University of Zurich[UZH]

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

ZNZ Advanced Course in Neuroscience
Mon 28.04.2014

Limbic System I

David P. Wolfer MD

Institute of Anatomy, University of Zurich
Institute for Human Movement Sciences and Sport, ETH Zurich
http://www.dpwolfer.ch
dpwolfer@anatom.uzh.ch, dwolfer@ethz.ch

Limbic system – outline

1 *Introduction*
- history
- definition

2 *Theories of hippocampal Function – rodent tests*
- declarative memory
- episodic memory
- cognitive map
- relational memory

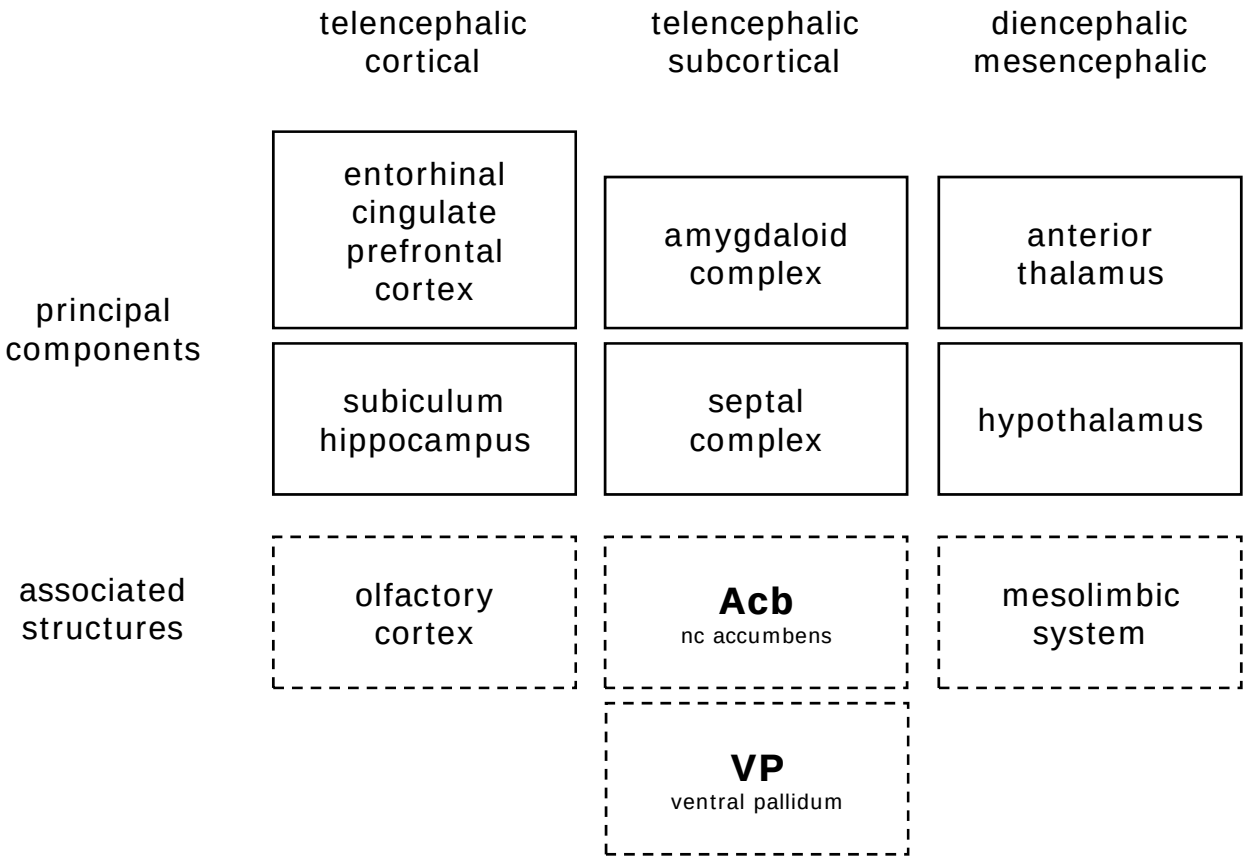
3 *The hippocampus beyond memory*
- exploratory behavior and anxiety
- species typical behaviors
- home cage behavior

