Emotional Memory, PTSD, and Clinical Intervention Updates

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OKC National Memorial
OKC National Memorial
OKC National Memorial

We come here to remember those who were killed, those who survived and those changed forever.
OKC Data

Psychiatric Disorders Among Survivors of the Oklahoma City Bombing

Carol S. North et al., JAMA. 1999;282:755-762.
Table 2. Predisaster and Postdisaster Diagnostic Disorders

<table>
<thead>
<tr>
<th>No. (%) of Subjects With Predisaster Disorder†</th>
<th>PTSD‡</th>
<th>Major Depression</th>
<th>Panic Disorder</th>
<th>Generalized Anxiety Disorder</th>
<th>Alcohol Use Disorder</th>
<th>Drug Use Disorder</th>
<th>Any Non-PTSD Diagnosis</th>
<th>Any Diagnosis‡</th>
<th>No Diagnosis 100 (54.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD, 27 (15.0)</td>
<td>16§</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>13</td>
<td>23§</td>
<td>4§</td>
</tr>
<tr>
<td>Major depression, 23 (12.6)</td>
<td>15</td>
<td>18§</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>18</td>
<td>18§</td>
<td>5§</td>
</tr>
<tr>
<td>Panic disorder, 5 (2.8)</td>
<td>4</td>
<td>5</td>
<td>4§</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5§</td>
<td>0§</td>
</tr>
<tr>
<td>Generalized anxiety disorder, 5 (2.8)</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>5§</td>
<td>0§</td>
</tr>
<tr>
<td>Alcohol use disorder, 48 (28.7)</td>
<td>18</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>17§</td>
<td>2</td>
<td>23</td>
<td>30§</td>
<td>18§</td>
</tr>
<tr>
<td>Drug use disorder, 17 (9.4)</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4§</td>
<td>10</td>
<td>11§</td>
<td>6§</td>
</tr>
<tr>
<td>Any predisaster disorder, 79 (43.4)</td>
<td>35</td>
<td>27</td>
<td>9</td>
<td>5</td>
<td>17</td>
<td>4</td>
<td>39</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>No disorder, 103 (56.6)</td>
<td>27</td>
<td>14</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>30</td>
<td>73</td>
</tr>
</tbody>
</table>

*Columns and rows do not sum because each subject could have more than 1 diagnosis.
†Percentages represent the total number of 182 subjects.
‡Includes only cases with bombing-related posttraumatic stress disorder (PTSD).
§P<.05.
TABLE 1. Diagnostic Criteria for PTSD.*

A person must have been exposed to a traumatic event.
The event involved a perceived or actual threat to the person’s own life or physical integrity or that of another, such as a physical or sexual assault, rape, a serious accident, a natural disaster, combat, being taken hostage, torture, displacement as a refugee, sudden unexpected death of a loved one, and witnessing a traumatic event.
The person’s response to the event involved fear, helplessness, or horror.
The person persistently reexperiences the event in at least one of several ways:
The person has intrusive recollections of the event.
The person has nightmares.
The person has flashbacks, which are particularly vivid memories that occur while he or she is awake and make him or her act or feel as though the event was recurring.
The person has intense psychological distress in response to reminders of the traumatic event.
The person has intense physiological reactions in response to reminders of the event (including palpitations, sweating, difficulty breathing, and other panic responses).
The person avoids reminders of the event and has generalized numbness of feeling, as indicated by the presence of at least three of the following:
The person actively avoids pursuits, people, and places that remind him or her of the event.
The person avoids thinking of or talking about the event.
The person is unable to recall aspects of the event.
The person has lost interest in or participates less in activities.
The person has felt detached or estranged from other people since the event.
The person has a restricted range of emotions or a feeling of numbness.
The person feels as though his or her life has been foreshortened or as though there is no need to plan for the future, with respect to his or her career, getting married, or having children.
The person has symptoms of increased arousal, as evidenced by the presence of at least two of the following:
The person has difficulty falling or staying asleep (sometimes related to fear of having nightmares).
The person is irritable and has feelings or outbursts of anger.
The person has difficulty concentrating.
The person has become more vigilant and concerned about safety.
The person has exaggerated startle reactions in response to sounds or movements.
The three types of symptoms must be present together for at least one month.
The disorder must cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

*There are three subtypes of PTSD. Acute PTSD refers to symptoms that last less than three months. Chronic PTSD refers to symptoms that last three months or longer. Delayed-onset PTSD refers to symptoms that begin at least six months after a traumatic event. Adapted from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.5
Post-Traumatic Stress Disorder

