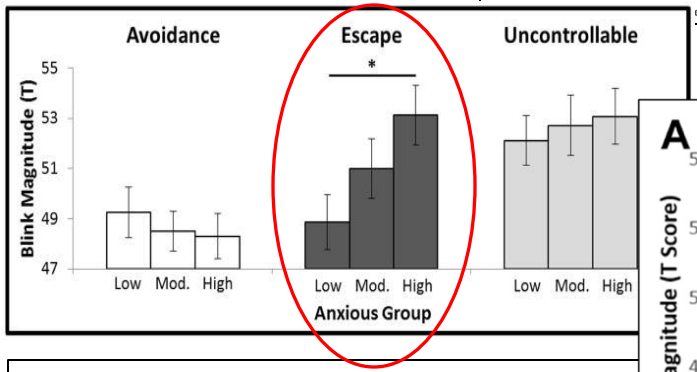
Coping in the Clinic: Effects of Clinically Eleva
Anxiety on Dynamic Neurophysiological
Mechanisms of Escape/Avoidance Preparati

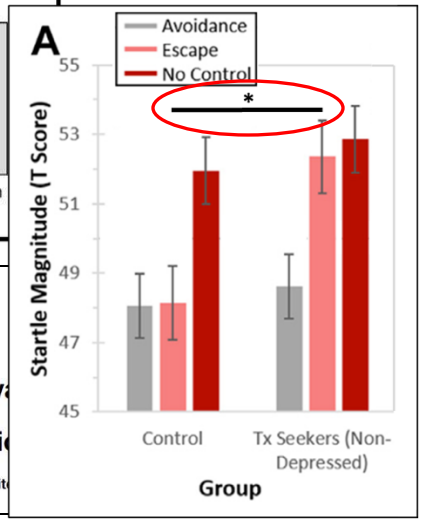
Christopher T. Sege, Danielle L. Taylor, James W. Lopez, Holly Fleischmann, Evan J. Whit
Lisa M. McTeague

Fight-Flight-Freeze Context: Escape Preparation

Can we reduce escape-specific fight/ flight/ freeze system malfunction without shutting the whole system down?







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Psychophysiology, 54 (2017), 857–863. Wiley Periodicals, Inc. Printed i
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Escaping aversive exposure

CHRISTOPHER T. SEGE, MARGARET M. BRADLEY, AND PETER J. LANG
Department of Clinical & Health Psychology, University of Florida Center for the Study of Emotion and Attention, Gainesville, Florida, USA

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The Project

- Target the fight/ flight/ freeze system at (with TMS) or below (with LIFU) the cortex to find the best way to modulate *escape-specific* activation
  - Cortical aspects of system **regulate** fight/ flight tendencies
  - Sub-cortical of system aspects **activate** fight/ flight responding

THE GENERAL DESIGN

Study 1

rTMS

Study 1
Sample

- **Comparison of 2 cortical targets (2 study days)**
  - Medial Prefrontal Cortex (mPFC; emotion regulation)
  - Supplementary motor area (SMA; motor planning)
- **55 anxiety/ related disorder treatment seekers to date**
  - 12 Generalized Anxiety, 7 Panic, 8 PTSD, 6 Social Anxiety, 4 Adjustment w/ Anxiety, 7 Anxiety NOS, 3 OCD, 3 Depression w/ Secondary Anxiety