4 *The amygdala and emotion*
… Part II of lecture 05.05.2014

Limbic system components – history

1878	P. Broca	anatomical definition: **grand lobe limbique** (limbus = border, seam), structures at border between cerebral hemisphere and diencephalon: cingulate cortex, hippocampus and adjacent cortex, olfactory cortex and bulb
1928 1929	P. Bard W.B. Cannon	hypothalamic theory of emotion: **hypothalamus** -> event evaluation, control of expression and experience of emotions
1937	J. Papez	**Papez circuit** of emotion: cingulate cortex -> hippocampus –> hypothalamus (mammillary body) -> anterior thalamus -> cingulate cortex
1952	P. MacLean	**Limbic system** (old mammalian brain) as interface between reptilian brain and new mammalian brain, includes prefrontal cortex and amygdala.
1957	B. Millner W.B. Scoville	Patient H.M: identification of **medial temporal lobe** structures as substrate of declarative memory -> a core component of the limbic system becomes the major target of cognitive neuroscience.

Components of the limbic system



Limbic system – outline

1 *Introduction*
- history
- definition

2 *Theories of hippocampal Function – rodent tests*
- declarative memory
- episodic memory
- cognitive map
- relational memory

3 *The hippocampus beyond memory*
- exploratory behavior and anxiety
- species typical behaviors
- home cage behavior

4 *The amygdala and emotion*
… Part II of lecture

Theories of hippocampal function - history

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

Theories of hippocampal function - history

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

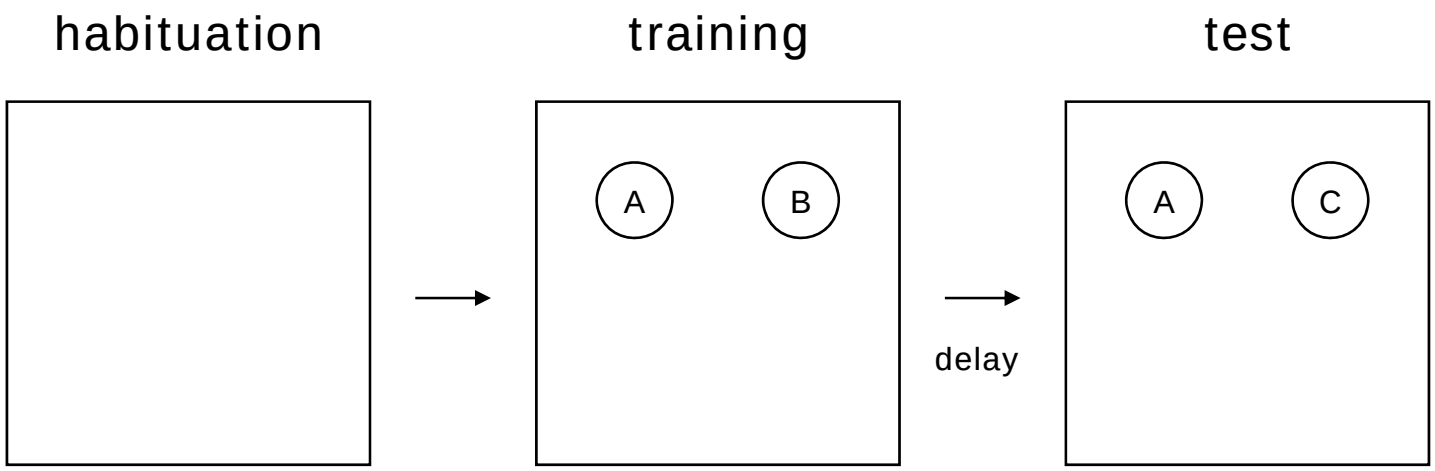
Theories of hippocampal function - memory

