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The Evolution of Post-traumatic Stress Disorder: Focus on Diagnostic, Evaluation, and Treatment Advances

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Objectives

- Review some of the basics about post-traumatic stress disorder (PTSD)
- Consider how perceptions of the disease, PTSD diagnostics, and assessment of symptoms have changed over time
- Discuss advances in the understanding of PTSD neurobiology
- Provide an overview of select treatments for PTSD and an update on the identification of potential biomarkers

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The Basics of PTSD

PTSD: Did You Know?

In the general population, women are 2x as likely as men to experience PTSD at some point in their lives. Of those who have experienced trauma, about 1 in 10 men and 2 in 10 women will develop PTSD[1,2]

Sexual assault is more likely to result in symptoms of PTSD than are other types of trauma, including combat[1]

Social support is a resilience factor against developing PTSD after trauma; research suggests it is more protective for women than men[1]

Many people with PTSD also experience chronic pain or other physical health problems[1]

PTSD often co-occurs with depression or other mental health conditions[1]

PTSD, post-traumatic stress disorder.

1. US Department of Veterans Affairs. Veterans Health Administration. 27 Things You Should Know About PTSD. Available at: https://www.va.gov/health/NewsFeatures/2013/June/27-Things-You-Should-Know-about-PTSD.asp. Updated June 27, 2013. Accessed May 14, 2018.
2. National Center for PTSD. Understanding PTSD and PTSD Treatment. February 2018. Available at: https://www.ptsd.va.gov/public/understanding_ptsd/booklet.pdf. Accessed May 14, 2018.

PTSD: Why Does It Matter?

A study of male veterans who served in the Vietnam War reported that those with PTSD had 2x the risk of death from heart disease*; each 5-point increase in symptom score corresponded to a 20% increase in risk of heart disease mortality[1]

Sleep problems, beyond being a defining symptom of PTSD, often develop into independent disorders in patients with PTSD and are associated with significant distress and impairment, including increased risk for suicidality[2,3]

Patients with PTSD have a higher risk of substance use disorders, and often have comorbid physical and/or mental health disorders[3]

Studies examining an association between PTSD and suicide among civilian populations have reported consistent evidence of a strong association, even after accounting for preexisting psychiatric comorbidity[4]

*During a 15-year follow-up period. PTSD, post-traumatic stress disorder.

1. Arenson M, Cohen B. *PTSD Res Q*. 2017;28(1).
2. Gehrman P et al. *PTSD Res Q*. 2016;27(4).
3. US Department of Veterans Affairs. Veterans Health Administration. 27 Things You Should Know About PTSD. Available at: https://www.va.gov/health/NewsFeatures/2013/June/27-Things-You-Should-Know-about-PTSD.asp. Updated June 27, 2013. Accessed May 14, 2018.
4. Gradus JL. *PTSD Res Q*. 2017;28(4).

PTSD: Overview

- PTSD is a psychiatric disorder that can affect individuals exposed to psychological trauma[1]
- Studies of the US general population have reported a lifetime PTSD prevalence of 6.8%–7.8% (highly variable across studies*)[2]
  - Most prevalence studies have evaluated the general population or military veterans
- The highest rates of PTSD (33%–≥50% of those exposed) are reported among survivors of rape, military combat and captivity, and ethnically or politically motivated internment and genocide[3]

*Variability is likely due to population type assessed and/or methodology of assessment.

PTSD, post-traumatic stress disorder; US, United States.

1. Michopoulos V et al. *Biol Psychiatry*. 2015;78(5):344-353.
2. Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Arlington, VA, American Psychiatric Association; 2013.

PTSD and Traumatic Events

- PTSD is one of the few psychiatric disorders requiring an identifiable causal external event[1]
- The most studied traumatic events leading to PTSD include[2]:
  - Combat exposure and injuries (among men) and rape, childhood sexual abuse, and domestic violence (among women)
- The severity and duration of a traumatic event and the risk for development of PTSD have a dose–response relationship[2]

PTSD can be caused by a variety of traumatic events[3]*

- Combat and military experiences
- Sexual or physical assault
- Learning of violent or accidental death or injury of loved one
- Child sexual or physical abuse
- Serious accidents
- Natural disasters
- Terrorist attacks

*Not an exhaustive list.

PTSD, post-traumatic stress disorder.

1. Zoellner LA et al. *Psychol Inj Law*. 2013;6(4):277-289.
2. Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.
3. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA, American Psychiatric Association; 2013.

