Limbic system – outline

1. Introduction
   - history
   - definition

2. Review of anatomy
   - amygdaloid complex
   - septal complex

3. Theories of hippocampal function
   - declarative memory
   - episodic memory
   - cognitive map
   - relational memory

4. The amygdala and emotion
   - theories of emotion
   - fear and fear conditioning

5. The hippocampus beyond memory
   - exploratory behavior and anxiety
   - species typical behaviors
   - home cage behavior
### Theories of hippocampal function - history

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1888</td>
<td>S. Brown &amp; H. Schäfer</td>
<td>early report of forgetfulness in a monkey with large bilateral temporal lobe lesions</td>
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<tr>
<td></td>
<td>until the 1930s</td>
<td>prevailing view of hippocampus as part of the olfactory system</td>
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<tr>
<td>1937</td>
<td>J.W. Papez</td>
<td>component of Papez circuit of emotion</td>
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<tr>
<td>1938</td>
<td>R. Jung &amp; A. Kornmüller</td>
<td>discovery of hippocampal EEG theta rhythm in rabbits, temporally linked to desynchronization of cortical EEG</td>
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<tr>
<td>1957</td>
<td>W. Scoville &amp; B. Milner</td>
<td>bilateral surgical lesions of medial temporal lobe associated with global amnesia in several patients including H.M.</td>
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<td>1960s</td>
<td>R. Isaacson &amp; D. Kimble</td>
<td>lesion studies fail to model amnesia in monkey or rats, but show deficits of exploration and behavioral disinhibition.</td>
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<td>1971</td>
<td>T. Hirano &amp; O. Vinogradova</td>
<td>first implantations of microelectrodes to record single unit activity in the hippocampus of freely moving animals</td>
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<tr>
<td>1978</td>
<td>J. O’Keefe &amp; L. Nadel</td>
<td>the hippocampus as a cognitive map</td>
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<tr>
<td>1982</td>
<td>J. Gray</td>
<td>septo-hippocampal theory of anxiety, updated 2000</td>
</tr>
<tr>
<td>1992</td>
<td>S. Tonegawa &amp; E.R. Kandel</td>
<td>first papers using genetically modified mice to investigate cellular mechanisms of cognitive function</td>
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</tbody>
</table>
# Theories of hippocampal function - memory

<table>
<thead>
<tr>
<th>Theories</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Declarative memory theory</strong></td>
<td>The hippocampus is part of a medial temporal lobe memory system that selectively mediates declarative memory in a time-limited manner.</td>
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<tr>
<td></td>
<td>- founded on global amnesia syndrome in human patients</td>
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<tr>
<td></td>
<td>- primate models of amnesia: DMTS and DNMTS tasks</td>
</tr>
<tr>
<td></td>
<td>- rodent models: object recognition / discrimination</td>
</tr>
<tr>
<td><strong>Episodic memory theory</strong></td>
<td>The hippocampus is a structure that mediates episodic memory, the recall of discrete events via mental time travel. Episodic-like memory in animals is the memory of “what”, “when” and “where”.</td>
</tr>
<tr>
<td></td>
<td>- founded on global amnesia syndrome in human patients</td>
</tr>
<tr>
<td></td>
<td>- bird model: what-where-when, rodent model: order of events</td>
</tr>
<tr>
<td><strong>Cognitive map theory</strong></td>
<td>The hippocampus harbors the locale system, a memory system that represents stimuli as a cognitive map with respect to an allocentric spatial framework and permits navigation in space.</td>
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<tr>
<td></td>
<td>- founded on single unit recordings in freely moving animals</td>
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<tr>
<td></td>
<td>- rodent models: radial maze, water maze, Barnes maze</td>
</tr>
<tr>
<td><strong>Configural, relational, contextual theories</strong></td>
<td>The hippocampus is a learning system that deals flexibly with overlapping sets of stimuli in which the meaning of each stimulus may depend on temporal sequence or presence of other stimuli.</td>
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<tr>
<td></td>
<td>- roots in instrumental and classical conditioning</td>
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<tr>
<td></td>
<td>- rodent: contextual conditioning, transitive inference, paired associate</td>
</tr>
</tbody>
</table>
Object recognition / discrimination

Measures of recognition memory:
- time exploring object
- exploration of A test < training
- exploration during test A<C

Control measures:
- activity during habituation
- total exploration time
- exploration A = B during training