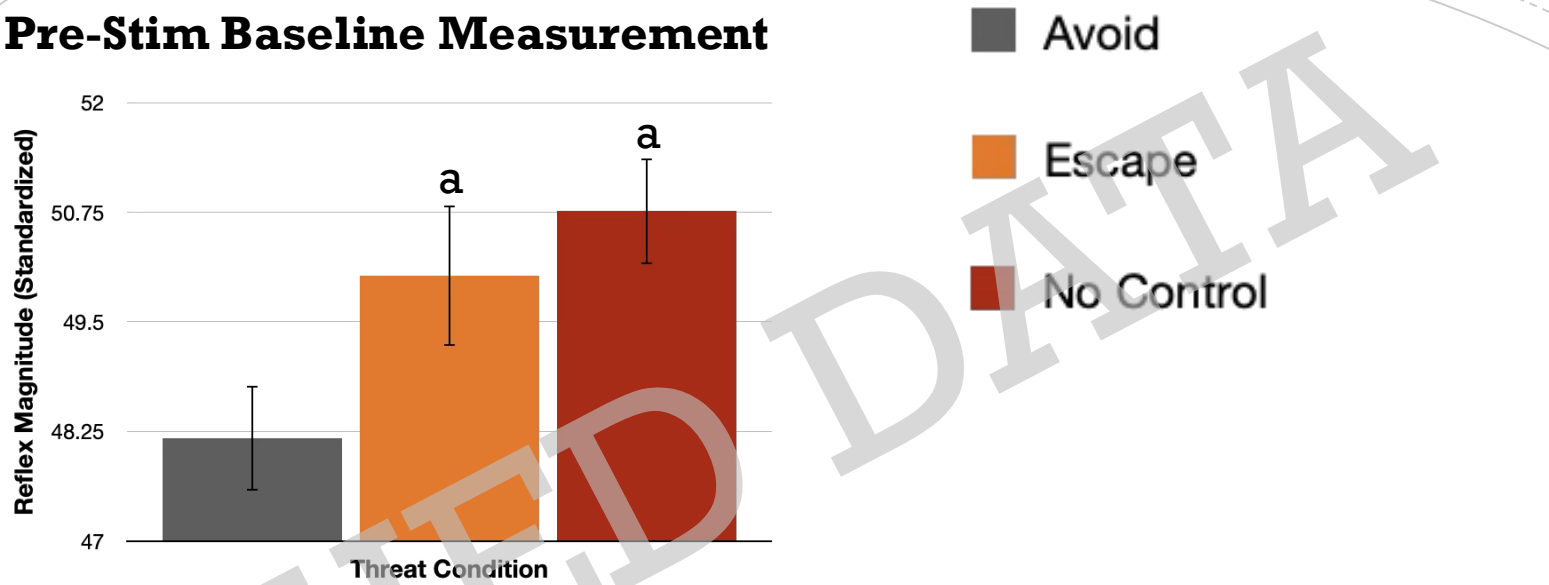
	Mild-Moderate Depression (n = 45)	Severe Depression (n = 10)
N (%) Women	36 (80.0)	6 (60.0)
N (%) US Racial/ Ethnic Minority	6 (13.3)	3 (30.0)
Age	32.8 (12.0)	31.2 (10.0)
STAI-T (Gen. Anxiety)	42.5 (9.5)	62.4 (8.8)
BDI-II (Depression)	9.0 (6.2)	34.9 (7.1)
IIRS (Impairment)	42.3 (18.4)	76.9 (17.1)

a = *different from avoid condition*

e = *different from escape condition*

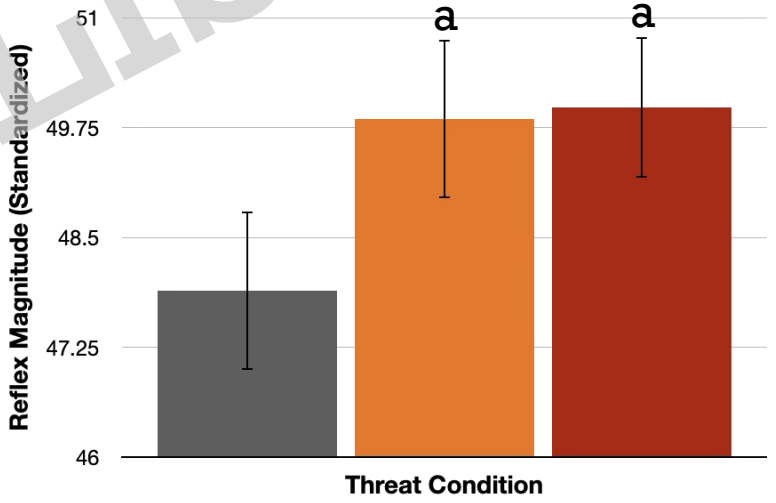
Study 1
Escape/ Avoid Task

Pre-Stim Baseline Measurement



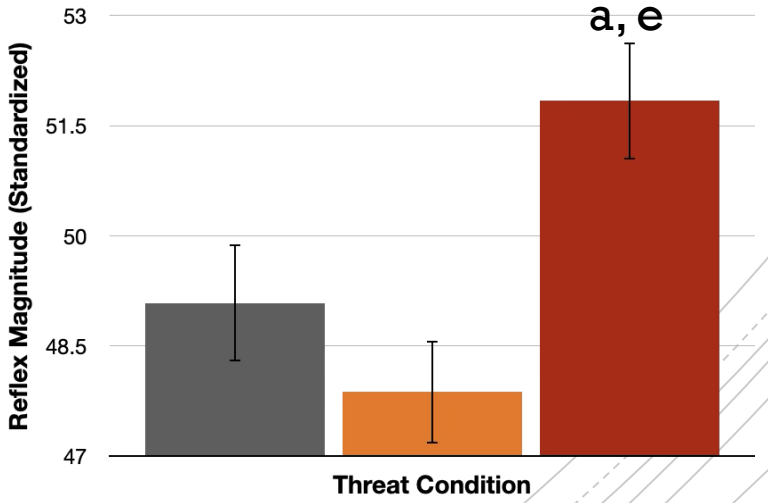
Condition Effect – $F(2,72) = 4.7, p = .01$, effect size = .12*

