Figure 4.5 ASSOCIATIVE PROCESSES believed to contribute to learning in *Aplysia* and in the hippocampus of mammals may share similar mechanisms. Both may involve a modulatory substance that produces activity-dependent enhancement of transmitter release from the presynaptic neuron. Stripes denote neurons in which coincident activity must occur to produce the associative change.
Long-Term Potentiation
Figure 4.4 IN LONG-TERM POTENTIATION the postsynaptic membrane is depolarized by the actions of the non-NMDA receptor channels. The depolarization relieves the magnesium blockade of the NMDA channel, allowing calcium to flow through the channel. The calcium triggers calcium-dependent kinases that lead to the induction of LTP. The postsynaptic cell is thought to release a retrograde messenger capable of penetrating the membrane of the presynaptic cell. This messenger, which may be nitric oxide, is believed to act in the presynaptic terminal to enhance transmitter (glutamate) release, perhaps by activating guanylyl cyclase or ADP-ribosyl transferase.
Long-Term Potentiation

Key properties:

- Input-specific.
- Requirement for postsynaptic depolarization.
- Often induced by high-frequency stimulation, can also be induced by physiological firing patterns.
- Pre- and/or postsynaptic mechanisms involved (retrograde messenger).
- May be dependent upon spike timing, favoring consolidation of connections delivering precisely timed spikes.
LTP

Hippocampus and cortex show similar forms of neuroplasticity
Vertebrate Models: The Hippocampus
Data from Rugg 1995
Vertebrate Models: The Hippocampus
Vertebrate Models: The Hippocampus
Vertebrate Models: The Hippocampus

- Schaffer collateral pathway
- CA3 pyramidal cells
- CA1 pyramidal cells
- Mossy fiber pathway
- Granule cells
- Dentate gyrus
- Output to fimbria
- Output to subiculum
- Cortical association areas
- Entorhinal cortex
- Via subiculum
- Perforant pathway
Vertebrate Models: The Hippocampus
Animal Models of Learning (Vertebrates)

Morris water maze: standard test for spatial memory in rodents

Rats with bilateral hippocampal damage cannot learn/remember the location of the hidden platform.
Animal Models of Learning (Vertebrates)

Rats with bilateral hippocampal damage cannot learn/remember the location of the hidden platform.

Injection of NMDA blockers into the hippocampus also abolishes behavioral improvement and learning (Richard Morris).

Another experimental method: genetic manipulation (“knockout”) of genes that make molecules thought to be involved in learning and memory. Gene knockout can be restricted to specific regions of the brain (Susumu Tonegawa).

Does boosting the number of NMDA receptors produce an increase in memory performance? Overexpression of NMDA receptors in genetically altered mice can result in enhanced learning (Joe Tsien, 1999).
Neuronal Memory: Unity or Diversity?

Studies suggest:

Intracellular signalling mechanisms and changes in gene expression are critical. Protein synthesis is required for long-term memory.

Common set of molecular mechanisms subserving different kinds of memory (e.g. explicit, implicit).

Mechanisms are evolutionarily conserved over a broad range of species, from invertebrates (Aplysia, Drosophila) to primates.
Human Memory

The cognitive neuroscience of memory aims at how humans record, retain and retrieve experience in terms of specific memory systems – networks of neurons that support different mnemonic processes (after Gabrieli, 1998)
Amnesia

Amnesia: difficulty in learning new information, or in remembering the past – resulting from neurological injury or disease.

Often occurs in the absence of other cognitive deficits – normal perceptual and motor skills, normal intelligence, intact language and social skills.

Causes of amnesia: focal or degenerative injury.
- Focal causes: head injury, electroconvulsive therapy, stroke, bilateral lesions of the medial lobe.
- Other forms of amnesia: dementia-related, Alzheimer’s etc.
Amnesia

Impairment: retrograde memory loss, often graded (very recent memories are most affected), time-limited, often sparing very old memories.

Impairment: anterograde memory, formation of new memories from the date of the lesion onwards, irreversible.

Global amnesia: usually after bilateral lesions of the medial temporal lobe, affects verbal and nonverbal material, all sensory modalities.
Amnesia

Retrograde amnesia

Anterograde amnesia
Timing of Anterograde and Retrograde Effects

Retrograde and anterograde amnesia after electroconvulsive therapy
Amnesia

Intact (often): remote memory, e.g. childhood.

Intact: short-term or working memory, information can be held for several minutes if rehearsal is allowed – but recall after distracting interval is impaired. No increased proficiency with repeated presentations if word lists etc.

Intact: motor, perceptual or cognitive capacities.
Amnesia: Diencephalic Lesions

Alcoholic Korsakoff’s syndrome (brain damage caused by vitamin deficiency).

Damage to medial thalamus, often mammillary nuclei (fimbria/fornix output of hippocampus).

Declarative memory is affected, but nondeclarative memory is preserved.

