Posttraumatic Stress Disorder: Treatment and Biology

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McLean Hospital
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Posttraumatic Stress Disorder

DSM-5 Criteria

A ‘Pathological’ Fear Reaction

• Clinically important (5% to 10% population, 15% to 25% veterans and at-risk populations); Able to study – we know when it starts

*DSM-5* (*‘ERANDS’* - Event, Rexperience, Aviodance, Negative/Decreased, Sympathetic)

• **Criterion A: Event:** The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence; *Note that the response often involves intense fear*

Characteristic symptoms include persistent:

• **Criterion B:** Intrusion Symptoms: Re-experiencing of the traumatic event (nightmares, flashbacks)

• **Criterion C: Avoidance** Symptoms: Avoidance of stimuli associated with the trauma

• **Criterion D: Negative** alterations in cognition and mood related to trauma; Decreased interest / anhedonia; alienation; numbing

• **Criterion E:** Increased arousal (Sympathetic Hyperactivation) (decreased sleep, startle, hypervigilance, irritable/aggressive and self-destructive behavior) and decreased concentration
Post-traumatic Stress Disorder

- **Epidemiology:** not recognized until 1980 DSM-3
  - lifetime / current prevalence = 8-13% / 3%
  - Lifetime trauma exposure risk = 40-75%
  - Lifetime prevalence among those exposed to sign trauma up to 25%
  - (diff studies: 15% Vietnam veterans, 24% young urban adults, 39% traffic accident victims)
  - **Significant percentage of prisoners have PTSD**

- **Risk factors:** parental separation in childhood, family hx of anxiety, pre-existing anxiety / depression, other psychiatric disorder, acute dissociation with trauma, family hx of antisocial behavior, female, poorer coping strategies.

- **Course:** Often preceded by acute stress disorder. Can begin at any age. Usually sx begin within first 3 mos but may initiate >6 months after the stressor. May improve or disappear within a few months, or may become chronic, relapsing condition.
Genes + Environment Increase Risk of Anxiety / Fear Disorders and Posttraumatic Stress

GENES

ENVIRONMENT

TRAUMA

Fear-Related Disorders PTSD
Fear is evolutionarily useful
LeDoux, 1996

but… Dysregulated Fear leads to Phobia, Panic, and PTSD

- Single or repeated exposure to extremely traumatic situations

- Characteristic symptoms of PTSD
  - Increased anxiety (and hypervigilance)
  - Declarative memory alterations
  - Problems in sleep and concentration
  - Flashbacks
  - Inability to inhibit fear
Neural Circuits Regulating Fear Processing

**SENSORIMOTOR CORTEX**
FUNCTION: Coordination of sensory and motor functions
IN PTSD: Symptom provocation results in increased activation

**THALAMUS**
FUNCTION: Sensory relay station
IN PTSD: Decreased cerebral blood flow

**PARAHIPPOCAMPAL GYRUS**
FUNCTION: Important for memory encoding and retrieval
IN PTSD: Show stronger connectivity with medial prefrontal cortex; decreases in volume

**FEAR RESPONSE**
FUNCTION: Evolutionary survival
IN PTSD:
- Stress sensitivity
- Generalization of fear response
- Impaired extinction

**HIPPOCAMPUS**
FUNCTION:
- Conditioned fear
- Associative learning
IN PTSD:
Increased responsiveness to traumatic and emotional stimuli

**ANTERIOR CINGULATE CORTEX**
FUNCTION: Autonomic functions, cognition
IN PTSD: Reduced volume, higher resting metabolic activity

**PREFRONTAL CORTEX**
FUNCTION:
- Emotional
- Regulation
IN PTSD:
- Decreased gray and white matter density
- Decreased responsiveness to trauma and emotional stimuli

**ORBITOFRONTAL CORTEX**
FUNCTION: Executive function
IN PTSD: Decreases in volume

**AMYGDALA**
FUNCTION:
- Conditioned fear
- Associative learning
IN PTSD:
Increased responsiveness to traumatic and emotional stimuli
Risk Factors for PTSD

• Pre-traumatic
  – Gender (F>M)
  – Prior personal/family psychiatric history
  – Childhood trauma
  – Genetic factors
  – Education and IQ