Symptom Presentation in PTSD

- PTSD is heterogeneous and often presents across several symptom domains, including[1]:
  - Re-experiencing, avoidance/numbing, and hyperarousal symptoms
- Common symptom presentation may differ by specialty:[2]
  - Primary care (eg, headaches, sleep disturbances, pain)
  - Mental health clinics (eg, depression, substance use, self-harm)
- Recognition of the condition is important, as even patients with subthreshold PTSD may have significant impairment that requires intervention[2,3]

PTSD, post-traumatic stress disorder.

1. Michopoulos V et al. *Biol Psychiatry* 2015;78(5):344-353.
2. Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.
3. Naylor JC et al. *Psychiatry Res*. 2013;206(2-3):318-320.

Potential Symptoms of PTSD in Adults*

- **Dysphoric or negative mood states** (eg, anger, guilt, shame)
- **Recurrent, involuntary, intrusive, fear-based reexperiencing of event**
- **Anhedonic mood states** (eg, disinterest, detachment, lack of positive emotion)
- **Concentration difficulties**
- **Difficulty remembering**
- **Reckless or self-destructive behavior**
- **Negative alterations in cognition** (eg, negative beliefs/ expectations, distorted blame)
- **Hyperarousal**
- **Sleep problems and/or nightmares**
- **Hallucinations; paranoid ideation**
- **Reactive to unexpected stimuli**
- **Dissociative symptoms** (eg, dissociative amnesia) Subtype specifier
- **Avoidance of trauma-related thoughts or reminders**
- **Difficulty regulating emotion** (eg, short temper, aggressive behavior with little provocation)
- **Heightened sensitivity to potential threats** (hypervigilance)

*Not an exhaustive list. PTSD, post-traumatic stress disorder.

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders.* Fifth Edition. Arlington, VA, American Psychiatric Association; 2013.

Mental Health Comorbidities: A Common Occurrence

- PTSD is highly comorbid with other mental disorders[1]
  - >90% of patients with PTSD have 1 or more lifetime comorbid mental disorders[1]
    - The most prevalent conditions include MDD, alcohol abuse/dependence, and anxiety disorders[1]
- Many symptoms of PTSD overlap with those of other mental disorders[1,2]
  - For example, many numbing and hyperarousal symptoms overlap with depressive symptoms, including loss of interest, detachment, difficulty concentrating, sleep impairment, and irritability[2]
- PTSD is differentiated from other mental disorders by the re-experiencing of symptoms (eg, nightmares, flashbacks)[1]

MDD, major depressive disorder; PTSD, post-traumatic stress disorder.

1. Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.
2. Zoellner LA et al. *Psychol Inj Law*. 2013;6(4):277-289.

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Evolution of Perceptions of PTSD, PTSD Diagnostics, and Symptom Assessment

The Introduction and Evolution of PTSD

- Although PTSD has been observed throughout history, it was first officially introduced in DSM-III (1980)
- The definition of PTSD has varied across DSM editions, but 4 core features have remained throughout
  1. Experiencing or witnessing a stressful event;
  2. Re-experiencing symptoms of the event, including nightmares and/or flashbacks;
  3. Efforts to avoid situations, places, and people that are reminders of the traumatic event; and
  4. Hyperarousal symptoms, such as irritability, concentration problems, and sleep disturbances

DSM, Diagnostic and Statistical Manual of Mental Disorders; PTSD, post-traumatic stress disorder.

Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.

Evolution of the Diagnosis of PTSD[1,2]

Early names:
Nostalgia
Soldier's heart

World War I:
Shell shock
War neurosis

World War II:
Combat stress
Combat fatigue
Traumatic neurosis

DSM-I:
Transient situational personality disorders: gross stress reaction

DSM-II:
Transient situational disturbances

Vietnam War:
Post-Vietnam syndrome
Traumatic war neurosis

	DSM-5 (2013)	DSM-IV (1994)	DSM-III-R (1987)	DSM-III (1980)
Definition of Trauma (Criterion A)	Exposure to actual or threatened death, serious injury, sexual violation by either: direct experiencing, witnessing other people experiencing the event, learning that event occurs to close family member or friend, or experiencing repeated exposure to details of the event	Experiencing or witnessed an event involving actual or threatened death or serious injury, or a threat to the physical integrity of self or others; the person's response involved intense fear, helplessness, or horror	Added: ie, physical life threat, psychological threat to well-being, physical or psychological threat to well-being of significant others	Experiencing a stressful event that would evoke significant symptoms of distress in almost everyone
Selected Differences	• PTSD is no longer clustered within Anxiety Disorder, but within Trauma and Stressor Related Disorders • Removal of the subjective component (emotional response) from the definition of trauma • Addition of "negative alterations in cognitions and mood" as a criterion	• Incorporates an individual's emotions into the definition of trauma • Expanded definition of trauma to include witnessing	• Diagnostic symptoms expanded from 12 to 17 • Identified age-specific features	• PTSD emerged as a separate diagnostic entity, placed among anxiety disorders

DSM, Diagnostic and Statistical Manual of Mental Disorders; PTSD, post-traumatic stress disorder.