Post-SMA Measurement



Change Effect – $F(2,72) = 0.1$, $p = .87, \eta_p^2 = .004$

Post-mPFC Measurement



Change Effect – $F(2,72) = 4.6$, $p = .02, \eta_p^2 = .11$*

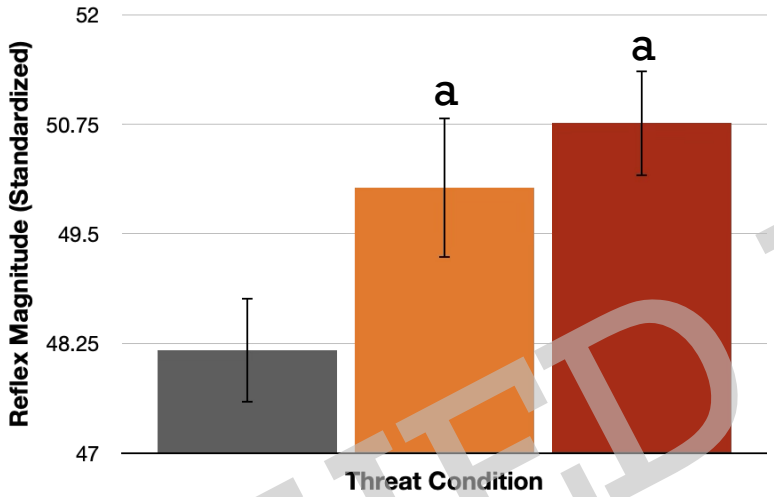
Avoid

Escape

No Control

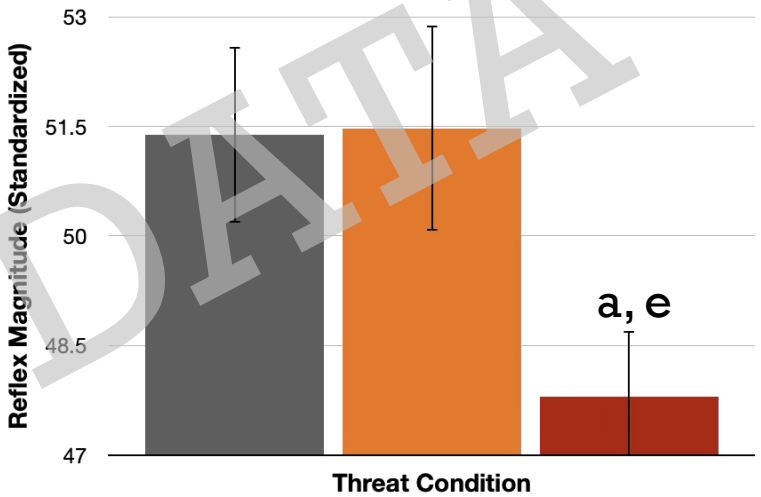
Study 1
Escape/ Avoid Task

Less Depressed Tx Seekers

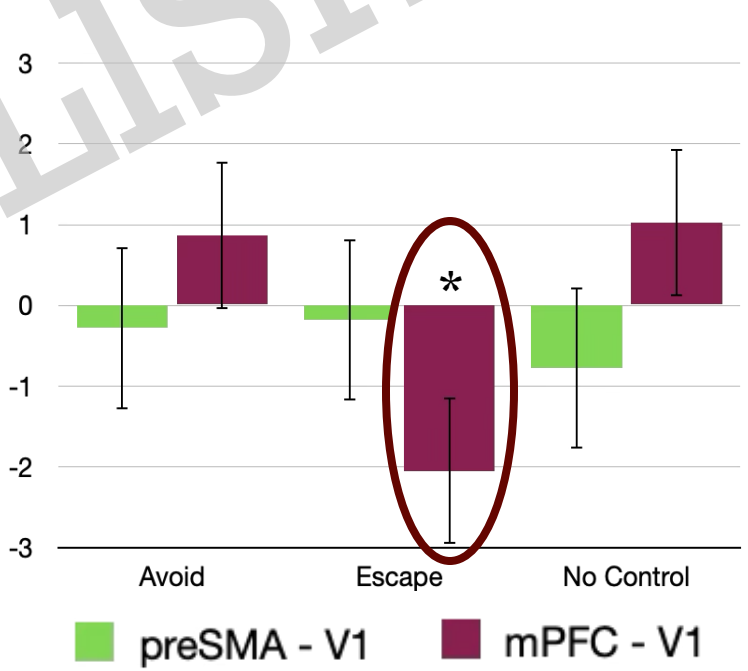


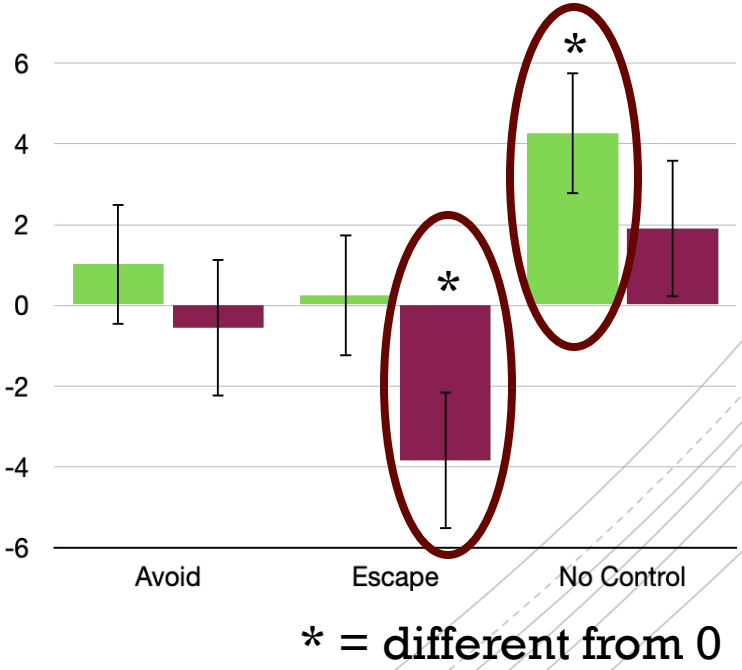
Condition Effect – $F(2,72) = 4.7, p = .01$, effect size = .12*

