Clinical Relevance of Biological Alterations in PTSD

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New developments in PTSD

- Conceptual shift
- New findings of prevalence, longitudinal course, comorbidity, neurobiology, risk
- Prospective vs retrospective methods
- Specific consequence of trauma, occurring under certain conditions
- More focused treatment approach (as highlighted in published treatment guidelines)
What has not changed

- Definition of PTSD: condition occurring after exposure to extremely traumatic event
- Phenomenology of PTSD:
  - Intrusive, avoidance, hyperarousal symptoms
  - Clinically significant social, occupational, functional impairment
  - Inability to shed memory of event and attendant distress
- Definition of trauma: clarification of severity and subjective response
What has changed: original formulation

- Intention: category for prolonged responses to trauma
- Assumptions:
  - traumatic events are rare
  - almost all persons would develop PTSD
  - condition is chronic, possibly permanent
  - response is “normal”
  - trauma is the major etiologic (if not sole) agent
Many people develop this disorder (10-18%), but only a proportion of those exposed.

Kessler et al. 1999.
Prevalence of trauma and PTSD

- Prevalence of Trauma
- Prevalence of PTSD
- Percent not developing PTSD

Categories: Witness, Accident, Threat, Attack, Molestation, Combat, Child, Rape
Most people who develop PTSD recover

Longitudinal course of PTSD

Shalev & Yehuda, 1999.
PTSD is not the only outcome following exposure

Israeli ER Study

- PTSD: 16
- Depression: 11
- Anxiety: 19
- No Disorder (n=141)

Australian ER Study

- PTSD: 1
- Depression: 8
- Anxiety: 25
- Eating Sub. Abuse: 26
- No Disorder (n=74)

Shalev et al. 1998.

Diagnoses in Prospective Studies of Trauma Survivors

- Anxiety only
- MDD + Anxiety
- MDD only
- PTSD, MDD, Anxiety
- PTSD + Anxiety
- PTSD + MDD
- PTSD only
- No Disorder
Consistent findings from an emergent literature

- Trauma exposure is extremely common
- PTSD occurs more rarely than trauma
- Most recover from PTSD; only a minority develop chronic and persistent symptoms
- Other psychiatric disorders can also develop following trauma and may or may not co-occur with PTSD
Towards a new formulation of PTSD

- PTSD represents a failure to recover from a universal set of emotions and reactions typically manifested by intrusive memories or nightmares.

- normal response
- maladaptive/abnormal response
- normal response for the most part that overshoots or fails to remit
Immediate Responses to Trauma Appear Universal

- Shock
- Horror
- Fear
- Terror
- Sadness
- Grief

- Where people appear to differ is that they seem to recover from trauma at different rates
- Some do not recover
Unanswered questions:

• Why do only some people develop disorder and/or recover
• What accounts for heterogenous outcomes following trauma
• What is the role of risk factors in producing PTSD
• What are the role of resiliency factors in either the development of or recovery from PTSD
Recovery model: disorder is a function of time

% w/PTSD symptoms

94% 47% 42% - 15% 94% 47% 42% - 15% 25% - 15%

W 3m 9m

Years

Group A Group B

Rothbaum et al., 1993’
Shalev & Yehuda, 1999.
Recovery model: disorder is part of a known trajectory

% w/ PTSD symptoms

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>W</td>
<td>94%</td>
<td>25%-15%</td>
</tr>
<tr>
<td>3m</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>9m</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

W years, 3m=3 months, 9m=9 months
Many Implications

- Failure to recover:
  - search for posttraumatic factors that inhibit recovery
  - may wish to delay treatment and allow natural restitution OR
  - administer prophylactic treatment in the immediate aftermath of trauma

- Risk model:
  - identify those with pretraumatic risk factors
Neurobiologic advances have been critical

• Basic science provides a comparison of PTSD biology with normal stress/fear responses
• Clinical neuroscience provides insight into how the PTSD response may differ from others
The response to trauma is both biological and psychological

- Amygdala fires before stimulus is completely interpreted
- Interpretation of events can prevent the amygdala from activating other stress reactions.
- Amygdala participates in formation of emotional memories particularly as other stress systems are activated.
- Persons must interpret what has happened and place it into context.
Acute and delayed effects of the normal response to stress/fear

- The response to a “stressor” is usually not prolonged and parameters return to basal levels within hours.
- “Long-term” effects usually observed only after exposure to a subsequent stressor (sensitization).
- Stress theory is based on effects occurring only while the stressor is still present.
Biologic alterations associated with chronic PTSD

- Increased activation of the amygdala
- Enhanced startle
- Increased SNS activation; catecholamines
- Alterations of the hippocampus
- Alterations of the HPA axis
Reactivity of the amygdala in PTSD

Rausch JL et al. *Arch Gen Psychiatry.* 1989;46:481-482.
Reduced anterior cingulate function in PTSD (an fMRI study)

Shin et al., Biological Psychiatry 50:932-942, 2001
Auditory Startle Response In PTSD (SC Habituation)

PTSD Is Associated With Increased Plasma Norepinephrine

PTSD Is Associated With Increased Plasma Norepinephrine

PTSD Is Associated With Decreased Plasma Cortisol Levels

PTSD Is Associated With Decreased Plasma Cortisol Levels

Lower cortisol levels in PTSD

Mean 24-Hr Urinary Cortisol

PTSD N=55
Normal Controls N=31
Depression N=20

The Glucocorticoid Receptor

Transcription of protein

CYTOSOL

NUCLEUS
Lymphocyte (MNL) Glucocorticoid Receptor Number in PTSD and Other Groups
The DST mimics the effects of Cortisol at the pituitary.
The DST

If negative feedback is strong, cortisol levels will show a dramatic decline (Enhanced Suppression).
The DST

If negative feedback is weak, cortisol levels will show a modest decline.