1. Echterling LG et al. Evolution of PTSD diagnosis in the DSM. In: Safir MP et al, eds. *Future Directions in Post-Traumatic Stress Disorder*. New York, NY: Springer; 2015.
2. Sareen J. *Can J Psychiatry.* 2014;59(9):460-467.

Heterogeneity of PTSD

According to DSM-5 criteria, there are ~636,120 different ways in which an individual can be diagnosed with PTSD

DSM, Diagnostic and Statistical Manual of Mental Disorders; PTSD, post-traumatic stress disorder.
Michopoulos V et al. *Biol Psychiatry* 2015;78(5):344-353.

Evolution of the Clinician-Administered PTSD Scale (CAPS)

- CAPS: A structured interview developed to measure the core set of PTSD symptoms, as outlined in the DSM-IV[1]
  - 22-item scale that has frequency and intensity rating scales for symptoms[1]
  - Demonstrated solid psychometric properties in trauma populations[1]
  - Considered the gold standard in PTSD assessment[1]
- With the release of DSM-5, the CAPS was updated (CAPS-5)[2]
  - 30-item scale that assesses 20 DSM-5-identified PTSD symptoms
  - Can be used to assess PTSD symptoms over the past week or to make current (past month) or lifetime diagnosis of PTSD

Key Changes to CAPS-5 From Previous Version[2]

- Identify a single (vs ≤3) traumatic event to serve as the basis of symptom inquiry
- Change from 22-item to 30-item questionnaire, corresponding to the DSM-5 (rather than the DSM-IV)
- Language reflects changes to existing symptoms, addition of new symptoms, and addition of dissociative subtype of PTSD
- Symptom items are rated with a single severity score (vs separate frequency and intensity scores)

PTSD, post-traumatic stress disorder.

1. Griffin MG et al. *J Trauma Stress*. 2004;17(6):497-503.
2. Veterans Administration. National Center for PTSD. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Available at: https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp. Accessed April 2018.

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Discussion

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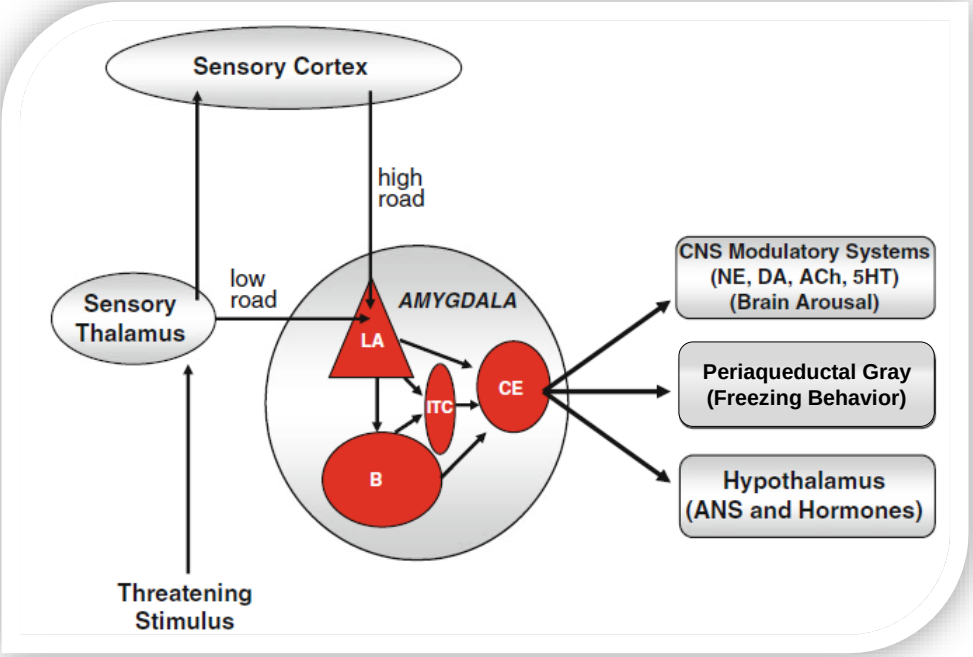
Recent Advances in the Understanding of PTSD Neurobiology