Declarative memory theory	Hippocampus is part of a medial temporal lobe memory system that selectively mediates declarative memory in a time-limited manner. - founded on global amnesia syndrome in human patients - primate models of amnesia: DMTS and DNMTS tasks - rodent models: object recognition / discrimination
Episodic memory theory	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”. - founded on global amnesia syndrome in human patients - bird model: what-where-when, rodent model: order of events
Cognitive map theory	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. - founded on single unit recordings in freely moving animals - rodent models: radial maze, water maze, Barnes maze
Configural, relational, contextual theories	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. - roots in instrumental and classical conditioning - rodent: contextual conditioning, transitive inference, paired associate

Theories of hippocampal function - memory

Declarative memory theory	Hippocampus is part of a medial temporal lobe memory system that selectively mediates declarative memory in a time-limited manner. - founded on global amnesia syndrome in human patients - primate models of amnesia: DMTS and DNMTS tasks - rodent models: object recognition / discrimination
Episodic memory theory	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”. - founded on global amnesia syndrome in human patients - bird model: what-where-when, rodent model: order of events
Cognitive map theory	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. - founded on single unit recordings in freely moving animals - rodent models: radial maze, water maze, Barnes maze
Configural, relational, contextual theories	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. - roots in instrumental and classical conditioning - rodent: contextual conditioning, transitive inference, paired associate

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, social stimuli

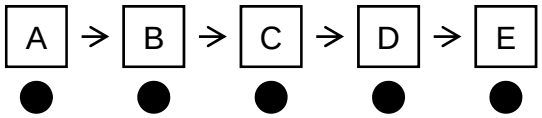
Theories of hippocampal function - memory

Declarative memory theory	Hippocampus is part of a medial temporal lobe memory system that selectively mediates declarative memory in a time-limited manner. - founded on global amnesia syndrome in human patients - primate models of amnesia: DMTS and DNMTS tasks - rodent models: object recognition / discrimination
Episodic memory theory	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”. - founded on global amnesia syndrome in human patients - bird model: what-where-when, rodent model: order of events
Cognitive map theory	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. - founded on single unit recordings in freely moving animals - rodent models: radial maze, water maze, Barnes maze
Configural, relational, contextual theories	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. - roots in instrumental and classical conditioning - rodent: contextual conditioning, transitive inference, paired associate

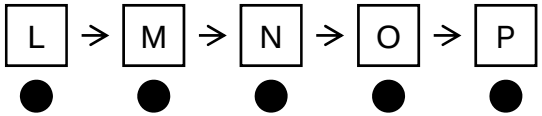
Odor sequence task

Training

3x sequence 1



3x sequence 2

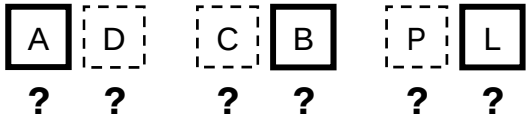


- repeated day 1-5
- delay within sequence 3s
- delay between sequences 3h

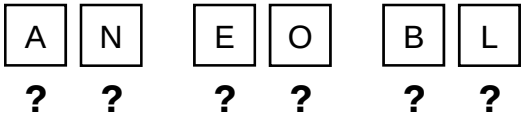
Dig in cup with scented sand
- training: one cup with reward
- test: 2 cups without reward

Choice tests

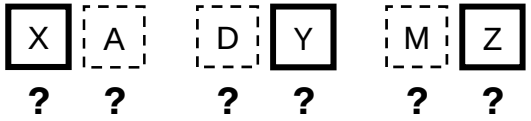
Within sequence: order
(requires hippocampus)



Between sequence: relative recency
(no discrimination)



odor novelty:
(hippocampus not required)