Severely Depressed Tx Seekers



Condition Effect – $F(2,18) = 3.3, p = .07$, effect size = .32^





* = different from 0

Study 1 Summary

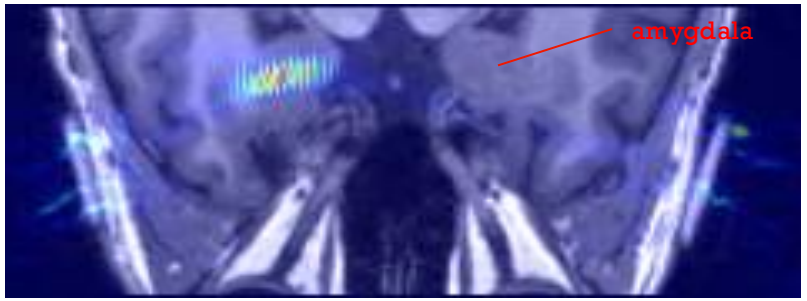
- Stimulating the cortex (medial prefrontal cortex) did improve the **regulation** of fight/ flight responding across contexts
  - *Not just an "off" switch (which also wouldn't work)*
- For some people who showed more of a *blunting* of fight/ flight, stimulating a different area **overcame this blunting**
  - *Points to different strategies for different people?*
- Next: does stimulating the amygdala have similar effects?

Study 2

LIFU

Study 2
Sample

- **Stimulation: LIFU to amygdala (fight/ flight regulation)**
  - One session active
  - A second session "sham;" no stimulation reached brain
- **15 anxiety/ related disorder treatment seekers to date (5 ongoing)**
  - 12 Generalized Anxiety, 7 Panic, 8 PTSD, 6 Social Anxiety, 4 Adjustment w/ Anxiety, 7 Anxiety NOS, 3 OCD, 3 Depression w/ Secondary Anxiety



	N = 15
N (%) Women	11 (73.3)
N (%) US Racial/ Ethnic Minority	2 (13.3)
Age	39.9 (12.0)
STAI-T (Gen. Anxiety)	46.7 (8.7)
BDI-II (Depression)	14.4 (8.7)
IIRS (Impairment)	43.7 (17.0)

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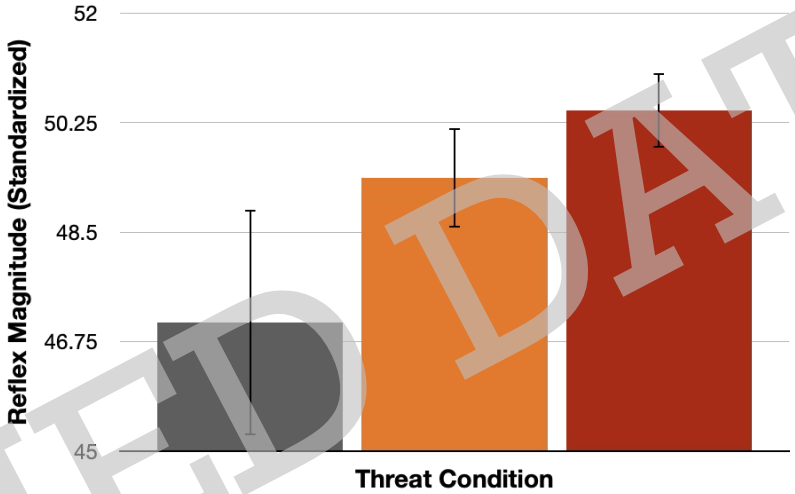
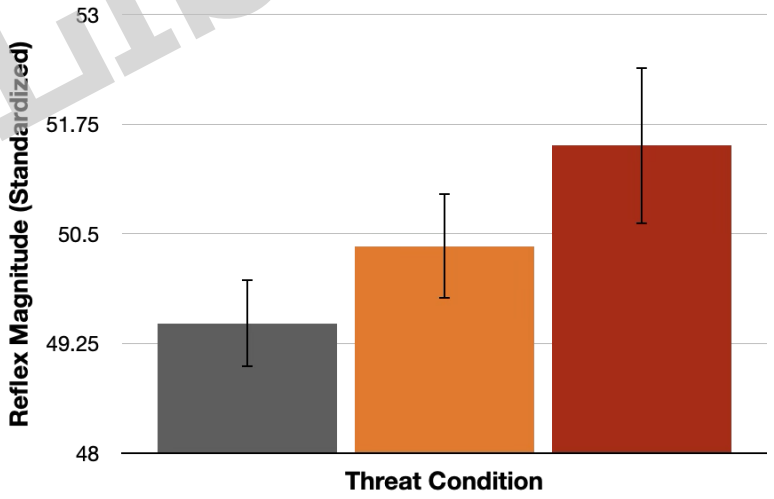
Study 2
Escape/ Avoid Task