• Post-traumatic
  – Lack social support
  – Material losses, ongoing stressors

Brewin et al., 2000; Ozer et al., 2003
Risk Factors for PTSD

• Traumatic and Peritraumatic (during the trauma):
  – Severity of the trauma (prolonged or repeated exposure, proximity)
  – Peritraumatic dissociation
  – Peritraumatic distress
  – Sense of vulnerability and loss of control
  – Physical pain
  – Decreased cortisol / increased heart rate at the time of trauma

Brewin et al., 2000; Ozer et al., 2003; Bui et al. 2010, 2011, 2012
Expert Consensus Guidelines
Intervention & Prevention

Early Intervention and Prevention

• Immediately after exposure:
  – Normalize distress
  – Educate patient, family and significant others
  – Repeated retelling of the event
  – Provide emotional support
  – Relieve irrational guilt
  – Refer to peer support group or trauma counseling
  – Consider short-term sleep medication for insomnia

Foa, Davidson, Frances, 1999
VA DOD 2017 Guidelines for Prevention of PTSD

• **Universal prevention**
  - Insufficient evidence therapy or meds acutely
  - Avoid forced trauma debriefing (critical incident stress debriefing)
  - Focus immediate needs, communication, family/social support, & psychoeducation and normalization emotional responses
  - Assess safety

• **Indicated prevention: ASD**
  - Individual trauma focused therapy with exposure +/- cognitive strategies
  - Insufficient evidence pharmacotherapy of ASD

• **More research needed evidence guided prevention interventions!**
Psychosocial Treatment for Anxiety Disorders and PTSD

• Cognitive-behavioral treatments
  – Exposure
  – Anxiety management techniques
• Eye Movement Desensitization and Reprocessing (EMDR)
• Psychodynamic treatments
• Group therapy
Psychotherapy for PTSD: Overview of Evidence-Based Individual CBTs for PTSD

- Cognitive Behavioral Treatment (CBT)
- Prolonged Exposure (PE)
- STAIR – Skills training in affect / Interpersonal regulation
- Cognitive Processing Therapy (CPT)
- Stress Inoculation Therapy (SIT)
- Eye Movement Desensitization and Reprocessing (EMDR)
- DBT-PTSD

Exposure (habituation) components of PTSD therapies can be understood as Pavlovian Extinction over time.
Premises of Trauma-Focused CBTs for PTSD

• Impediments
  – Avoidance
  – Emotional numbing
  – Unhelpful thoughts

• Keys to recovery
  – Approach, not avoid
  – Feel feelings
  – Consider alternative, more balanced thoughts
Prolonged Exposure

• Often 12-16 sessions; 60-90 min each

• Interventions
  – *In vivo* (“in real life”) exposure
    • successive approaching of feared places & situations until anxiety subsides
  – Imaginal exposure
    • repeated retelling of traumatic event until distress subsides
Pharmacological Treatments for PTSD

• 1) Antidepressants  SSRIss/SNRIss
• 2) What about benzodiazepines?
• 3) Other medications
  – Mood Stabilizers
  – Antipsychotics
  – Adrenergic Blockers (prazosin)
Low Remission Rates in PTSD: Antidepressants are effective options but low remission

Remission Rates in PTSD (%)\(^1,2\)

<table>
<thead>
<tr>
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<tr>
<td>Venlafaxine(^1)</td>
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<tr>
<td>Sertraline</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Paroxetine(^2)</td>
<td>25</td>
</tr>
<tr>
<td>Placebo</td>
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</table>

\(^1\) Venlafaxine study: CAPS-SX ≤20; Davidson JR. et al. *J Clin Psychopharmacology*. 2006


This information concerns a use that has not been approved by the US FDA.
Positive but relatively small effect sizes in SSRI Meta-analysis:
Possibly greater signal for paroxetine, fluoxetine and venlafaxine

Hoskins et al. 2015
Monoamine Dysfunction: Principal Evidence for Noradrenergic and Serotonergic Dysfunction in PTSD / MDD

**Norepinephrine (NE) dysregulation**
- Evidence suggests possibility of overactivation of NE release or hypersensitivity of receptor systems

**Serotonergic (5HT) dysregulation**
- Overall evidence for decreased activity of serotonin system
Physiology of NE and 5HT Firing

NE

- Crucial role in organizing the behavioral state
  - Arousal / Vigilance / Stress response
  - Modulation of emotional memory systems
  - Burst firing with switch from calm wakefulness vigilance / attention


5HT

- Most active with quiet, internally directed activity
- Inhibited by orientation

