My Worst Nightmare Come True: Was Freud Really Right?

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From a psychobiological and computational viewpoint, this lecture will interrelate preclinical knowledge to recent clinical observations in order to understand severe forms of post traumatic stress disorder (PTSD) and the critical biological aspects of their resolution. The theory is based on recent experiments that elucidate the role of the hippocampus and the role of sleep in the formation of declarative memories.
Hypotheses: Dreaming is regulated

1) Dream subject matter is biased by recent, hippocampal driven replay

2) Hippocampal replay is biased by the strength and longevity of associative LTP in region CA3. This strength of encoding is subject to emotional control by the behavioral context

3) For any contextual-emotional memory, successful teachback produces
   a) declarative access, and
   b) decay of this memory in CA3 via CRASHRE / DOWN GRADY

   **specific form** \\
   LTD
1. The amygdala mediates the symptoms of PTSD

2. The hippocampus stimulates the amygdala activity

PTSD is a normal function pushed to an extreme.
<table>
<thead>
<tr>
<th>Type of Criteria</th>
<th>Criteria</th>
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</table>
| Re-experiencing | • Recurrent, intrusive, and distressing recollections  
• Recurrent, distressing dreams  
• Flashbacks  
• Intense psychological distress at exposure to events that symbolize or resemble the traumatic event  
• Physiological reactivity to cues that symbolize or resemble the traumatic event |
| Avoidance       | • Inability to recall an important aspect of the trauma  
• Avoiding activities or situations associated with the acute event |
| Arousal         | • Insomnia  
• Irritability or outbursts of anger |

Table 1: Some major symptoms of PTSD grouped to aid in the diagnosis (Spitzer et al., 1994).
Hippocampus – 1950's

The case of H. M.:

total anterograde amnesia
partial retrograde amnesia

Consolidation experiments:

Recently acquired memories are easily destroyed by ECS (ECT) and just as easily strengthened by increased arousal

**BOTH MANIPULATIONS OCCURING AFTER (!) LEARNING.**
1960's
REM sleep deprivation blocks learning

1970's
Hippocampal dependent memories are ubiquitous but best described in humans as episodic and declarative.

1980's – present
An intermediate-term memory storage necessary for learning and storing (in long-term memory) complex, contextual memories.

Electrophysiological observations of teachback
1990's

Replay of associational information

Computational models of replay and hippocampal function

Behavioral correlates of replay

The formation of declarative memory is time dependent (Green, Spellman, and Levy)

Cognitive processes dependent upon spontaneous replay
D. Hartley, 1801

Dreaming alters the strength of associative links in memory

S. Freud, 1880's

Traumatic experiences cause nightmares.

To get over the nightmares, a patient must understand the meaning of the nightmare, coming to grips with what happened in the forgotten past.
Animal and Human Studies

Amygdala:

mediates the expression of fear

learns simple associations between stimuli and emotionally salient events

mediates the emotional control of ITM encoding strength

Hippocampus:

is necessary for declarative memory

is the ITM for contextual information

is the source of replay that is teachback
Amygdala

1930s  Kluver-Bucy Syndrome
Docility, inappropriate behavior, hypersexuality, hyperorality

1980s to present
Basolateral complex required for fear conditioning

Effects of Bilateral Amygdala Lesions
As reviewed by Rolls (1999), The Brain and Emotion

Increased trust and confidence in character judgements over control
Unregulated approach behavior (hyperorality, hypersexuality, docility)
Decreased avoidance behavior (psychic blindness)
Impairment of the fear response
Decreased secretion of peripheral hormones
General impairment of learning in affective experiences
STM - short term memory
LTM - long term memory
ITM - intermediate term memory
Why is a good lecture better than reading a chapter with the same (and even more) information?

More associations

Stronger associated emotions

What are the kinds of things we remember from a lecture?

Who sat near you

What they were wearing

How you got to class

How long you stayed interested
Where were you when you found out that

1. Kennedy was shot
2. The challenger exploded
3. O.J. was being chased by the police

What can you tell me about the last wedding you attended as an invited guest?

Why is the apprenticeship system used for advanced learning?
1. cognitive mapping spatial

2. declarative memory

3. configural learning

4. context learning

5. trace conditioning!!
Model designed from the anatomy and physiology of hippocampus to solve problems that require an intact hippocampus.

An autonomous recoder of spatial/temporal patterns that, by virtue of the recodings, creates good context-dependent predictions.