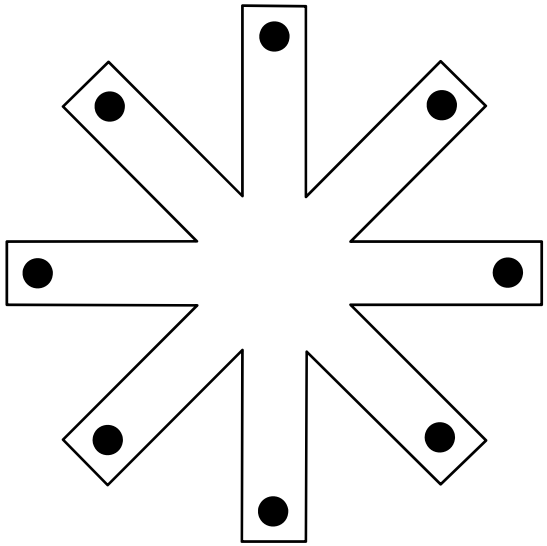
DeVito and Eichenbaum H, J Neurosci 31:3169,2011

Theories of hippocampal function - memory

Declarative memory theory	Hippocampus is part of a medial temporal lobe memory system that selectively mediates declarative memory in a time-limited manner. - founded on global amnesia syndrome in human patients - primate models of amnesia: DMTS and DNMTS tasks - rodent models: object recognition / discrimination
Episodic memory theory	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”. - founded on global amnesia syndrome in human patients - bird model: what-where-when, rodent model: order of events
Cognitive map theory	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. - founded on single unit recordings in freely moving animals - rodent models: radial maze, water maze, Barnes maze
Configural, relational, contextual theories	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. - roots in instrumental and classical conditioning - rodent: contextual conditioning, transitive inference, paired associate

Radial-maze tasks

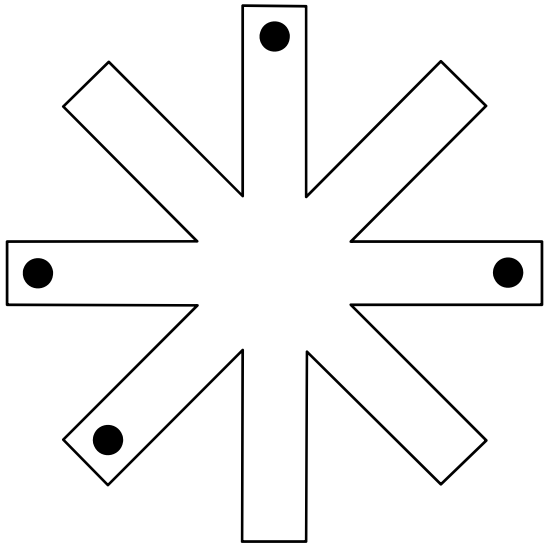
spatial working memory



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

● bait

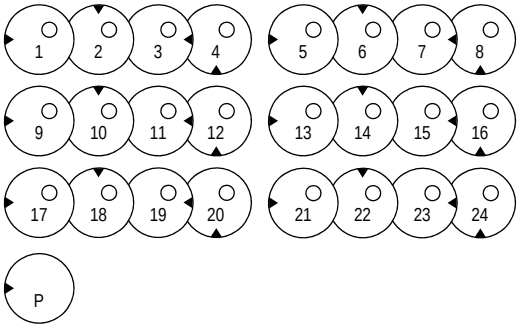
spatial working and reference memory



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



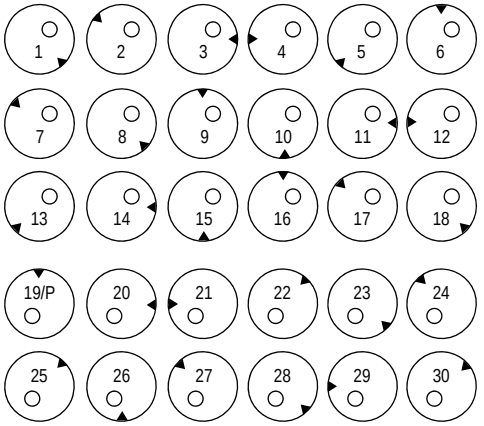
Cue navigation task
with massed training