Euthymia

- Amygdala
- Locus Coeruleus
- NE
- CRF
- Dorsal PFC
- Ventral PFC
- Hippocamp
- 5-HT
- Euthymia
- Stress
- Fear
- Tolerance
- Resilience
- External sensory
- Internal memory
- Locus Coeruleus
- Raphe Nucleus
PTSD/MDD

- Amygdala
- Locus Coeruleus
- NE
- CRF
- Ventral PFC
- Dorsal PFC
- Hippocamp
- 5-HT
- Locus Coeruleus
- Raphe Nucleus

- External sensory
- Internal memory

- Stress
- Fear
- Tolerance Resilience
Treatment of PTSD / MDD

- TMS/ECT
- Psychotherapy
- SNRIs / NRIs
- SSRIs
- Benzodiazepines

Brain regions:
- Amygdala
- Hippocampus
- Locus Coeruleus
- Raphe Nucleus
- Dorsal PFC
- Ventral PFC

Chemicals:
- NE
- CRF
- 5-HT
What about Benzodiazepines and PTSD?

**Consistent concerns**

- **APA 2004 Guidelines:** Benzodiazepines cannot be recommended as monotherapy for PTSD
- **IOM report 2014:** Benzodiazepines and atypical antipsychotics for combat-related PTSD is contraindicated and strongly discouraged
- **VA DOD 2017 Guidelines:** Strong recommend against
  - *pre-clinical evidence suggests that benzodiazepines may actually interfere with the extinction of fear conditioning and/or potentiate the acquisition of fear responses and worsen recovery from trauma*
- Risk substance abuse and interference with extinction learning. Not first line for sleep either.
- Clearly NOT recommended monotherapy
- Possible cautious adjunctive or brief use associated symptoms (e.g. panic, insomnia) but not first line and not early
A Review of Atypical Antipsychotic Medications for PTSD

• N=18 trials (10 RCTs)
• risperidone & quetiapine: positive effects
  – Mainly on hypervigilance and intrusions
  – ES small
  – No data on long-term SE (metabolic)
• Other antipsychotics: not enough data

Ahern et al. 2011
Small RCT Olanzapine monotherapy in PTSD (n=28): Substantial Side Effect Burden

- 8 week flexible-dose RCT (mean dose 9mg/d)
- Olanzapine group v. placebo showed greater reduction of CAPS score at week 8, LOCF
- Substantial weight gain in 6/14 Olanzapine subjects


*p<0.05 vs. placebo
Quetiapine Monotherapy for PTSD RCT: VA Study (n=80)

Mean quetiapine dose = 258mg/day (range 50 to 800mg)
** P < 0.01. *P < 0.05.

This information concerns a use that has not been approved by the US FDA.
Lack of Efficacy for Adjunctive Risperidone for Military–related Antidepressant-Resistant PTSD

- N=247 diagnosed with military-related PTSD and ongoing symptoms despite at least 2 adequate SRI treatments
- Results:
  - Change in CAPS scores from baseline to 24 weeks was not significantly different between the groups
  - Risperidone did not reduce symptoms of depression or anxiety

This information concerns a use that has not been approved by the US FDA.
Prazosin Preferable to Quetiapine in Military PTSD: Naturalistic Study

- 237 Veterans with PTSD
- n=62 received prazosin, and 175 received quetiapine.
- Short-term effectiveness similar for prazosin (61.3%) and quetiapine (61.7%; P = 0.54).
- Prazosin group significantly more likely to continue their therapy to study end date compared with quetiapine (48.4% vs 24%; P < 0.001; odds ratio, 3.0; 95% confidence interval, 1.62-5.45)

**Conclusion:**

*Similar efficacy but greater tolerability and acceptability*

Inconsistent support prazosin: insomnia and nightmares better than monotherapy

• Alpha-1 adrenergic receptor antagonist, anti-hypertensive – permeates CNS and decreases noradrenergic hyperactivity

• Titrate slowly dosing to tolerability and response, usual range 1 to 16mg/d titration but some recommendations minimum 6mg/d often not met (Alexander et al. 2016)

• Two Different meta-analyses 6 RCTs (n=240: Kchachatryan et al., 2015; n=191: George et al., 2016)
  ➢ Prazosin more effective than placebo for nightmares (George), sleep quality and disturbance, and overall PTSD symptoms