Autonomous recoder – the learned firing patterns (recodings) are dependent on local, Hebbian synaptic modification and the random connectivity of the network.
1a. Simplified hippocampal model

![Diagram of EC/DG and CA3 with inhibitory neuron]

1b. Sparse, random recurrent excitation in CA3

![Diagram of CA3 cells with excitatory synapse]
<table>
<thead>
<tr>
<th>Fundamental Network Properties</th>
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<tbody>
<tr>
<td>1. Neurons are McCulloch-Pitts-Type threshold elements: input is a weighted sum; output is binary threshold of this sum with no memory of past</td>
</tr>
<tr>
<td>2. Synapses modify associatively based on a local Hebbian-type rule and have a time-spanning, associative</td>
</tr>
<tr>
<td>3. Most connections are excitatory</td>
</tr>
<tr>
<td>4. Recurrent excitation is sparse and randomly connected</td>
</tr>
<tr>
<td>5. Inhibitory neurons control activity, approximately</td>
</tr>
<tr>
<td>6. Recurrent excitation is stronger than external excitation</td>
</tr>
<tr>
<td>7. Activity is low but not too low</td>
</tr>
</tbody>
</table>
Summary of Network Computations

Somato-dendritic excitation/inhibition

\[ y_j(t) = \frac{\sum_i w_{ij}(t-1) c_{ij} z_i(t-1)}{\sum_i w_{ij}(t-1) c_{ij} z_i(t-1) + K_I \sum_i x_i(t) + K_R \sum_i z_i(t-1) + K_0} \]  

(1)

Output

\[ z_j(t) = \begin{cases} 1 & \text{if } y_j(t) \geq 0 \text{ or if } x_j(t) = 1; \\ 0 & \text{otherwise} \end{cases} \]

Typical synaptic modification rule

\[ w_{ij}(t+1) = w_{ij}(t) + \varepsilon z_j(t) [z_i(t-1) - w_{ij}(t)] \]

Definitions

- \( y_j \) net excitation of \( j \)
- \( x_j \) external input to \( j \)
- \( z_i \) recurrent input \( i \)
- \( z_j \) output of neuron \( j \)
- \( K_I \) feedforward inhibition scaling constant
- \( K_R \) feedback inhibition scaling constant
- \( K_0 \) resting conductance
- \( c_{ij} \) \( \{0,1\} \) variable of connectivity, kept constant once initialized
- \( w_{ij} \) the excitatory weight (synaptic strength), neuron \( i \) to \( j \)
- \( \varepsilon \) rate constant of synaptic modification
- \( t \) time
A Random Recorder of Context and Specific Events

that Learns Sequences ..., and

Can Perform Sequence Completion Faster than Real

Time \equiv Prediction Generation
The story goes in two directions at this point.

1) the hippocampus as an intermediate-term memory
   THE CASE OF PATIENT, H.M.

2) the hippocampus as a recoder
   THE PROCESSOR OF LAST RESORT

Recode polysensory sequences for the long-term memory system (neocortex)

Hippocampal recoding finds good chunks and teaches them to neocortex.
Teachback occurs when information is coming into hippocampus

a) bored

b) simple, thoughtless tasks, e.g.,
   eating, grooming, taking a shower

c) drowsiness and slow wave sleep
<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Neural Activity in the Hippocampus</th>
<th>Neural Activity in the Neocortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Slow wave sleep</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>REM sleep</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 3: Neural firing during three stages of the arousal/sleep continuum.
Three stages of sleep – awake, slow wave sleep, and REM sleep – are correlated with neural activity in the hippocampus and neocortex at that time (for review, see Pavlides and Winson (1989) and Noda et al. (1970)). The inverse relationship between hippocampal and neocortical firing is relevant to the relationship between sleep, memory, and hippocampal-neocortical interactions.
Queue Priority

- Each replay can only encapsulate a single (perhaps fractional) episode

- Such a brief event implies a queue-like situation because not more than one episodic memory may be transmitted back to the neocortex at a time. That is, each memory must await a turn at being replayed

- Replay is a biased, random process

- High queue priority derives from strong and pervasive, long-lasting long-term potentiation

- A highly emotional experience leads to long-lasting long-term potentiation

Table 4: Key Concepts Concerning Queue Priority. Queue priority is a critical hypothesis of the theory. This competition for replay between CA3-stored memories is probabilistic where the rank of such probabilities is called queue priority.
ま？ぬ
T.I.

