Anxiety and Related Disorders: Neurobiology and Treatment

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Disclosures

Dr. Ressler is a founding member of Extinction Pharmaceuticals/ Therapade Technologies, which exist to develop d-Cycloserine for use to augment the effectiveness of psychotherapy. He has received no equity or income from this relationship within the last 3 years.

Patents: D-cycloserine and psychotherapy, targeting PACAP for extinction, targeting tachykinin 2 for prevention of fear, targeting angiotensin to improve extinction of fear.

Funding: NIMH, HHMI, NARSAD, Burroughs Wellcome Foundation
Genes + Environment Increase Risk of Fear Disorders and Posttraumatic Stress
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

Hippocampus
Amygdala
The Human Amygdala and Fear

Etkin & Wager, 2007
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, hotflushes
- 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

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

LA
CeA
Basolateral
Amygdala
Monoamine Dysfunction: Principal Evidence for Noradrenergic and Serotonergic Dysfunction in Anxiety / 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

• 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


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

Regulation Of Amygdala By NE
Feed-Forward CRF-NE-CRF Stress System

TH Levels Decrease With Antidepressants or ECT

TH=Tyrosine Hydroxylase

Enhanced 5-HT Release Following Chronic Antidepressant Treatment

* $p < .05$

- **Hypothalamus**
  - Control
  - Chronic paroxetine

- **Hippocampus**
  - Control
  - Chronic paroxetine

- **Frontal Cortex**
  - Control
  - Chronic paroxetine

Stress and Antidepressant Effects on Hippocampal Neurogenesis and Atrophy

Control

Stress

Antidepressant

• NE and 5HT modulation of cortical-hippocampal-amygdala pathways likely modulates:
  – attention and vigilance
  – response to aversive experience
    • perceived stress
    • perceived fearful stimuli
NE Release In Amygdala Stimulated By Aversive Events

NE Level (% Of Baseline)

Time (min)

* $P < .005$.
** $P < .01$.

Regulation Of Amygdala By NE & 5HT

Summary

• NE enhances learning of fearful and other amygdala-dependent events
• NE blockade may ↓ or block fear learning
• 5-HT in some paradigms inhibits fear learning
• This inhibition appears to be due to 5-HT activation of inhibitory interneurons
Anxiety/MDD

Dorsal PFC

Ventral PFC

External sensory
Internal memory

Amygdala

Hippocamp

NE

CRF

5-HT

Locus Coeruleus

Raphe Nucleus

Stress
fear
Aversion
tolerance
Treatment of Anxiety / MDD

ECT

Dorsal PFC

Ventral PFC

Amygdala

Hippocamp

Benzodiazepines

SNRIs / NRIs

NE

CRF

Locus Coeruleus

Raphe Nucleus

SSRIs

5-HT

Psychotherapy?
Grady Trauma Project: Civilian inner-city trauma
Understanding the Genomic Structure of PTSD

Our Ongoing GWAS:
1M SNPS (Illumina Omni-1M) + CNVs

N=8000 all-traumatized
~30% PTSD, ~60% no PTSD
~40% male, ~60% female

Psychiatric Genomic Consortium-PTSD subgroup (in progress):
>10,000 cases
>50,000 trauma controls
(lead by Koenen, Nievergelt, Liberzon, Ressler)

Schizophrenia
PGC2 10/2012
25K cases
62 loci

To Date:
>5500 Salivary DNA samples
>750 whole blood, serum, plasma, buffy coats
~500 Startle / human physiology
~500 whole genome methylation
~500 Gene expression array
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

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
ORIGINAL ARTICLE
A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a risk factor.

MW Logue1,2,11, C Baldwin1,3,11, G Cuffe3,11, K Freimer1,11, R Myers3,11, C Dardashti1,11, J Hakonarson2,11, J Kwon1,11, J Parnell1,11, R Maguire1,11, M Hackett1,11, S Purcell1,11, D Richman5,6, and M Hulshoff Pol7,11

A Genomic-Wide Identified Risk Variant for PTSD is a Methylation Quantitative Trait Locus and Confers Decreased Cortical Activation to Fearful Faces

Lynn M. Almli1, Jennifer S. Stevens1, Alicia K. Smith1, Varun Kilaru1, Qian Meng2, Janine Flory3, Elizabeth B. Binder4, and Kerry J. Ressler1,10

ARCHIVAL REPORT
Genome-wide Association Study Identifies New Susceptibility Loci for Posttraumatic Stress Disorder

Pingxing Xie, Henry R. Kranzler, Can Yang, Hongyu Zhao, Lindsay A. Farrer, and Joel Gelernter

Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for post-traumatic stress disorder in women

Guia Guffant a, Sandro Galea b, Lulu Yan b, Andrea L. Roberts c, Nadia Solovieff d,e,f, Allison E. Aiello g, Jordan W. Smoller d,e,f, Immaculata De Vivo c, Hardeep Ranu h, Monica Uddin i,j, Derek E. Wildman j, Shaun Purcell d,e,f,k, Karestan C. Koenen b,*

Genomic predictors of combat stress vulnerability and resilience in U.S. Marines
A genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene

Caroline M. Nievergelt a,d,e, Adam X. Maihofer a, Maja Mustapic a,b, Kate A. Yurgil d, Nicholas J. Schork c, Mark W. Miller e,f, Mark W. Logue8,h, Mark A. Geyer a, Ursula E. Pfeffer1,11, and Michael E. Neale1,11
Modeling Fear Disorders

1) Identify Genes Associated with Developmental Risk: e.g., FKBP5

Pre-existing Sensitivity (gene + environment)

Learning of Fear

2) Identify New Risk Pathways: Convergent Genomics e.g., PACAP

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

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

PTSD

3) Enhance Extinction e.g., target plasticity
Enhanced Suppression of Cortisol Following Dexamethasone Administration in Posttraumatic Stress Disorder

Rachel Yehuda, Ph.D., Steven M. Southwick, M.D., John H. Krystal, M.D., Douglas Bremner, M.D., Dennis S. Charney, M.D., and John W. Mason, M.D.