• Multiple studies support effect nightmares including soldiers with PTSD (e.g. Raskind et al. 2013, n=67)
  ➢ Follow up analysis found higher baseline systolic BP positive predictor good response (Raskind et al. 2016)

❖ Large negative (mainly augmentation) trial in military combat related PTSD (clinical trials.gov, VA/DoD Guidelines) dampened enthusiasm PTSD (Raskind et al, 2018)

*Off label medication
Anticonvulsants for PTSD

- **Mostly Case Reports and Open Series**
- Valproate (Depakote)* Negative RCTs Divalproex (Depakene)
- Gabapentin (Neurontin)
- Pregabalin (Lyrica) *Positive small RCT
- Carbamazepine (Tegretol)
- Oxcarbazepine (Trileptal)
- Lamotrigine (Lamictal) *Mixed RCTs
- Topiramate (Topamax) *Negative RCTs
- Tiagabine (Gabitril) *Negative RCTs

This information concerns a use that has not been approved by the US FDA.
PE+paroxetine vs. PE+Placebo

- Adult survivors of 9/11 with PTSD
- 10-week PE+paroxetine (n=19) vs. PE+PCB (N=18)
- PE plus paroxetine resulted in greater improvement in PTSD symptoms and remission at 10 weeks
- But: The subset of patients who continued randomized treatment for 12 additional weeks showed no group differences.

Schneier et al. 2012
PE vs. Paroxetine vs. Combination

228 participants with PTSD from motor vehicle accident

Randomized to 12 weeks of PE (N=144), paroxetine (N=57), or a combination (N=57)

PE significantly greater SCID assessed remission rate compared to paroxetine

No other significant differences in PTSD remission (SCID and PDS)

**chi-square = 4.83, df = 1, p = .027

Popiel et al. 2015
Lack of evidence for Naltrexone for comorbid combat PTSD and alcohol dependence (n=88)

- 12 week RCT: four arms
  1. Paroxetine + naltrexone (n=22)
  2. Paroxetine + placebo (n=20)
  3. Desipramine + naltrexone (n=22)
  4. Desipramine + placebo (n=24)

- **Naltrexone reduced craving but did not significantly reduce any alcohol use outcome relative to placebo**

- However, Desipramine relative to Paroxetine reduced heavy drinking days (F=7.22; p<0.01) and number of drinks per drinking day (F=5.04, p<0.05)

- Desipramine was superior to paroxetine with respect to study retention

Combined Approaches May Address PTSD and Alcohol Use Disorder: *Seeking Safety* and *Sertraline*

- 69 participants with PTSD (full or sub-threshold) and drug dependence
  - Randomized to Seeking Safety (SS) treatment (12 sessions) with sertraline or placebo
  - SS is a present focused CBT for ETOH + PTSD

- Greater reduction in PTSD symptoms in combined SS + sertraline group from pre to post (M difference = -16.15, p = .04, d = 0.83)

- Sustained at 6- and 12-month follow up

- No differences in alcohol use disorder symptoms

Ketamine for PTSD

- Ketamine = antagonist of glutamate $N$-methyl-$D$-aspartate (NMDA) receptor
- Small study (n=41)
  - 18-55 year-olds with primary Dx PTSD (DSM-IV) and CAPS $\geq$ 50
- Ketamine hydrochloride (0.5mg/kg) vs. midazolam (0.045 mg/kg), one IV infusion
- **Rapid reduction in core PTSD symptoms in patients with chronic PTSD, and benefit up to 1 week**
- Ketamine SE’s:
  - short-lived dissociative symptoms (< 120 min)
  - 3 patients required acute treatment with $\beta$-blockers b/c of blood pressure elevation (systolic bp$>180$ mm HG and/or diastolic bp $>100$mm HG)
  - Blurred vision, dry mouth, restlessness, fatigue, nausea/vomiting

This information concerns a use that has not been approved by the US FDA.