(Reduced Suppression)
Suppression of cortisol to 0.50 DEX

PTSD

11.8

1.2

No PTSD

13.4

2.8
Suppression of cortisol to 0.50 DEX

PTSD

No PTSD

GR receptors are also more responsive in PTSD
Low dose DST in PTSD: Published studies

- Yehuda et al. 1993
- Yehuda et al. 1995
- Goenjian et al. 1995
- Stein et al. 1997
- Kellner et al. 1997

Percent Suppression of Cortisol

- Avg. Control
- Yehuda et al. 1993
- Yehuda et al. 1995
- Goenjian et al. 1995
- Stein et al. 1997
- Kellner et al. 1997
GR Sensitivity: DEX stimulated lysozyme activity in mononuclear leukocytes

PTSD (n=14) Controls (n=12)
Longitudinal Course Of PTSD

Shalev & Yehuda, 1999.
When do we first begin to see biologic effects of trauma, is there a trajectory over time?

Shalev & Yehuda, 1999.
Heart Rate In Acute Aftermath Of Trauma

Shalev et al. 1998.
Auditory Startle In Acute Aftermath Of Trauma

Shalev et al. 1998.
Cortisol levels in acute aftermath of motor vehicle accidents

Yehuda et al. 1998.
Cortisol in acute aftermath of rape

Lower cortisol levels in immediate aftermath of rape associated with prior assault

Resnick et al. 1995.
Studies Of Persons At Risk For PTSD

- Difficult to predict trauma
- Those at occupational risk are not typical of persons “avoidant” of traumatic stress
- Those with early trauma are already exposed
- PTSD 3 times more likely in children of Holocaust survivors in response to trauma vs demographically-matched controls

Yehuda et al. 1998.
Prevalence of PTSD by parental PTSD

*P < .0005.

Cortisol In Offspring By Risk Factor Of Parental And Personal PTSD

What do rape victims with prior assault have in common with adult children of Holocaust survivors?
Childhood trauma subdivided by parental PTSD

Comparison Subjects (n=41)

- Offspring no Parental PTSD (n=19)
- Offspring one parent PTSD (n=15)
- Offspring two parents PTSD (n=17)

Sexual abuse
Physical neglect
Physical abuse
Emotional neglect
Emotional abuse

(Yehuda et al., Stress and Development, 2001)
Consequences Of Low Cortisol In Acute Aftermath Of Trauma

↑ Catecholamines

“Overconsolidation” or pairing of memories and distress

Traumatic reminders would be distressing

Distress leads to further pairing with nonspecific stimuli

Failure of habituation and extinction

Survivor frequently anxious (HPA becomes activated)

Other problems
The Stress Response Cascade

- Chronic responses to trauma appear to develop because of a failure to recover from the normal effects of stress.
- This is possibly due to prior experience, or other factors -- such as how one is interpreting what is going on -- that interfere with reduction of arousal.
Conclusions

• What is universal is the immediate response to trauma
• What can augment or delay this response are individual characteristics which have biologic correlates
• The biology of PTSD, strictly speaking, is not the biology of stress
Critical Variables for Treatment

• Longlasting responses to trauma result not simply from the experience of fear or helplessness, but from how the body interprets these responses.
• The reaction to stress is biological, but is influenced by what you think at the time of a trauma, which in turn, is most influenced by pretraumatic factors (such as past trauma).
• Mental health treatment is about figuring out “what gets in the way” of stress recovery.
Interfering with proper storing of emotional memories

- Thoughts that might perpetuate arousal: “It is my fault;” “I am being punished;” “the world is not safe.”
- Thoughts that might attenuate arousal: “I did the best I could” “These things happen – you can’t control everything” and “the world is usually safe, and fortunately I survived this event.”
What does it mean to “get over” a traumatic experience?

• If I survived this, I can survive anything
• There was a purpose to my survival
• My survival compels further social action, even if it is just to give testimony or provide an example for others.
• My survival stimulates me to invest in building community
• My survival gives me perspective.
Resilience or Pathology?

“The Holocaust is with me everyday and practically every minute. In my dreams the Nazi’s chase me, but when I wake up I see they are no longer there. I can’t go back to sleep right away, but at least I know I am safe from them. Some days the memories make me feel like I can’t go on, but usually it is the opposite – they remind me that I can….”

Ruth S. (3/25/03)
Holocaust survivor
(b. 1913)