Variants: more objects, multiple training trials, object displacement
Odor sequence task

**Training**

- **3x sequence 1**
  - A → B → C → D → E
  - repeated day 1-5
  - delay within sequence 3s
  - delay between sequences 3h

- **3x sequence 2**
  - L → M → N → O → P

Dig in cup with scented sand
- training: one cup with reward
- test: 2 cups without reward

**Choice tests**

- **Within sequence: order** (requires hippocampus)
  - A → D → B → C → L → P

- **Between sequence: relative recency** (no discrimination)
  - A → N → E → O → B → L

- **odor novelty** (hippocampus not required)
  - X → A → D → Y → M → Z
Radial-maze tasks

spatial working memory

Errors:
- working memory = reentry after bait collect
- procedural (bait or arm neglect)

spatial working and reference memory

Errors:
- working memory = reentry after bait collect
- reference memory: entry to unbaited arm
- procedural (bait or arm neglect)
Water-maze tasks

Place navigation task with massed training

Place navigation task with spaced training and reversal

Cue navigation task with massed training

control task for sensory motor performance

Training parameters:
- escape latency
- swim path
- cumulative search error
- Whishaw’s error

Probe trial parameters:
- quadrant time
- annulus crossings
- zone time
- proximity

Advanced Course in Neuroscience - Limbic System II - 07.05.2012
Water-maze tasks

Matching to place task with varying delays

Serial reversal task with training to criterion
Transitive inference task

Odor discrimination training

Choice test of non-transitive novel pairing

Choice test of transitivity

ordered mental representation of relations

A > B > C > D > E  ● reward

solved by rat with hippocampal lesion, based on single associations

not solved by rat with hippocampal lesion, single associations are all ambiguous
Social transmission of food preferences

Phase I

Phase II

Phase III

Odor guided paired associate learning in mice and rats

Memory measure:
- amount food eaten
A > B in phase III

Control measures:
- amount food eaten in phase I
- amount food eaten A+B in phase III
- interaction time phase II
Emotions

- Stimulus
- Conscious sensation "feeling"
- Cortical processing
- Subcortical processing
- Motor and autonomic control systems
- Periphery
- Behavioral response
- Autonomic and endocrine response

Related structures:
- Amygdala
- Hypothalamus
- Brainstem
Pavlovian (cued) fear conditioning

- measured response
  - defensive behavior (freezing, vocalization, flight)
  - reflex potentiation (startle)
  - hypoalgesia
  - autonomic arousal (blood pressure, heart rate)
  - HPA axis stimulation
Cued and contextual fear conditioning

**Training**
- Training chamber
- CS
  - US
  - Baseline
  - 1-3 training cycles
- Co-termination of CS and US

**Tests**
- Test chamber
  - CS
  - CS test
  - Baseline
- Training chamber
  - Context test
Trace fear conditioning

**Training**
- Training chamber
- CS US
  - Baseline
  - 5+ training cycles
  - Trace interval between CS and US

**Tests**
- Test chamber
- CS US
  - Baseline
  - CS test
- Training chamber
- CS US
  - Context test
Fear conditioning circuitry

- stimuli
  ↓↓↓↓
- thalamus
  └── sensory cortex
  └── ventral hippocampus
    └── needed for contextual and trace conditioning

- La (lateral nc)
- BM (basomedial nc)
- BL (basolateral nc)

- CeL (central nc, lateral)
- CeM (central nc, medial)

- BST (bed nc of stria terminalis)
- hypothalamus
- brainstem
  ↓↓↓↓ defensive responses

- hippocampus
The hippocampus beyond memory

Lesions of the hippocampus or other experimental manipulations that affect hippocampal function in rodents have also effects that are unrelated to memory function:

**Exploration**
- hyperlocomotion in novel or aversive environment

**Novelty**
- delayed exploration, delayed or no habituation
- increased exploratory activity toward new objects

**Shuttlebox**
- facilitated active avoidance learning

**Anxiety**
- reduced anxiety-related parameters in anxiety tests
- increased center time in open field test
- increased open arm entries in plus maze test
- reduced dark time in light-dark transition test

**Perseverance**
- inability to suppress inadequate spontaneous or learned responses
- tendency to develop stereotypical behavior
- reduced spontaneous alternation on T-maze

**Nesting**
- reduced nest quality, more unused nesting material

**Burrowing**
- reduced burrowing activity in burrowing test