Exact causes for medial thalamic disruptions (interactions with medial temporal lobe system?) are still unclear.
Amnesia: Medial Temporal Lesions

Causes: resection (surgery), anoxia, herpes simplex encephalitis, infarction, or sclerosis.

First lesions in most cases of Alzheimer’s D. occur in medial temporal lobe.

Medial temporal lobe system:
- parahippocampal region (parahippocampal and perirhinal cortices)
- hippocampal region
- amygdala (role?)
Patient H.M.

Bilateral resection of the medial temporal lobe (1953) to ameliorate severe epileptic attacks, possibly due to a bicycle accident at age 9 (“a frankly experimental operation”).

First report of “a very grave, recent memory loss” in 1954 by Scoville.

Scoville and Milner (1957): memory appears to have a distinct neural substrate, inspired animal models of amnesia.


**Patient H.M.**

H.M. has above normal intelligence (IQ 117).

Normal digit span (working memory measure) of 6-7 items

“Every day is alone in itself ... everything looks clear to me, but what happened just before? ... It’s like waking from a dream. I just don’t remember.”
Patient H.M.

H.M.’s lesion: surgeon’s estimate (left); MRI result (right) – although some of the posterior hippocampus was not removed, the tissue appeared atrophied.
Patient H.M.

After: Corkin et al., 1997

(a) H. M.'s brain

(b) Normal brain
Patient H.M.

Corkin et al., 1997
**Patient R.B. and G.D.**

Study of R.B. and other patients (G.D. etc.) showed that damage limited to (a specific subfield of) the hippocampal formation was sufficient to produce clinically significant anterograde memory loss.

*Lesion: limited to the CA1 field of hippocampus (bilateral).*
Patient G.D.: Memory Test

But: G.D. had near-normal recall of autobiographical (episodic) memories over all decades of his life (no evidence of severe retrograde amnesia)
Patient G.D.  

Rempel-Clower et al., 1996

normal hippocampus  

hippocampus of patient G.D.
**Role of Hippocampus**

Hippocampus is involved in transfer of short-term into long-term memories. It is not the repository of long-term memory.

Lesions of subfield CA1 lead to severe anterograde but only limited retrograde amnesia. Anterograde amnesia is aggravated and retrograde effects extend further into the past if lesions extend into entorhinal or perirhinal cortices.

Long-term memories are consolidated within neocortex.
Spared Learning in Amnesics

Amnesia often does not affect skill learning, sensorimotor learning, some cognitive skills (e.g. learning to read words in a mirror), some semantic knowledge (verbal information about people etc.), conditioning, priming.
Delayed nonmatch-to-sample task (Mishkin, 1978) – test of recognition memory. (“...only a few days are needed to instill this principle of choosing the novel object, since it is one to which the naturally inquisitive monkey is already predisposed.”)
Animal Models
Animal Models

Mishkin, 1982

Animal models attempted to address the question which brain regions actually were causing the severe amnesia in cases like H.M.
GARNISH
PET Study of Memory

Task: Word stem completion task (priming)

GAR _____
PET Study of Memory

Task: Word stem completion task

Before scans are taken: S’s view list of 15 words.

Scan – Word stems are presented.
Four conditions:
No response: quietly view word stems.
Baseline: Complete word stems forming the first word that comes to mind (word stems are unrelated to the words seen before).
Priming: like baseline, except some word stems can be completed to form previously seen words (implicit memory)
Memory: S’s are instructed to use the stems to recall earlier presented words (explicit memory).
PET Study of Memory

Memory-task related activation of hippocampus

Squire et al., 1992
PET Study of Memory

Squire et al., 1992

Other findings:

- increased activation (over baseline) of right prefrontal cortex in memory task

- decreased activation (over baseline) of right occipital cortex in priming

- some activation of right hippocampus during priming (“contamination” by unintentional conscious recall?)

- lateralization of hippocampal activation (right hemisphere) probably due to visual presentation of words/word stems.
**PET Study of Memory**

Related study by *Schacter et al., 1996*, aimed at clarifying the role of hippocampus in human explicit versus implicit memory.

Attempted “improvements” over Squire et al., 1992:

- priming while eliminating “contamination” by conscious recall.
- separation of “effort to recall” from actual recollection.
PET Study of Memory

Priming task:
S’s study lists of words, shallow semantic processing is imposed by asking them to count the number of t-junctions in the words. This procedure is designed to ensure poor explicit memory of the items. Then, scans are conducted upon presentation of word stems from studied words (priming) or non-studied words (baseline).

Explicit memory task:
High-recall: target words are shown (4 times) and S’s are making “semantic judgments” (“how many different meanings does the word have”)
Low-recall: target words are shown (once) and S’s are asked to count t-junctions.
**PET Study of Memory**

Schacter et al., 1996

Baseline minus Priming: decreased blood flow in extrastriate visual areas.

Low Recall minus Baseline: (high effort, low accuracy) increased blood flow in left prefrontal and secondary visual cortices.