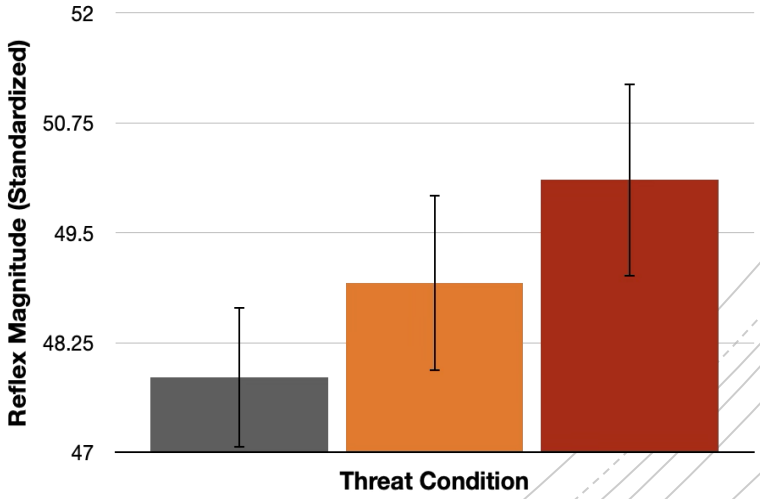
Pre-Stim Baseline Measurement



Post Active Stimulation



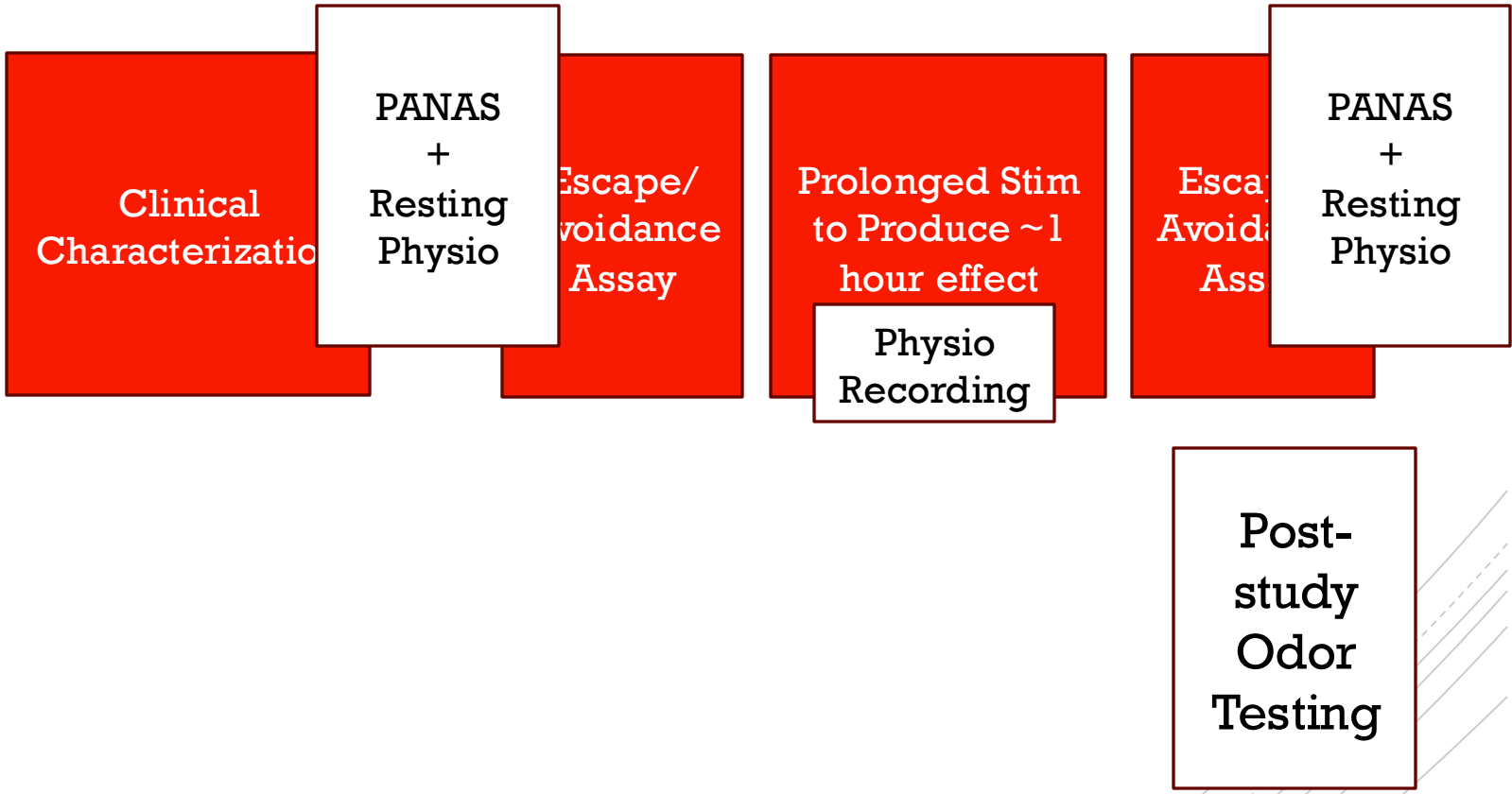
Post Sham Stimulation



Study 2
Mood State Variables

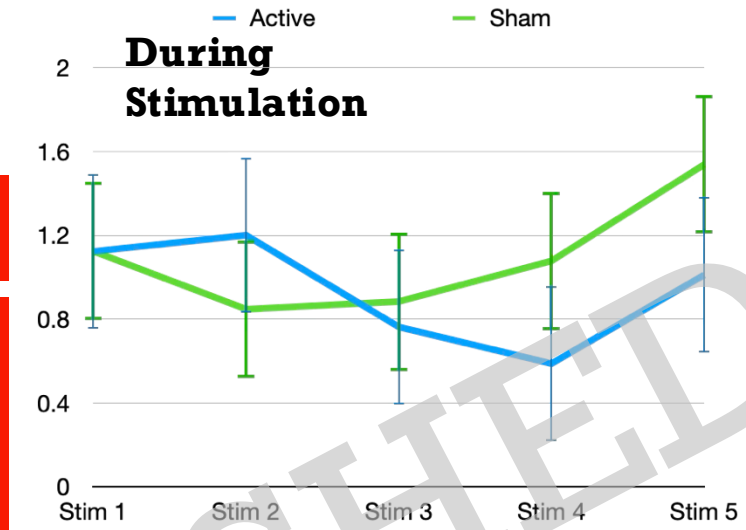
- Meanwhile, in 6 out of 8 subjects were correct in guessing which session was active
  - *Something is cluing subjects in…*
- …and, several subjects cited mood effects after the active session as the clue
  - *"After the active stimulation, things that usually bother me didn't as much"*
  - *"I felt tired after the active session"*
- For others, behavior change was noted by research staff (e.g., just seeming more relaxed)