...

control task for sensory
motor performance

○ hidden platform
● visible platform
▸ release point

Place navigation task
with spaced training and reversal



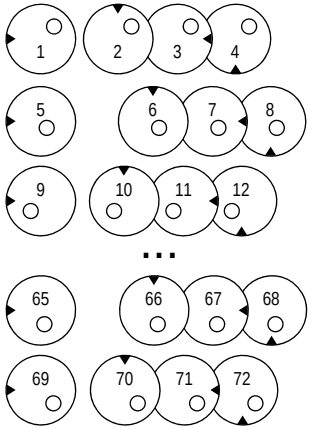
Training parameters:
- escape latency
- swim path
- cumulative search error
- Whishaw's error

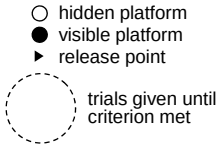
Probe trial parameters:
- quadrant time
- annulus crossings
- zone time
- proximity

Morris et al, Nature 297:681,1982

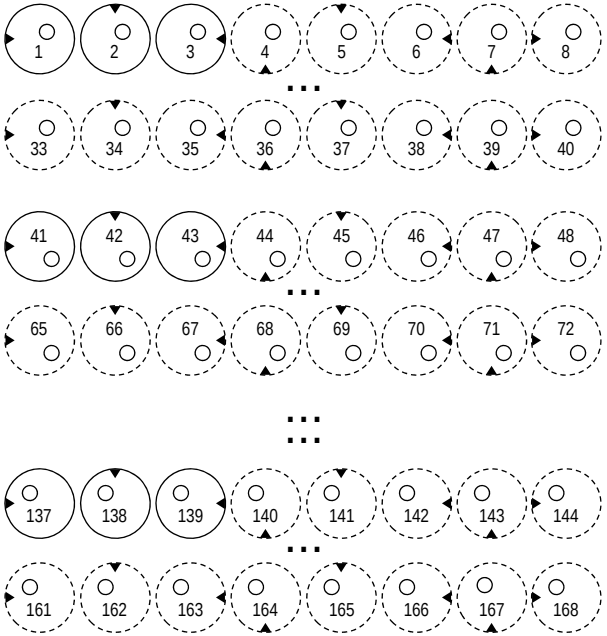
Water-maze tasks

Matching to place
task with varying delays





Serial reversal task
with training to criterion

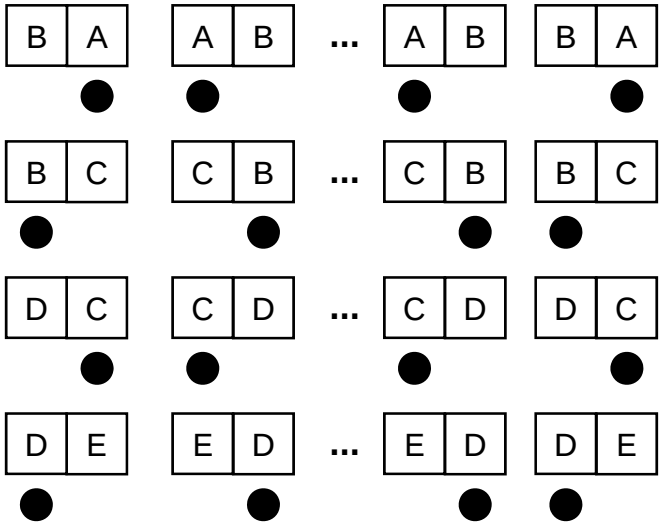


Theories of hippocampal function - memory

Declarative memory theory	Hippocampus is part of a medial temporal lobe memory system that selectively mediates declarative memory in a time-limited manner. - founded on global amnesia syndrome in human patients - primate models of amnesia: DMTS and DNMTS tasks - rodent models: object recognition / discrimination
Episodic memory theory	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”. - founded on global amnesia syndrome in human patients - bird model: what-where-when, rodent model: order of events
Cognitive map theory	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. - founded on single unit recordings in freely moving animals - rodent models: radial maze, water maze, Barnes maze
Configural, relational, contextual theories	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. - roots in instrumental and classical conditioning - rodent: contextual conditioning, transitive inference, paired associate