Feder et al, 2014
Marijuana, Cannabinoids and PTSD

Cannabinoid system interesting potential target for drug development PTSD:

- Preclinical data supporting roles in fear consolidation and extinction (Ganon-Elazar, 2013) and amygdala (Hill et al., 2013)
- Human PET imaging data suggest abnormal CB-1 receptor signalizing (upregulation with low occupancy) in PTSD (Neumeister et al., 2013)
- Lower circulating endocannabinoids in PTSD (Hill et al., 2013)
- Cannabidiol (CBD) may have anxiolytic effects with THC’s euphoric and addictive potential (Blessing 2015)

  • Open support and small RCT (n=10) synthetic cannabinoid (nabilone) may reduce PTSD related nightmares (Frasier 2009; Jetly et al 2015)
• Media and anecdotal reports marijuana helpful for PTSD symptoms, and now legalized some states
• Lack controlled study smoking MJ (THC) and PTSD ...BUT open data do not show lower rates in smokers (Johnson, 2016) and longitudinal inpt vet study (n=2276) found greater violence, PTSD and ETOH use with MJ use and lower PTSD with stopping MJ (Wilkinson, 2015)
Risks: depression, drug dependence
• Marijuana use may in long term exacerbate underlying pathophysiology PTSD through CB-1 receptor adaptations: More research targeted agents needed
Transcranial Magnetic Stimulation (TMS):
Promise for PTSD in small RCTs with 10 TMS sessions targeting dorsolateral prefrontal cortex .....but variable study quality, dose and location

- Meta Analysis (Karsen et al., 2014) large effect size for TMS in Prefrontal Cortex
  - Cohen et al., 2004: (right) hi vs lo vs sham N=24, CAPS decreased, hi>lo
  - Boggio et al., 2010: right vs left vs sham N=30, PCL decreased
  - Watts et al., 2012: (right) lo vs sham N=20
- Nam et al. 2013: (right) lo vs sham, N=18, CAPS decrease
- Second meta-analysis n=64 PTSD similar findings (& Berlim et al 2014)
- **Mechanism**: Potentiates fear extinction, disrupts traumatic memories
VA DOD 2017 Guidelines for Pharmacotherapy of PTSD: Evidence Levels

• New: Recommend trauma focused evidence based therapies first over any pharmacotherapy
  ...BUT consider availability, feasibility and patient preference

• Recommend with moderate evidence for monotherapy
  - Antidepressants SSRIs (sertraline, paroxetine, fluoxetine) and one SNRI (venlafaxine)

• Suggest with Weak evidence for
  - Nefazodone, imipramine, phenelzine
  - Limited evidence for efficacy and serious potential adverse effect profiles
• **Weak evidence against**
  - Atypical antipsychotics: quetiapine, olanzapine
  - Citalopram, amitriptyline
  - Antiepileptic drugs: lamotrigine, topiramate

• **Strong evidence against (efficacy and/or risk)**
  - Cannabis or cannabis derivatives
  - Antiepileptic drugs: Divalproex, tiagabine
  - Guanfacine
  - Risperidone
  - Benzodiazepines, Ketamine
  - Hydrocortisone
  - D-cycloserine (weak against as augmentation CBT outside research)

• **NO rec for or against / weak or insufficient evidence**
  - Other antidepressants, prazosin for nightmares only, non benzo sleep agents
  - All augmentation or combination strategies
  - All integrative therapies & non-pharm biological interventions such as rTMS, ECT and VNS
The PTSD Coach

- Free app created by the VA’s National Center for PTSD and the DOD’s National Center for Telehealth and Technology

- Provides:
  - Information about PTSD and treatment
  - Self-assessment tools
  - Links to urgent services

The PTSD Coach, 2012, JAMA
Exercise: can it treat PTSD?

- Cross sectional and treatment studies suggest efficacy mostly aerobic exercise for depression, anxiety and panic
  - Most studies 8-14 weeks, 3-4X week, 20-30 minutes
  - Limitations: adherence in practice
- Much less data in PTSD
- 3 small open trials non-military adolescents and adults with decreased PTS symptoms
- RCT support for exercise augmentation inpatient usual care with 12 week exercise program (n=81)

Conclusions

• Evidence based trauma focused therapies strongly recommended

• Effective pharmacologic therapies exist for PTSD but best data for SSRI/SNRI and effects not universal

• Significant unmet need for more efficacious prevention, initial and next step refractory treatment

• More research needed on who responds to what treatment, how to personalize the interventions
## Call for Research:
Top Therapeutic Targets for PTSD from experts in the PTSD Psychopharmacology Working Group ($N = 27$)