The Amygdala: A Critical Role in Fear Processing

- The amygdala plays a critical role in fear[1]
- It consists of a group of interconnected nuclei, with differing functions, including[1]:
  - Computation of possible danger and emotional salience[2]
  - Control of expression of behavioral, autonomic, and endocrine fear responses[1]
  - Activation of amine modulatory systems (ie, adrenergic, serotonergic, dopaminergic, and cholinergic systems)[1]
  - GABA-ergic signaling[1]



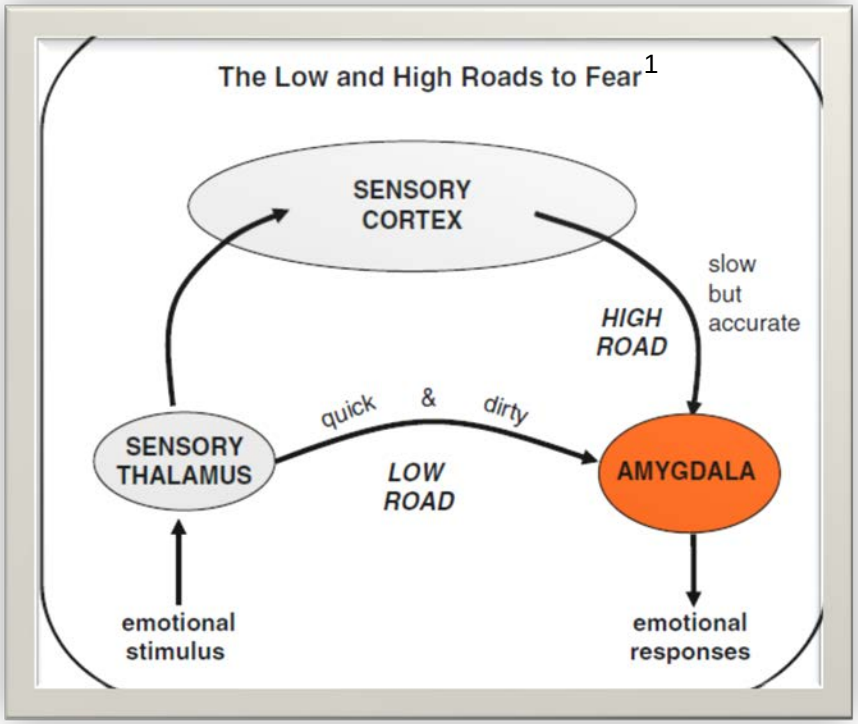
LA: Sensory gateway of amygdala
B: Receives projections from hippocampus and regions that may convey environmental contextual information
CE: Major output area that projects to brainstem regions
ITCs: Have inhibitory control over CE, lowering output

Ach, acetylcholine; ANS, autonomic nervous system; B, basal; CE, central; DA, dopamine; GABA, gamma-aminobutyric acid; ITCs, intercalated cells; LA, lateral; NE, norepinephrine; 5-HT, serotonin.

1. Debiec J, LeDoux J. The amygdala and the neural pathways of fear. In: Shiromani P et al, eds. *Post-Traumatic Stress Disorder: Basic Science and Clinical Practice.* Philadelphia, PA: Springer; 2009.
2. Silverstein DN, Ingvar M. *Front Syst Neurosci.* 2015;9:101.

