Fear is evolutionarily useful
LeDoux, 1996

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

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

What are the neuroanatomical substrates of fear memory?

The Human Amygdala and Fear

The Walking Dead

PANIC ATTACK:
"All of a sudden I felt dizzy, my legs gave out on me, and I couldn't catch a breath. It felt like someone was choking me. I could feel my heart was beating too fast and I was terrified I was dying. I knew I had to get away before I lost it."

Increased heart rate
Chills, hot flushes
Nausea / abdominal distress
Shortness of breath
Expressions of fear

Chest discomfort
Sweating
Lightheadedness / faint
Choking sensation
Fear of dying / losing control

PANIC ATTACK = 'Fear Attack' in Fear-related Disorders

PANIC ATTACK

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PANIC ATTACK = 'Fear Attack' in Fear-related Disorders

PANIC ATTACK

Panic Disorder
Simple Phobia
Social Phobia (Agoraphobia)
Posttraumatic Stress Disorder
Acute Stress Disorder

The Human Amygdala and Fear

Etkin & Wager, 2007
The Fear Response is a Hardwired Process involving the Amygdala

Fear / Panic Symptoms:
- Lateral hypothalamus: heart rate, blood pressure
- Dorsal vagal N.: bradycardia, ulcers
- Parabrachial N.: panting, respiratory distress
- Retic. Pontis Caudalis: increased startle response
- Paraventricular N.: corticosteroid release
- Basolateral learning / expression
- Central Gray Area: freezing, social interaction
- CeA: Freezing, social interaction

The Fear Response is a Hardwired Process involving the Amygdala

Posttraumatic Stress Disorder
A Pathological Fear Reaction
- Clinically important (5% to 10% population, 15% to 25% veterans); Amenable to study – we know when it starts

DSM-5
- Criterion A: The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence; Note that the response 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; alienation; numbing
- Criterion E: Symptoms of increased arousal (decreased sleep, startle, hypervigilance, irritability/defensive and self-destructive behavior) and decreased concentration

Posttraumatic Stress Disorder (cont’d)
- Traumatic events include (but not limited to):
  - Military combat
  - Violent personal assault (rape, physical attack, gun violence, robbery, mugging)
  - Being kidnapped / taken hostage
  - Terrorist attack
  - Torture
  - Natural / manmade disasters
  - Severe automobile accidents
  - Experiencing fire, etc
- Note: Traffic accidents most common cause in general population
- Disorder appears to be more severe when the stressor is of human design (eg, torture or rape)


Posttraumatic Stress Disorder (cont’d)
- Epidemiology: Not recognized until 1980 DSM-III
  - Lifetime / current prevalence = 8% to 13% / 3%
  - Lifetime trauma exposure risk = 40% to 75%
  - Lifetime prevalence among those exposed to significant 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 mos after the stressor. May improve or disappear within a few months, or may become chronic, relapsing condition

Neurobiology of Fear Disorders

Learning Theories

• "The central issue appears to be one of determining why there is recovery in some survivors, but not others"

i) Over-Learning of Trauma Memory:
- Peritraumatic vulnerability
- Perceived trauma characteristics
- Initial stress reaction – Shalev ER study: increased HR in the 23% of pts immediately after trauma of those who went on to develop PTSD compared to those who did not (increased sympathetic?)


ii) Failure of Extinction:
- Not erasure of memory
- Rather creation of new competing inhibitory memories
- Reinstatement of fears with stress / unconditioned stimulus (US) exposure / aversive experience
- Therefore constant re-experiencing of fear may lead to continual re-activation of trauma memories
- Role of dissociation in formation of trauma memory and subsequent resistant to extinction?
- State dependency?
- Cortico-limbic disconnection?
- Evidence that subcortical fear memories are particularly indelible to extinction (concept of thalamic 'learning too early')
- Role of cortex in extinction


iii) Failure of Recovery:
Severity of PTSD Symptoms


Neurobiology of PTSD

Psychosocial Treatment for PTSD

• Cognitive-behavioral treatments
  - Exposure
  - Anxiety management techniques
• Eye Movement Desensitization and Reprocessing (EMDR)
• Psychodynamic treatments
• Group therapy

Treatment of Fear Disorders
Psychotherapy Conclusions

- Strongest evidence for exposure techniques
- Anxiety management effective
- No clear advantage of combined strategies
- EMDR-data mixed, but appears to share exposure principles
- Less empirical evidence with psychodynamic, hypnotic therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population</th>
<th>Results</th>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>Combat</td>
<td>Superior to PBO</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Combat</td>
<td>Both superior to PBO</td>
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<td>Fluoxetine</td>
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<td>Sertraline</td>
<td>187</td>
<td>Civilian</td>
</tr>
</tbody>
</table>
Sertraline Efficacy in PTSD

- Impact of Event Scale (IES)
- Davidson Trauma Scale (DTS)