Am J Psychiatry 1983
FK506 binding protein = FKBP5

Ultrashort negative feedback on GR sensitivity
Both Adult Trauma and Child Abuse strongly predict Adult PTSD symptoms

### Level of Non-Child Abuse Trauma

<table>
<thead>
<tr>
<th>Level of Non-Child Abuse Trauma</th>
<th>N</th>
<th>PTSD Symptom Scale (PSS) Mean + sem</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>159</td>
<td>3.58 + 0.50*+</td>
<td>2.60 – 4.56</td>
</tr>
<tr>
<td>1 Type</td>
<td>183</td>
<td>7.30 + 0.74$+</td>
<td>5.83 – 8.76</td>
</tr>
<tr>
<td>2-3 Types</td>
<td>265</td>
<td>11.57 + 0.72+</td>
<td>10.16 – 12.98</td>
</tr>
<tr>
<td>&gt; 4 Types</td>
<td>215</td>
<td>16.74 + 0.88+</td>
<td>15.00 – 18.47</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>No Child Abuse</td>
<td>566</td>
<td>8.03 + 0.44 *</td>
<td>7.17 – 8.90</td>
</tr>
<tr>
<td>1 Type of Child Abuse</td>
<td>189</td>
<td>14.65 + 0.87 $</td>
<td>12.94 – 16.36</td>
</tr>
<tr>
<td>2 Types of Child Abuse</td>
<td>54</td>
<td>20.93 + 1.95 +</td>
<td>17.02 – 24.84</td>
</tr>
</tbody>
</table>

30% have experienced some form of child abuse

Binder et al., JAMA, March, 2008
Variants of a stress response gene (FKBP5) + Child Trauma: Effects on PTSD and Amygdala Activation

Binder et al., 2008

JAMA

White...Hariri, 2012
Genes, Brain and Behavior
Hippocampal Volume Reduction in PTSD


J Douglas Bremner, MD, Emory University
Hippocampal activation and structural differences in FKBP5 risk allele carriers

Statistical parametric map of brain activation during the processing of threat incongruent versus threat congruent faces in TC/TT > CC

Fani et al., 2013, *JAMA Psychiatry*

FKBP5 Genotype and Structural Integrity of the Posterior Cingulum

Fani et al., *in press, Neuropsychopharmacology*
1) Identify Genes Associated with Developmental Risk: e.g., FKBP5

2) Identify New Risk Pathways: Convergent Genomics e.g., PACAP

Modeling Fear Disorders

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

- 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

Learning of Fear

PTSD

Pre-existing Sensitivity (gene + environment)

Extinction

Diminished response to cues

Over time

Recovery
PACAP is a central stress regulator
Examining PACAP peptide levels in Humans

Ressler et al., Nature, 2011
ADCYAP1R1 risk allele is associated with increased amygdala activation (and decreased amygdala-hippocampal connectivity) when viewing fearful faces ($N=49$)
Potential Role for PAC1 / PACAP in stress + estrogen response
Modeling Fear Disorders

1) Identify Genes Associated with Developmental Risk: e.g., FKBP5

2) Identify New Risk Pathways: Convergent Genomics e.g., PACAP

3) Enhance Extinction e.g., target plasticity

PTSD

Pre-existing Sensitivity (gene + environment)

Learning of Fear

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Discrimination
Fear is limited to specific trauma cue

Extinction
Diminished response to cues Over time
NMDA blockade prevents extinction, while an NMDA agonist (D-cycloserine – DCS) enhances Extinction


Falls, et al. Given systemically or Intra-amygdala
J Neurosci, 1992

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

NMDA Receptor Enhancer IMPROVES Psychotherapy (extinction) across Anxiety Disorders

Social Anxiety  
![Graph showing improvement in Social Anxiety]

Obsessive – Compulsive  
![Graph showing improvement in Obsessive Compulsive]

PTSD / Panic  
![Graph showing improvement in PTSD/Panic]

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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

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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.
Modulating Fear through Circuitry Modulation

Chhatwal et al., *Nature Neurosci*, 2008
Choi et al., *PNAS*, 2010
Gafford et al., *PNAS*, 2012
Andero et al., *Science Transl Med*, 2013
Jasnow et al., *J Neurosci*, 2013
Parsons et al., *Nature Neurosci*, 2013
Rationally Designed Therapies Based on Amygdala Biology
Rationally Designed Therapies Based on Amygdala Biology

Select Neuronal Populations in Amygdala

- **CS (CS)**
- **US (US)**

**Marker** | **Function**
--- | ---
GRP | ?
? | Fear On
Thy1 | Extinction
Parv | Inhibitory
SST | Inhibitory
FoxP2 | ITC-Extinction
MOR | ITC-Extinction
CRF | Fear On?
PKCd | Fear Off
Tac2 | Fear On
VP | Excitatory
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 inhibits CeM output

Jasnow et al., 2013, *J. Neurosci*
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 fear-related disorders.

Jasnow, Ehrlich, Rainnie et al., 2013, *J Neurosci*
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recovery
Many other students & volunteers
Donald Rainnie, PhD
Barbara Rothbaum, PhD
Michael Davis, PhD
NIMH (MH069884, MH071537)
NSF, Burrough’s Wellcome Fund, NARSAD, ADAA, HHMI
Massachusetts General Hospital
Department of Psychiatry

Presents

39th Annual
Psychopharmacology Conference

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BOSTON, MA