Direct and Indirect Fear Detection Pathways

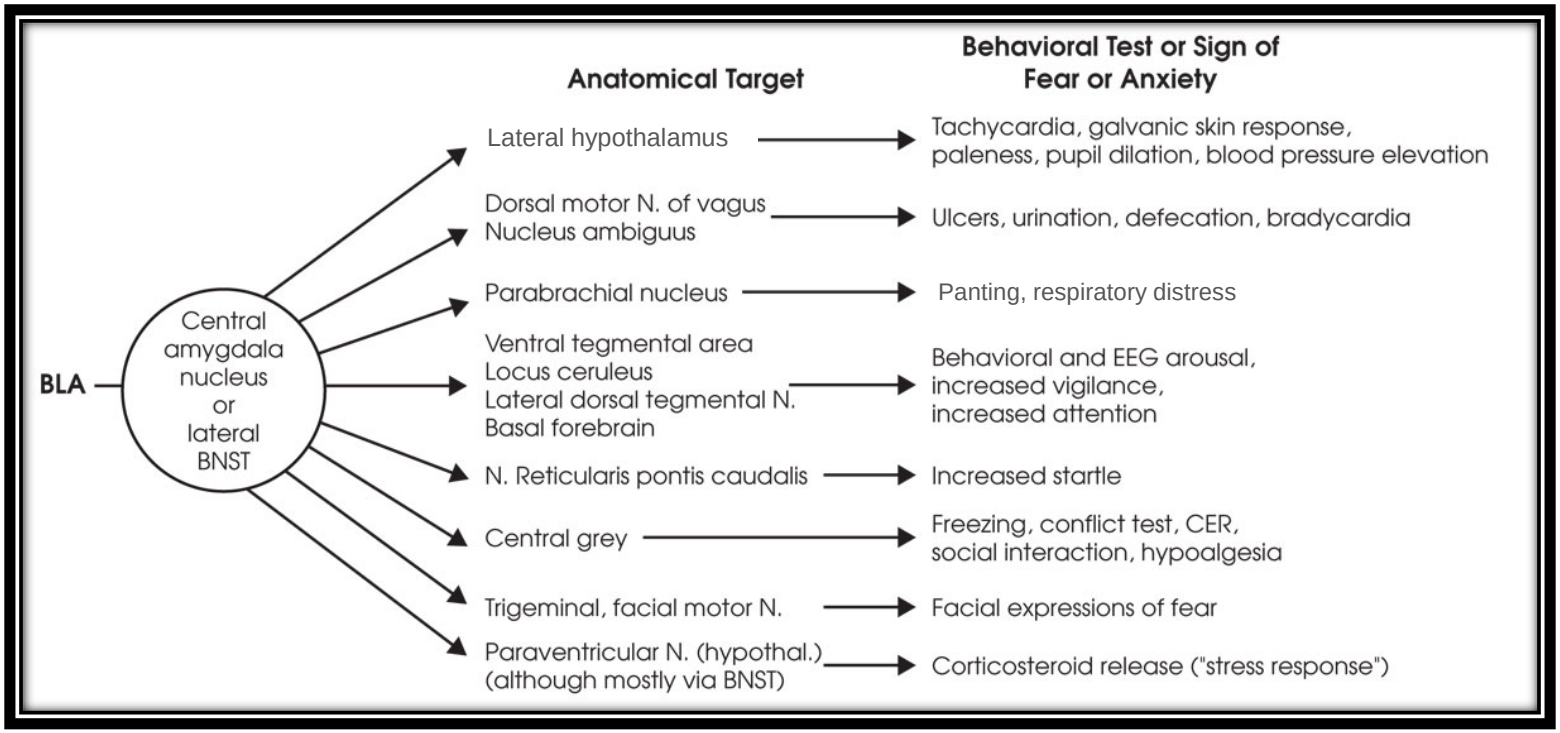
- Sensory information reaches lateral nucleus through 2 sensory inputs[1]
  - Thalamic pathway ("low road") conveys a rapid and imprecise signal
  - Cortical pathway ("high road") delivers more refined and detailed representation, but includes additional synaptic connections, making transmission longer
- Evidence exists for 4 parallel pathways from inferior temporal cortex to amygdala ("high roads"), each having different correlated behavioral characteristics and propagation times[2]



1. Debiec J, LeDoux J. The amygdala and the neural pathways of fear. In: Shiromani P et al, eds. *Post-Traumatic Stress Disorder: Basic Science and Clinical Practice.* Philadelphia, PA: Springer; 2009.
2. Silverstein DN, Ingvar M. *Front Syst Neurosci.* 2015;9:101.