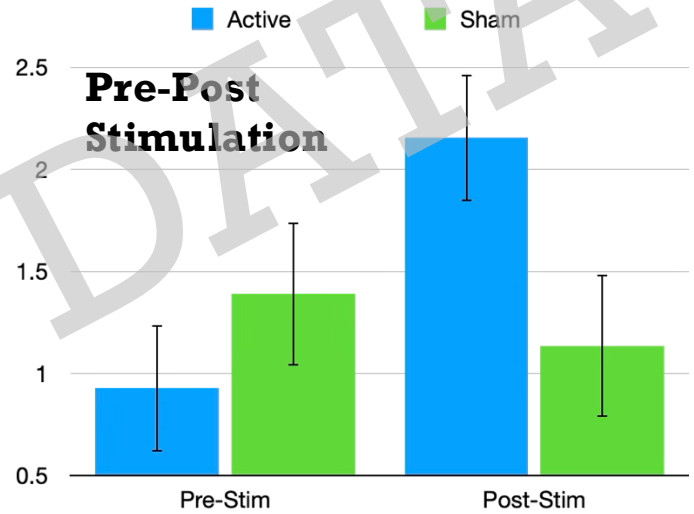
Study 2
Mood State Variables



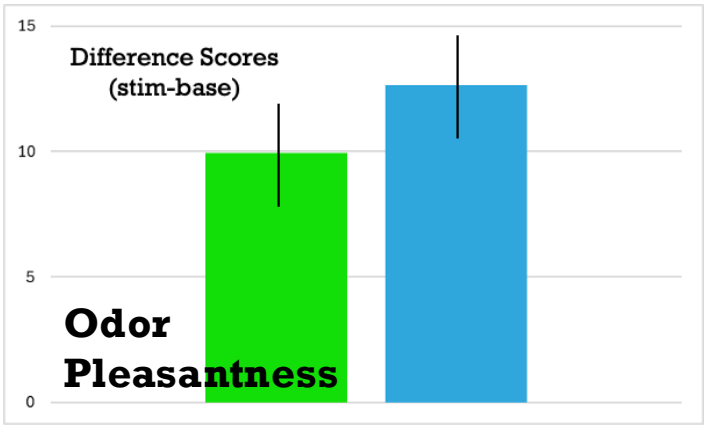
Study 2
Mood State Variables

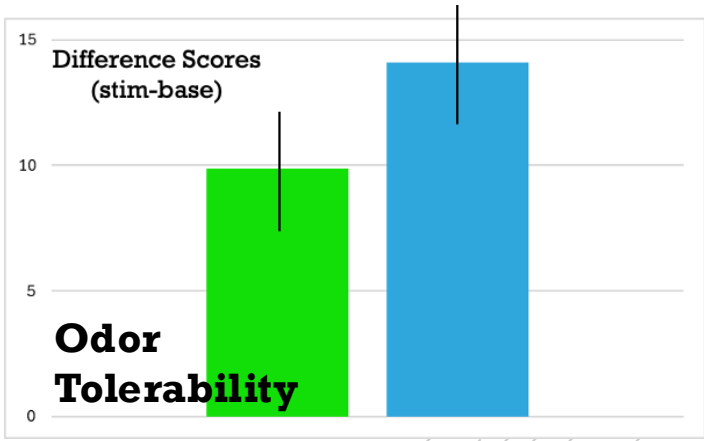
Heart Rate Variability





Odor Testing

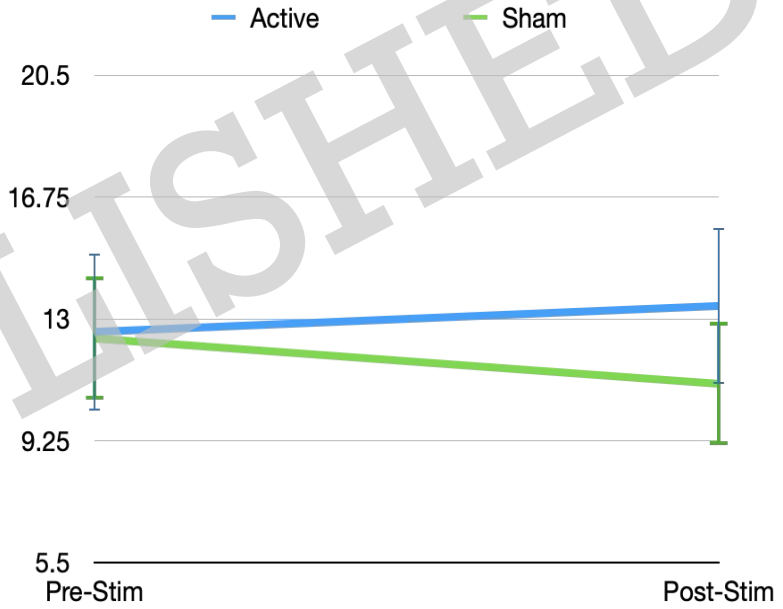




Study 2
Mood State Variables