• DSM-IV criteria

1. The person has been exposed to a traumatic event in which of the following present:
   – The person experienced, witnessed, or was confronted with an event or events that involved 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.
Post-Traumatic Stress Disorder

DSM-IV criteria
1. The traumatic event is persistently re-experienced (nightmare or recurrent intrusive thoughts).
2. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness.
3. Persistent symptoms of increased arousal (difficulty falling asleep, hypervigilance, irritability, exaggerated startle response).
4. Duration is more than 1 month.
**Table 2. Prevalence of Traumatic Events and Rates of PTSD in Response to Such Events among Men and Women.**

<table>
<thead>
<tr>
<th>Traumatic Event</th>
<th>Prevalence of Event</th>
<th>Rate of PTSD in Response to Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>percent</td>
<td>percent</td>
</tr>
<tr>
<td>Rape*</td>
<td>0.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Molestation*</td>
<td>2.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Physical assault*</td>
<td>11.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Accident*</td>
<td>25.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Natural disaster*</td>
<td>18.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Combat*</td>
<td>6.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Witnessed death or injury†</td>
<td>40.1</td>
<td>18.6</td>
</tr>
<tr>
<td>Learned about a traumatic event†</td>
<td>63.1</td>
<td>61.8</td>
</tr>
<tr>
<td>Sudden death of loved one†</td>
<td>61.1</td>
<td>59.0</td>
</tr>
<tr>
<td>Any traumatic event*</td>
<td>60.7</td>
<td>51.2</td>
</tr>
<tr>
<td>Any traumatic event†</td>
<td>92.2</td>
<td>87.1</td>
</tr>
</tbody>
</table>

*Data are from Kessler et al.4
†Data are from Breslau et al.16,17
Why some people develop PTSD while others do not?
Questions for Psychiatrists

1. Can we stop their PTSD relapse?
2. Can we selectively delete their traumatic memory?
3. Can we prevent the PTSD development?
Memory Formation Process

- Acquisition or Encoding
- Consolidation/Storage
- Retrieval
- Extinction
Memory Types

- Cognitive Memory
- Working Memory
- Spatial Memory
- Emotional Memory
- Others
Emotional Memory & Amgydala

- Amgydala magnifies emotional memory
- BasoLateral Nucleus (BLA), rather than Central Nucleus, is the key site for emotional memory
- Neurosteroids could modify the emotional memory formation
Glucocorticoid and PTSD

- High CSF CRH levels in PTSD patients. (Baker DG et al. 1999. Am J Psychiatry)
Glucocorticoids and Memory

- Glucocorticoids enhances memory consolidation in inverted U curve fashion.

Glucocorticoid effect on object recognition memory require training-associated emotional arousal.

Okuda et al., 2004, PNAS
Fig. 1. Posttraining administration of corticosterone enhanced 24-hr object recognition performance of rats in the WITHOUT-habituation (A) but not the WITH-habituation (B) condition. Rats received a single injection of corticosterone or vehicle immediately after the 3-min training trial. Corticosterone administered in a dose of 1.0 mg/kg significantly enhanced 24-hr object recognition memory of rats in the WITHOUT-habituation condition but failed to affect memory of rats in the WITH-habituation condition. **, \( P < 0.0001 \) compared with the corresponding vehicle control group (\( n = 11–13 \) per group).
Glucocorticoids and Memory

- Glucocorticoids impairs Spatial Memory Retrieval Process.

**b**

![Bar chart showing time spent in quadrant (s) for different corticosterone concentrations.](image)

- **Y-axis:** Time spent in quadrant (s)
- **X-axis:** Corticosterone (mg per kg)

- **Vehicle**
- **0.3 mg per kg**
- **1.0 mg per kg**
- **3.0 mg per kg**

The chart indicates a significant increase in time spent in the quadrant for the vehicle and 0.3 mg per kg conditions compared to 1.0 and 3.0 mg per kg.
Glucocorticoids and Fear Memory

Lesion study indicates that Amygdala (BLA) is critical for fear memory formation.