は > まま
か < ま
か > め
せ < め
TRANSITIVE INFEERENCE

A > B, B > C, C > D, D > E

A ? E

B ? D

For the B > D answer a hippocampus is necessary.
Nefazodone
which the trauma occurred, claimed that they initially "remembered" the trauma in the form of somatosensory flashback experiences, as visual, olfactory, affective, auditory, or kinesthetic imprints (Fig. 1). As the trauma came into consciousness with greater clarity, more sensory modalities were activated, and a capacity to tell what actually had happened emerged over time (Fig. 2). These data support the notion that "memories" of a trauma tend, at least initially, to be experienced as fragments of the sensory components of the event that patients invariably seem to claim to be exact representations of elements of the original trauma.
Table 1: Means, Standard Deviations, Effect Sizes, and Analyses of Variance for Target Symptoms During Nefazodone Treatment of 10 PTSD Patients*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline (N = 10)</th>
<th>Week 16 (follow-up) (N = 9)</th>
<th>Baseline vs Week 16 (df = 2.16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>PTSD symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPS total</td>
<td>82.9</td>
<td>17.8</td>
<td>57.4</td>
</tr>
<tr>
<td>Reexperiencing</td>
<td>19.3</td>
<td>9.8</td>
<td>12.6</td>
</tr>
<tr>
<td>Avoidance/Numbing</td>
<td>36.3</td>
<td>6.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Hyper arousal</td>
<td>27.3</td>
<td>5.0</td>
<td>17.3</td>
</tr>
<tr>
<td>DTS total</td>
<td>99.3</td>
<td>20.4</td>
<td>64.2</td>
</tr>
<tr>
<td>Reexperiencing</td>
<td>25.0</td>
<td>10.0</td>
<td>15.3</td>
</tr>
<tr>
<td>Avoidance/Numbing</td>
<td>40.5</td>
<td>9.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Hyper arousal</td>
<td>34.0</td>
<td>5.1</td>
<td>20.6</td>
</tr>
<tr>
<td>PSQI</td>
<td>13.2</td>
<td>2.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Sleep/night, h</td>
<td>4.4</td>
<td>0.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>25.6</td>
<td>9.1</td>
<td>14.0</td>
</tr>
<tr>
<td>BDI</td>
<td>24.6</td>
<td>9.6</td>
<td>21.6</td>
</tr>
</tbody>
</table>
1. The hippocampus is ITM necessary for declarative and episodic memory

   NOT SUFFICIENT

2. There is an active replay process

3. This replay is biased

   random

4. Erasure requires a specific set or pattern of neocortical activity.
<table>
<thead>
<tr>
<th>Key Component</th>
<th>Functional Description</th>
<th>PTSD Relevance</th>
</tr>
</thead>
</table>
| 1. Hippocampus: ITM store   | • Necessary for the encoding of long-lasting declarative memories in the neocortex  
• Not sufficient for declarative memories                                                                                                                      | While declarative amnesia persists in PTSD, the details of the traumatic event remain in the ITM store of the hippocampus.                                                                                     |
| 2. Multifaceted Amygdala    | • **Central Nucleus:** Mediates fear response to emotionally painful experiences.  
• **Basolateral Nucleus:** Indirectly modulates strength of episodic memories and fear conditioning and bridges hippocampal activation to central amygdala activation. | Hippocampally primed nightmares and spontaneous recollections result from the hippocampus driving the amygdala and neocortex. Amygdala mediates anxiety and fear but is not spontaneously active. |
| 3. Teachback/Replay         | • Hippocampal region CA3 drives neocortical encoding of long-lasting declarative memories (consolidation) by replaying hippocampally stored episodes  
• Chance of replay (queue priority) determined by emotional content of episodes                                                                                                                                     | Replay primes the amygdala and thus drives PTSD symptoms: nightmares, flashbacks, and possibly anger.                                                                                                           |
| 4. Erasure/Queue Demotion   | • Weakens, with high specificity, the relevant hippocampally stored memories  
• Demotion in the replay queue depends on successful encoding                                                                                                                      | A normal, uninterrupted sleep cycle is required for successful neocortical encoding and the accompanying synaptic encoding in the hippocampus. It is also required for erasure and queue demotion. PTSD symptoms will continue as long as queue priority of the traumatic event is high. There is poor declarative encoding of new events because the ITM store and replay are dominated by the earlier traumatic event and therefore erasure is necessary. |

Table 2: Hypothesized Regional Brain Functions Relevant to PTSD. The table summarizes the link between the four key ideas and PTSD symptomatology. The functional description of each describes its normal function and helps to elucidate abnormal complications related to PTSD.
• The hippocampus is necessary but not sufficient for declarative memory (section 3.1)

• There is competition for replay during SWS (i.e., queue priority, section 3.4.1)

• The outcome of the competition is determined by a biased random process that depends on the longevity and emotionality of the stored event (section 3.4.1)

• Hippocampal replay biases dream content via short term LTP in neocortex and amygdala (section 3.5)

• Erasure in CA3 is memory specific and requires appropriate cell firing patterns (section 3.5)

• Sleeping through a nightmare is necessary for this memory specific weakening process in CA3 (section 3.5) and memory strengthening in neocortex.

• Nefazodone downgrades the autonomic fear generated by nightmares so the nightmares do not cause awakening (section 2.0)

• There is a new drug class that suggests further research to develop drugs of greater specificity within this class.

Table 5. The major innovations