Transitive inference task

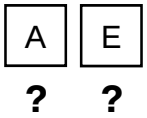
Odor discrimination training



ordered mental representation of relations

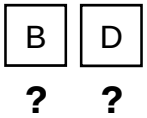
reward

Choice test of non-transitive novel pairing



solved by rat with hippocampal lesion, based on single associations

Choice test of transitivity

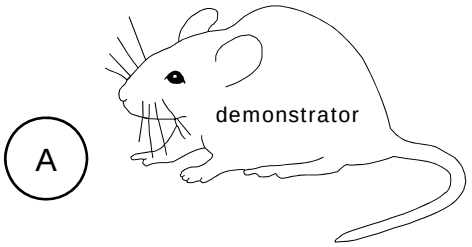


not solved by rat with hippocampal lesion, single associations are all ambiguous

Dusek and Eichenbaum, PNAS 94:7109,1997

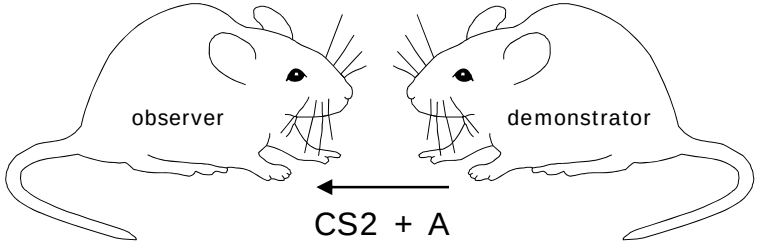
Social transmission of food preferences

Phase I



Odor guided
paired associate learning
in mice and rats

Phase II

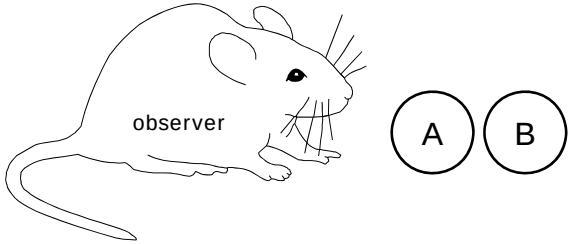


Memory measure:
- amount food eaten
  A > B in phase III

delay

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

Phase III



Winocur, Behav Brain Res 38:145, 1990

Limbic system – outline

1 *Introduction*
- history
- definition

2 *Theories of hippocampal Function – rodent tests*
- declarative memory
- episodic memory
- cognitive map
- relational memory

3 *The hippocampus beyond memory*
- exploratory behavior and anxiety
- species typical behaviors
- home cage behavior

4 *The amygdala and emotion*
… Part II of lecture

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

Current problems with behavioral testing of mice

Mice are not small rats	Lack of ethological relevance: most behavioral tests were originally developed for rats and insufficiently adapted to mice
Mice are not small humans	Behavioral tests are often expected to model human behavior and symptoms of human psychiatric diseases
A mouse is not a mouse	Genetic background: inconsistent, false positive or negative results due to large behavioral differences between mouse strains
Low throughput	Behavioral phenotyping is too inefficient in view of the exploding number of mouse models to be analyzed
Animal welfare	Outcome of behavioral phenotyping studies is strongly affected by laboratory environment and the human observer as stress factor

→ New, alternative approaches are needed

→ Automated behavioral testing in the home cage solves some but not all of the current problems