Glucocorticoids and Fear Memory

- Amygdala (BLA) and Hippocampus (Dorsal CA1) are important sites for fear memory formation.
- Circuitry study is still incomplete, however, possible other sites include Cingulate, Prefrontal Lobe, and other cortical areas.
A

AMYGDALA NUCLEI LESIONS

- ** vehicle
- □ dexamethasone (0.3 mg/kg)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Retention Latencies (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sham</td>
<td>200 (±50)</td>
</tr>
<tr>
<td>central</td>
<td>100 (±30)</td>
</tr>
<tr>
<td>basolateral</td>
<td>50 (±10)</td>
</tr>
</tbody>
</table>

B

INTRA-AMYGDALA INFUSIONS

- ◼ vehicle
- ◼ RU 28362 (1.0 ng)
- □ RU 28362 (3.0 ng)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Retention Latencies (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>central</td>
<td>100 (±30)</td>
</tr>
<tr>
<td>basolateral</td>
<td>300 (±50)</td>
</tr>
</tbody>
</table>
dorsal hippocampus:

- Vehicle
- RU 28362 (3.0 ng)
- RU 28362 (10.0 ng)

change in retention latencies (%)

- sham
- central
- basolateral
Glucocorticoids and Memory

1. What is the function of glucocorticoids in fear memory retrieval?

2. What is the function of glucocorticoids in fear memory reconsolidation?
Fear Memory Research

- Give mice electric foot shock stimulus paired with auditory tone stimulus.
- 24 hours later, expose the shocked mice to the same environment (context) or different environment but provide the same tone stimulus (auditory cue-dependent).
- The freezing time is recorded as the index of fear memory.
Retrieval Study
Memory Retrieval Study

- Presentation of Information to CNS.
- Wait till the new memory has been consolidated (4 hours to 24 hours or longer).
- Intervention procedure is performed (pharmacological or surgical) prior to memory measurement.
Retrieval-Context (24 hours)

Retrieval-Context (48 hours)

Retrieval-Cue (48 hours)
Retrieval Study Conclusion

• Glucocorticoids impairs contextual and cue-dependent fear memory retrieval.
• This impairing effect does not influence the fear memory stability, i.e. it only blocks the retrieval process itself.
Possible Confounding Factors

• General Anxiety Level
• Locomotor Activity
• Sensory Function
• Motor Coordination Function
Open Field Test
Open Field Test

- Total time spent in the central zone area.
- Frequency of central zone entry.
- Total distance the animal moved.
- Average speed of their movement.
Elevated Plus Maze Test
Elevated Plus Maze Test

• Frequency of their entrance into closed and open arms.

• Time they spend in closed and open arms respectively.
Elevated Plus Maze

Vehicle

cort3.0

Close Arm Time

Open Arm Time

Time (sec)
RotaRod Test
RotaRod Test

- Goal: Testing motor coordination
- Measurement: Time to Fall
Pain Threshold Test
Pain Threshold Test

• Goal: Testing the Sensational Function
• Measurement: Level of electricity shock to cause different activities, including flinch, jumping and vocalization.
Pain Threshold

Footshock Strength (mA)

- flinch
- jump
- vocalization

- vehicle
- metyrapone
- cort 0.3
- cort 1.0
- cort 3.0
- cort 10.0
Control Study Conclusion

Glucocorticoids Injection does not influence:

• General Anxiety Level
• Locomotor Activity
• Sensory Function
• Motor Coordination
Reconsolidation Study
Reconsolidation Study

• Goal: After the fear memory is consolidated, is there a way to modulate its stability?

• Method: Footshock $\rightarrow$ Wait for different length of time (2 days and 14 days) $\rightarrow$ Reactivate the context fear memory $\rightarrow$ Provide Corticosterone Injection immediately after the reactivation $\rightarrow$ Measure the contextual fear memory 24 hours later.
CONTEXT (24 hour)

% Time Spent Freezing

- no injection
- vehicle
- metyrepone
- cort1.0
- cort3.0
- cort10.0
- anisomycin

(50mg/kg) corticosterone (mg/kg)
REACTIVE (14 DAY)

% Time Spent Freezing

- no injection
- metyrapone
- cort0.3
- cort1.0
- cort3.0
- cort10.0
- anisomycin
Conclusion and Potential Clinical Significance (1)

- Glucocorticoids impair fear memory retrieval $\rightarrow$ Potential Pharmacological treatment option for maintenance therapy.
Conclusion and Potential Clinical Significance (2)

Glucocorticoids impair fear memory reconsolidation → Potential capability to delete emotional traumatic memory permanently and cure the PTSD patients.
Other Potential Significance

• Ethical issues of selectively deleting human memory

• Misuse of this technique with its social consequence
The End
VA PTSD Data

- Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study.

VA Data

- Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD.

Acquisition Study
<table>
<thead>
<tr>
<th>Corticosterone (mg per kg)</th>
<th>Vehicle metyrapone (50mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>3.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Vehicle Metabolon
e
0.3 1.0 3.0 10.0 corticosterone (mg per kg) (50 mg/kg)

Acquisition-CUE

FREEZE TIME PERCENTAGE (%)

* **

**