Mood Scales: Positive and Negative Affect Schedules (PANAS)

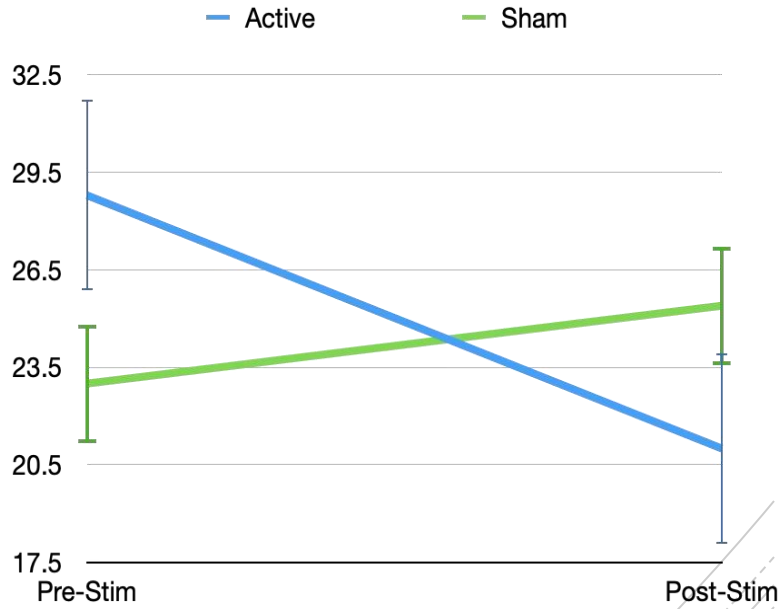
Negative Emotions



Example Items

Distressed *Scared*
Upset *Ashamed*
Guilty

Positive Emotions



Example Items

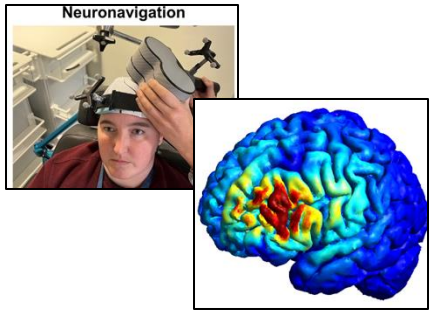
Alert *Interested*
Attentive *Enthusiastic*
Excited