<table>
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<tr>
<th>Target</th>
<th>Score</th>
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<tr>
<td>NMDA Receptor Antagonists</td>
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<tr>
<td>Cannabinoid Receptor Modulators</td>
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<td>Glucocorticoid Receptor Agonists</td>
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<td>Glucocorticoid Low-Activity Partial Agonists and/or Antagonist</td>
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<td>Anticonvulsants</td>
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<tr>
<td>D2 Receptor Agonists</td>
<td>8</td>
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Krystal et al., 2017
Modeling Fear Disorders

- Pre-existing Sensitivity (gene + environment)
- Learning of Fear (Traumatic event)
- Consolidation of Fear (Hours – days following event)
- Expression of Fear (Memories, Nightmares, Flashbacks, Avoidance, Sympathetic Response, Startle)

**PTSD**

- Generalization: Recruitment of Non-associated cues
- Sensitization: Increased Fear With repeated exposure
- Discrimination: Fear is limited to specific trauma cue
- Extinction: Diminished response to cues Over time

Fear Extinction
NMDA blockade prevents extinction, while an NMDA agonist (D-cycloserine – DCS) enhances Extinction


Given systemically or Intra-amygdala


Enhancement of Extinction in Humans
D-Cycloserine and Virtual Reality Exposure:
Barbara Rothbaum, PhD and colleagues
Therapy for Acrophobia


Reduction in Fear

Virtual Floor

Placebo
D-cycloserine
Initial data suggested that NMDA Enhancer IMPROVES Psychotherapy (extinction) across Anxiety Disorders

Social Anxiety

Obsessive – Compulsive

PTSD / Panic

Meta-Analysis: D-cycloserine Augmentation of Behavioral Therapy for the Treatment of Anxiety Disorders

Ms. Allyson Bontempo, B.S., Ms. Kaitlyn E. Panza, B.A., and Dr. Michael H. Bloch, M.D., M.S.
Yale University Child Study Center

Review

A Meta-Analysis of D-Cycloserine and the Facilitation of Fear Extinction and Exposure Therapy

Melissa M. Norberg, John H. Krystal, and David F. Tolin

Background: Translational research suggests that D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) receptor agonist, might facilitate fear extinction and exposure therapy by either enhancing NMDA receptor function during extinction or by reducing NMDA receptor function during fear memory consolidation. This article provides a quantitative review of DCS-augmented fear extinction and exposure therapy literature.
D-Cycloserine Augmentation of Exposure Therapy: Promise but Failed Efficacy Trials

- Early preclinical data demonstrated promise for DCS and fear extinction
- 4 Trials to date with a total of 274 adults with PTSD
  - 1 found significant improvement with DCS but only at 6 month follow up (Difede et al. 2014)
  - 1 found DCS worse than placebo (Litz et al. 2012)
  - 2 found no differences between groups (de Kleine et al. 2012, Rothbaum et al. 2014)
- Consistent with Ori et al. 2015 and McGuire 2017 meta-analysis (20 RCTs, n=5 in PTSD):
  - Despite early positive trials, additional meta-analyses showed no significant effect of DCS augmentation of cognitive and behavioral therapies across anxiety and PTSD
  - This may be related to DCS-mediated increased neuroplasticity, which may worsen symptoms (enhance reconsolidation / sensitization) if behavioral therapy is not efficacious
  - Ideally one would be able to specifically enhance Extinction only
Rationally Designed Therapies Based on Amygdala Biology

Select Neuronal Populations in Amygdala

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<th>Marker</th>
<th>Function</th>
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<td>GRP</td>
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<tr>
<td>Thy1</td>
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<tr>
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<td>SST</td>
<td>Inhibitory</td>
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<td>FoxP2</td>
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<tr>
<td>VP</td>
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Switching on and off fear by distinct neuronal circuits

Cyril Herry¹*, Stephane Ciocchi¹*, Verena Senn¹, Lynda Demmou¹, Christian Müller¹ & Andreas Lüthi¹
Optogenetically activating the Thy-1 neurons *in vivo* inhibits fear consolidation

Take home:
If we can target the ‘Fear Off’ neurons specifically, it would create a novel and powerful new way to treat PTSD and fear-related disorders.

Jasnow, Ehrlich, Rainnie et al., 2013, *J Neurosci*
PTSD Current Treatment Summary
Expert Consensus Guidelines

Noncomorbid children, adults, geriatric patients
- Mild PTSD: Psychotherapy first
- More severe: Psychotherapy first or combine meds/psychotherapy

Comorbid population
- Combine meds/psychotherapy from start