Triggering Fear and Anxiety Symptoms and Resulting Behavioral Responses

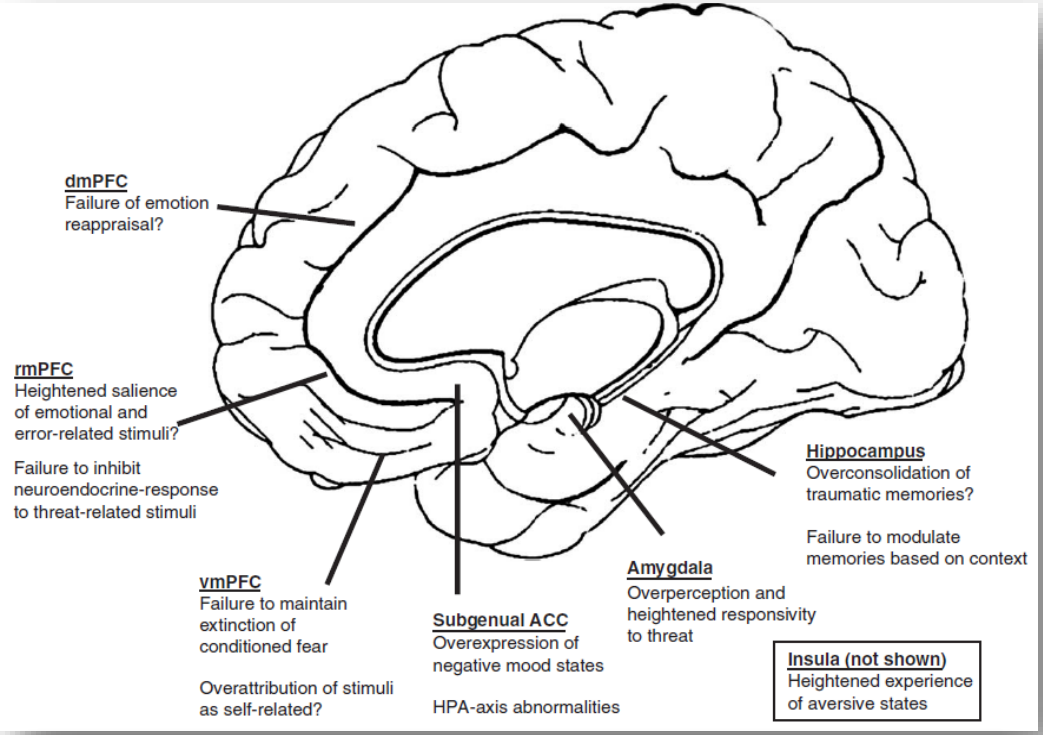
Outputs of the Central Nucleus or Lateral Division of the BNST to Various Target Structures and Possible Functions of These Connections



BLA, basolateral nucleus of the amygdala; BNST, bed nucleus of the stria terminalis; CER, conditional emotional response; EEG, electroencephalogram; hypothal, hypothalamus; N, nucleus.
Berlant JL. *Primary Psychiatry*. 2003;10(10):41-49.

Neural Regions Implicated in PTSD: The Prefrontal Cortex and Its Role in Contextualization

- PTSD has been conceptualized as a state of heightened responsivity to threatening stimuli or insufficient inhibitory control over exaggerated threat-sensitivity
  - Roles have been identified for mPFC, amygdala, extended amygdala, and hippocampus in mediating PTSD symptom formation
- Such models have been unable to fully explain the complexity of PTSD
  - Other processes are relevant, including fear conditioning, habituation, and extinction; cognitive–emotional interactions; and self-related and social emotional processing
- mPFC may play a role in contextualization, which could be dysregulated in PTSD
  - Process by which key dimensions of situational context are appraised, represented, and used to guide actions



Categories of Contextual Variables in the mPFC
Cognitive: Judges relevance of stimuli to memories and goals
Social: Judges extent to which stimuli are self-related
Internal: Judges overall homeostatic state of the internal milieu

ACC, anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; HPA, hypothalamic pituitary adrenal; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; PTSD, post-traumatic stress disorder; rmPFC, rostral medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex.
Liberzon I, Sripada CS. *Prog Brain Res.* 2008;167:151-169.

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Discussion

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PTSD Treatments and Biomarkers

Treatment of PTSD: Psychological and Pharmacological

- Treatment generally requires a combination of psychological and pharmacological approaches[1]
- Psychological treatments are considered first-line[1]
  - Treatments include CBT, prolonged exposure, and eye movement desensitization and reprocessing therapy
  - A potential barrier is the limited number of available trained therapists
- SSRIs have demonstrated efficacy in reducing symptoms and are considered first-line[1]
- Other medications may be required to alleviate insomnia and nightmares[1]
  - Alpha 1-adrenergic blockers, atypical antipsychotics, hypnotics, nonbenzodiazepines, and antihistaminergic drugs have been used to impact sleep, nightmares, and hyperarousal[1,2]

CBT, cognitive behavioral therapy, PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors.

1. Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.
2. Gehrman P et al. *PTSD Res Q*. 2016;27(4).

Selected Therapies That Have Demonstrated Efficacy in Treating PTSD

Psychotherapies	
Cognitive Behavioral Therapy (CBT)	CBT comprises a group of therapeutic methods that usually include relaxation and exposure techniques and cognitive restructuring techniques that aim to change dysfunctional beliefs[1]
Prolonged exposure or exposure therapy (ET)	In exposure therapy a patient is asked to vividly recount a traumatic event repeatedly until his or her emotional response decreases. The patient is also asked to gradually confront safe but fear-evoking trauma reminders[2]
Eye movement desensitization and reprocessing (EMDR)	EMDR uses eye movements or other forms of bilateral stimulation to desensitize patients to anxiety and integrate information processing[3,4]
Pharmaceutical therapies	
Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRI antidepressants are considered first-line medication treatments for PTSD; however, SSRIs alone are not usually effective in treating insomnia and nightmares associated with PTSD[5,6]
Alpha 1-adrenergic blocker	Alpha 1-adrenergic blockers have demonstrated efficacy in reducing nightmares and hyperarousal related to PTSD[5,7]
Other therapies	
Transcranial magnetic stimulation (TMS)	TMS uses a pulsed magnetic field to noninvasively modulate neuronal activity[8]

PTSD, post-traumatic stress disorder.