High Recall minus Baseline: (high explicit recall, low effort) increased blood flow in bilateral hippocampus
**PET Study of Memory**

Role of the hippocampus in topographic memory?

Study by Maguire et al., 1997 – PET imaging of London taxi drivers as they overtly described routes between destinations in London.

This task is compared to the recall and description of famous landmarks that have never been visited by the S’s.

Nontopographical tasks included recall of film plots between given points in the story line and recall and description of single film frames.
PET Study of Memory

- T+:
  - S+: routes
  - S-: famous landmarks

- T-:
  - S+: film plots
  - S-: film frames

number repetition baseline
PET Study of Memory

Example route
PET Study of Memory

Subtraction images of routes recall versus landmarks recall (11 taxi drivers)
Hippocampus and Spatial Navigation

(a) Virtual environment allowing spatial navigation; (b) PET scan obtained during spatial navigation shows activation of hippocampus.
Encoding and Retrieval

Encoding of memory:
- shallow (e.g. perceptual)
- deep (e.g. semantic meaning)

Craik and Lockhart: type of encoding is an important determinant of subsequent retrieval (not “intention”). - “levels of processing effect”. Very robust!

What are the neural substrates involved?


**Encoding and Retrieval**

PET study by Kapur et al., 1994:

**Task:** S’s are exposed to series of visually presented nouns (same list of 80 words is used for both encoding levels).
- shallow encoding: detect the presence of the letter “a”.
- deep encoding: categorize each noun as living/nonliving.
- Memory performance is higher for deep encoding.

**Main result:** deeper encoding is accompanied by increased activity of left inferior prefrontal cortex.
Encoding and Retrieval

Increased rCBF “deep” minus “shallow” – projection images.

Kapur et al., 1994
Encoding and Retrieval

What does this result mean?

Is the left inferior prefrontal cortex the “place” where the (deeply encoded) memory is stored?

Kapur et al. argue that the increased activation is a correlate of “semantic processing”, which then may lead to a more easily retrievable memory trace elsewhere (medial temporal lobe?).
Encoding and Retrieval

Remembering of word-events is a laboratory analog of episodic memory (In Kapur et al., only “what” dimension was used)

Nyberg et al. studied encoding and retrieval of episodic memories (event memories, “what”, “where”, and “when”) – word lists presented with different instructions (encoding) – then recall (retrieval)
Encoding and Retrieval

Two conclusions:
- Episodic encoding and retrieval of different types of event information share a **common** neuroanatomical basis.
- Processing of individual aspects ("what", "where" and "when") recruits **additional** regions.
Encoding and Retrieval

Questions to raise about these previous studies:
- what about the medial temporal lobe system?
- Is the spatial resolution of PET satisfactory?
Encoding and Retrieval

fMRI studies of encoding and retrieval: Gabrieli et al., 1997.

Goal: functional specialization of different structures within the human medial temporal lobe system.

Tasks:
Retrieval task: S’s are shown b/w line drawings of objects – During scanning, S’s are shown words that either match or don’t match the previously seen objects – S’s make judgments of familiarity or novelty.
Encoding task: S’s are shown color pictures of indoor/outdoor complex scenes and are asked to remember the pictures (novel or familiar).
Encoding and Retrieval
Encoding and Retrieval

**Retrieval task**: activation of anterior subiculum.

**Encoding task**: activation of posterior parahippocampal cortex.
Encoding and Retrieval

Pixel counts for both structures
Encoding and Retrieval

Parahippocampal cortex (input)
Subiculum (output)
Encoding and Retrieval

Problem with Gabrieli’s task: cross-modal association task (pictures – words).

Does hippocampal activation only occur when such cross-modal associations need to be formed or is the hippocampus activated also during “simpler” recognition memory within the same modality?

Study by Stark and Squire, 2000.
Encoding and Retrieval

Stark and Squire, 2000:

Task:
S’s view lists of 80 items (targets, either words or line drawings) – after 30 min., S’s are scanned and presented with 80 targets/80 foils (intermixed), must indicate familiarity (recognition memory). Test is done twice (3 min. in between).
Average fMRI scans (targets/foils) for 11 S’s during recognition memory for “words” or “objects”.

Encoding and Retrieval
Encoding and Retrieval

What about “false memories”?

Series of words: “water, ice, wet, dark, freeze” – true items

False item: “cold”

Schacter et al. (1996): medial temporal lobe is activated for “retrieval” of both true and false items - suggests that MTL recovers semantic, but not sensory properties of episodic information (false items have not actually been encountered).

New study (2001) promotes sensory as well as semantic encoding...
Encoding and Retrieval

Words are presented alternately by two different speakers (videotaped, m/f). Subjects are instructed to remember not only the words, but also the speaker.

False items are “recalled” as often as true items...

MTL activations show a dissociation between two MTL regions for the type of information recovered (sensory versus semantic).
Encoding and Retrieval

Images 1-5 taken at 2.5 sec. intervals