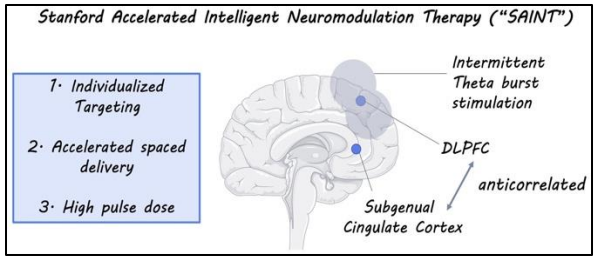
Study 2 Summary

- Starting to look like stimulating cortex might by a better way to impact fight/ flight regulation across contexts (e.g., escape vs. avoidance)
  - *Might make some sense – improving the cortex's ability to regulate fear*
- Meanwhile, we're seeing evidence that amygdala stimulation with LIFU impacts broad mood state
  - *Could be very useful as a supplement to behavioral treatment*
  - *We need a lot more work to figure out best parameters – which we are doing now*
- In the future, could the best strategy be to *combine* rTMS and LIFU?

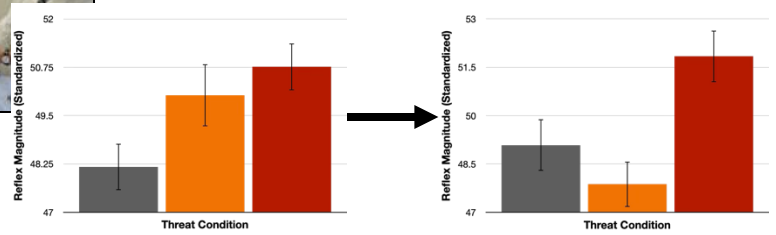
General Discussion

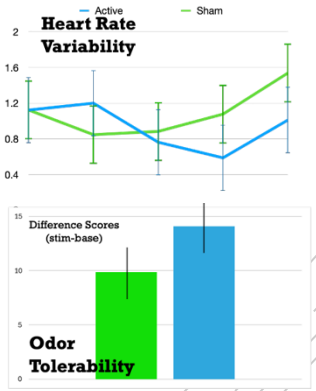
Non-invasive brain stimulation has advanced tremendously in its ability to treat psychiatric conditions (depression, OCD, nicotine use) that haven't responded to other treatments





Ability to treat *specific psychological processes and behaviors* – including fight/ flight system regulation – could extend brain stimulation's reach even further





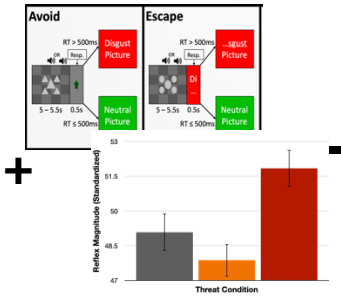
No reason to think that this will only work with fight/ flight system treatment

Treatment Possibilities

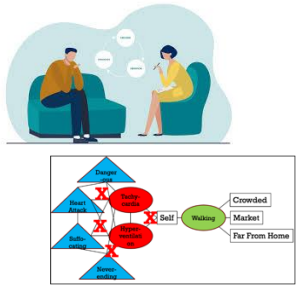
- Precursor or add-on to behavioral therapy?

Stim + Fight/ Flight Retraining

+



Behavior Therapy



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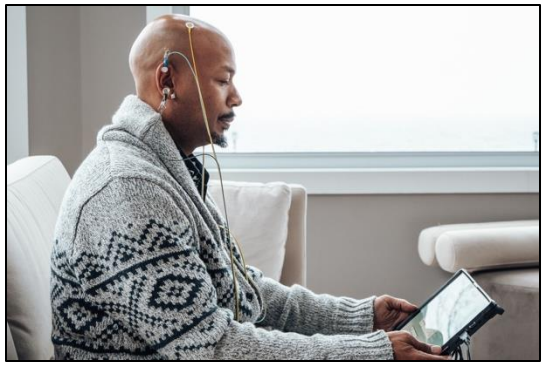
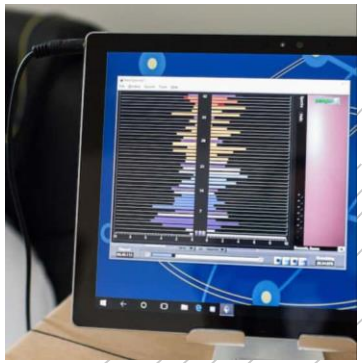
Response Rate

Drop-out

- Use in neurofeedback training?





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BRAIN & BEHAVIOR RESEARCH FOUNDATION

NIH National Institute of Mental Health

K23 Award: 5K23MH123931

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NIAAA National Institute on Alcohol Abuse and Alcoholism

Brain Stimulation Lab

- Mark George
- Lisa McTeague
- Kevin Caulfield

SMART Division

- Thomas Uhde
- Alyssa Rheingold
- Bernadette Cortese
- Ali Wilkerson

University of Florida

- Peter Lang
- Margaret Bradley

Project Coordinators

- Claire Cox
- James Lopez
- Sam LaPorta
- Jacob Weaver
- Christina Marsicano

Our generous study volunteers

MUSC admin/ support staff

All of you!