1. Mello PG et al. *Int J Psychiatry Med.* 2013;46(4):339-357.
2. Schnurr PP et al. *JAMA.* 2007;297(8):820-830.
3. Chen YR et al., *PLOS One.* 2014;9(8):e103676-e103676.
4. Shapiro F. *Perm J.* 2014;18(1):71-77.
5. Sareen J. *Can J Psychiatry*. 2014;59(9):460-467.
6. Hoskins M et al. *Brit J Psychiatry.* 2015;206:93-100.
7. Raskind MA et al. *Am J Psychiatry.* 2013;170:1003-1010.
8. Clark C et al. *Curr Psychiatry Rep.* 2015;17:83.

TMS as a Treatment for PTSD

- Many patients do not adequately respond to traditional therapies
  - Intense emotions triggered by exposure therapy may be intolerable and can lead to discontinuation; such therapies can also be labor-intensive and require training to administer
  - Treatment with pharmacotherapy can be limited by intolerance, side effects, noncompliance, and contribution to polypharmacy
- TMS uses a pulsed magnetic field to noninvasively modulate neuronal activity; when delivered repeatedly, it is referred to as repetitive TMS
  - Variables modulating the interaction between the device and the brain include type of coil utilized, frequency of stimulus delivery, duration of pulse sequence, interstimulation rest periods, strength of magnetic field, total number of pulses in each session, and regularity of administered treatments
- While optimal treatment parameters remain to be defined, evidence suggests 2 promising targets: the right dorsolateral prefrontal cortex and the mPFC
  - Functional imaging studies have implicated alterations in the activity of these regions in PTSD

PTSD, post-traumatic stress disorder; mPFC, medial prefrontal cortex; TMS, transcranial magnetic stimulation.

Clark C et al. *Curr Psychiatry Rep*. 2015;17(10):83.

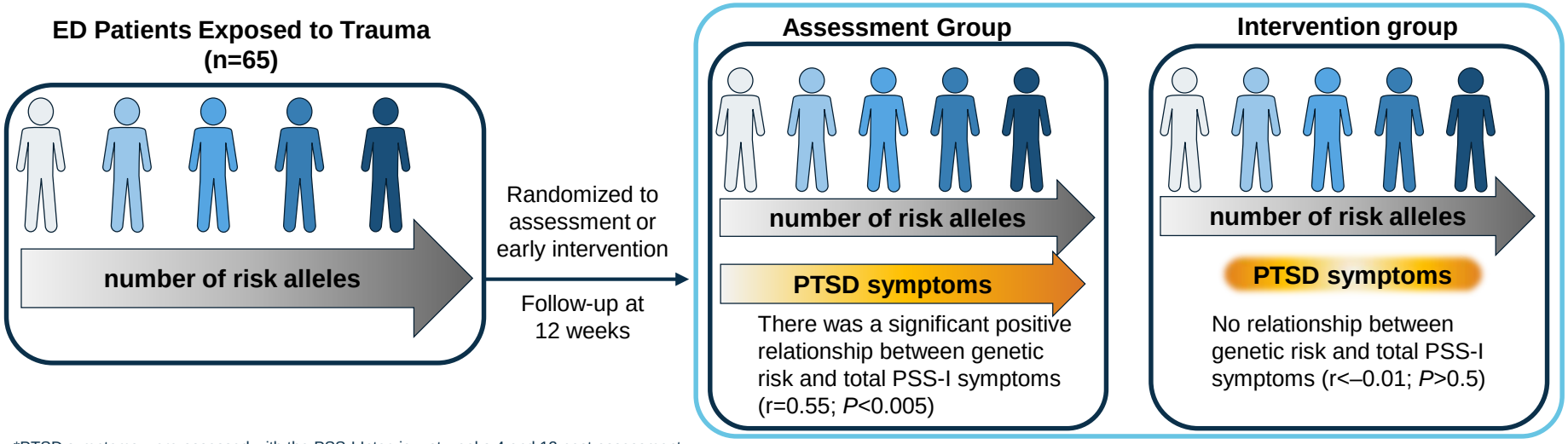
Early Intervention in PTSD: Considering Genetic Risk