Paroxetine Flexible-Dose PTSD Study

- Mean dose at endpoint = 32.5 mg/day

New Research and Future Approaches

Summary

- The Problem
  - PTSD and trauma-related depression are significant, under-diagnosed, and under-treated in our population
- Biological and Psychological Mechanisms
  - Child abuse and trauma
  - Adult level of trauma
  - Resilience
  - Genetic risk
- Advancing Treatment
  - Psychotherapy – with primary evidence for exposure
  - SSRIs and symptom-based pharmacotherapy
  - Future approaches may produce drugs that enhance emotional learning of psychotherapy to target the specific causes of the disorder
- Intervening in adults, especially parents, may help decrease the ongoing inter-generational cycles of violence that appear to be endemic in some cities

Modeling Fear Disorders

1) Identify Genes Associated with Developmental Risk: FKBP5
2) Identify New Risk Pathways: Convergent Genomics e.g., PACAP
3) Enhance Extinction e.g., target plasticity

PTSD

- Pre-existing Sensitivity (gene + environment)
- Expression of Fear
  - Memories, Nightmares, Flashbacks
  - Avoidance, Sympathetic Response, Startle
- Discrimination Fear is limited to specific trauma cue
- Extinction Diminished response to cues Over time
FK506 binding protein = FKBP5
(immunophilin-petidyl-proline isomerase activity-TPR domain)

Both Adult Trauma and Child Abuse strongly predict Adult PTSD symptoms

Variants of a stress response gene (FKBP5) + Child Trauma: Effects on PTSD and Amygdala Activation

Hippocampal Volume Reduction in PTSD
Hippocampal activation and structural differences in FKB5 risk allele carriers

FKBP5 Genotype and Structural Integrity of the Posterior Cingulum
Fani et al., in press, Neuropsychopharmacology

Finding Genes Involved in PTSD and Fear Neurocircuitry: Convergent Genomics Approach

- Identify genes in hypothesis neutral fashion that are associated with PTSD (pooled GWAS N~400)
- Identify genes in hypothesis neutral fashion associated with Fear Conditioning or Extinction Learning (mouse amygdala mRNA array)
- Prioritize genes that are shared in the above

Top Convergent Candidate
ADCYAP1R1
- adenylate cyclase activating polypeptide-1 pituitary expression, neural development
- Pooled GWAS p=.00002
- 6 mRNA transcripts present in Mouse amygdala regulated by fear and extinction

PACAP is a central stress regulator
PACAP
Pituitary
Adrenal gland
Cortex
Nucleus accumbens
Erythrocytes
Neurohypophysis
HEA, HPA axes
Sympathetic nervous system

Examining PACAP peptide levels in Humans

ADCYAP1R1, PAC1R is associated with PTSD in highly traumatized females

Ressler et al., Nature, 2011

Fani et al., 2013, JAMA Psychiatry

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Modeling Fear Disorders

1) Identify Genes Associated with Developmental Risk: FKB5

Pre-existing Sensitivity (gene + environment)

FKBP5

Expression of Fear Memories, Nightmares, Flashbacks Avoidance, Sympathetic Response, Startle

PTSD

Expression recovery

PTSD

Generalization Recruit 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

Expression recovery

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Recent Replication and Extensions


Potential Role for PAC1 / PACAP in stress + estrogen response

ADCYAP1R1 risk allele is associated with increased amygdala activation (and decreased amygdala-hippocampal connectivity) when viewing fearful faces (N=49)

Stevens et al., PNAS, 2014

Modeling Fear Disorders

1) Identify Genes Associated with Developmental Risk: FKBP5
2) Identify New Risk Pathways: Convergent Genomics e.g., PACAP
3) Enhance Extinction e.g., target plasticity

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

NMDA Receptor 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

Grill et al., PNAS, 2010

Rosellini et al., J Neurosci, 2010

Jasnow et al., J Neurosci, 2013

Modulating Fear through Circuitry Modulation Promises to Lead to New Targeted Therapies

Chhatwal et al., Nature Neurosci, 2008

Choi et al., PNAS, 2010

Gafford et al., PNAS, 2012

Andero et al., Science Transl Med, 2013

Jasonw et al., J Neurosci, 2013

Parsons et al., Nature Neurosci, 2013

VIRTUAL IRAQ

Trial of DCS enhancement of PTSD Double-Blind Exposure Therapy

Barbara Rothbaum, PI

- Goal: 90 completers (N=30/group) participants with PTSD to Exposure to Virtual Iraq

- Therapy:
  - education and information gathering session
  - 4 exposure therapy sessions

- Assessments:
  - pre-treatment
  - post-treatment
  - 3 months follow-up

- Measures:
  - PTSD clinical measures pre, post, and during exposures
  - Psychophysiological (startle, GSR) responding to standard activation paradigms
  - Neurochemical (cortisol) measures
  - Genetic measures

Many Students & Volunteers

NIMH (MH069884, MH071537)

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