Methodology

- A study evaluated the effects of early intervention on the development of PTSD
  - 65 ED patients exposed to trauma were randomized to receive either 3 sessions of an exposure intervention, beginning shortly after trauma exposure, or assessment only, and PTSD symptoms were assessed*
  - Patients were genotyped for 10 genes previously associated with stress-response and assigned an additive risk score

Results

- Number of risk alleles was significantly associated with the likelihood of PTSD diagnosis (both groups)
- In patients with higher risk scores, early intervention was associated with significantly fewer symptoms of PTSD at 12 weeks compared to assessment only



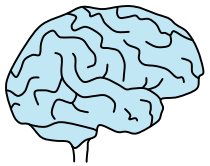
*PTSD symptoms were assessed with the PSS-I Interview at weeks 4 and 12 post-assessment.

ED, emergency department; PSS-I, PTSD Symptom Scale-Interview; PTSD, post-traumatic stress disorder.

Rothbaum BO et al. *J Clin Psychiatry.* 2014;75(12):1380-1387.

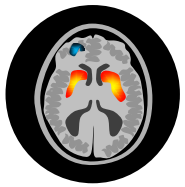
Potential Biomarkers for PTSD*

Neurotransmitters, peptides, and hormones[1]



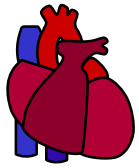
↑ Serotonin receptor 1A
↓ Serotonin Transporter
↓ Neuropeptide Y
↑ Norepinephrine
↑ Cannabinoid 1 receptors
↓ Allopregnanolone
↑ Arginine vasopressin

Neuroimaging and physiology[1]



↓ Hippocampal volume
↑ Amygdala reactivity
↓ ACC activity during emotion processing

Cardiac Physiology[1]



↑ Heart rate reactivity in response to loud tones

HPA Axis[1]

↑ Glucocorticoid negative feedback
↑ Corticotropin releasing hormone
↑ Glucocorticoid receptors
↓ FKBP5

Lymphatic and Immune System[1]

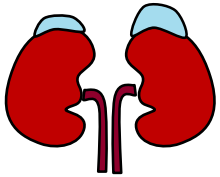
↑ Immune cell sensitivity to glucocorticoids
↑ Inflammatory cytokines
↑ NFκB
↑ C-reactive protein

Genetic and Epigenetic Markers

Polymorphisms in genes for[2]
- PACAP
- FKBP5

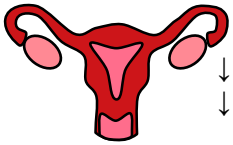
DNA methylation at genes for[3]
- Glucocorticoid receptor
- Corticotropin-releasing hormone
- Arginine vasopressin

Adrenals[1]



↓ Baseline cortisol
↑ DHEA
↑ DHEA-S

Reproductive Hormones[1]



↓ Testosterone in men
↓ Estradiol in women

*Causal relationships for these markers have not been established. Many are associated with other psychiatric conditions, some of which are often comorbid with PTSD (ie, not exclusive to PTSD).

ACC, anterior cingulate cortex; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; FKBP5, FK506 (tacrolimus) binding protein 5; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PACAP, pituitary adenylate cyclase-activating polypeptide.

1. Michopoulos V et al. *Biol Psychiatry.* 2015;78(5):344-353.
2. Sheerin CM et al. *Curr Opin Psychol.* 2017;14:5-11.
3. Rampp C et al. *Prog Mol Biol Transl Sci.* 2014;128:29-50.

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Closing

Upcoming Virtual Fora*

Event	Speaker(s)	Date	Time
Neuromodulation Techniques: State Of The Science	• Philip G. Janicak, MD • Michael Thase, MD	July 11, 2018	12:00 pm ET
Measurement-Based Care in Psychiatry: Clinical & Administrative Perspectives	• Charlotte Ostman, BA, MSW • James Greer, MD	July 25, 2018	12:00 pm ET
Introducing RASP: Relapse Assessment in Schizophrenia Patients	• Heidi Waters, MBA, PhD	August 8, 2018	12:00 pm ET
An Update from NCQA©: Focusing on HEDIS® Behavioral Health Measures	• Junqing Liu, PhD, MSW • Lauren Niles, MPH • Nora Fritz, BA	August 22, 2018	12:00 pm ET

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The Evolution of Post-traumatic Stress Disorder: Focus on Diagnostic, Evaluation, and Treatment Advances

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