For slides, electronic handouts, and related material, see **www.pobox.com/~rudolf/psychology**.

Overview

Memory is a complex topic. We will discuss the various forms of memory that exist from a theoretical and psychological perspective, discuss various influences on memory encoding and recall, and then examine the neural structures that are responsible for these different forms of memory, including the medial temporal lobe and diencephalic structures, the basal ganglia, and the prefrontal cortex. We will briefly consider consolidation, reconsolidation, and the role of sleep.

Types of memory

There are many forms of memory. As the process of subdividing 'memory' is based on neuroscientific, as well as psychological dissociations, the number of distinct forms of memory thought to exist has changed over the years — there are some major controversies in this area of cognitive neuroscience. *Memory* is simply the ability of something to retain information, thus changing its input→output function (the output it produces in response to a given stimulus). By this definition, sandpits, blackboards, and computers have memory. But there are, of course, much more sophisticated forms of memory.

Individual versus phyletic memory; perceptual versus motor memory; activation

Before getting into the nitty-gritty, it's worth mentioning some points made by Fuster (*1*), who writes about memory systems from a neurobiological perspective. These are as follows. (1) *Individual* memories are changes in brain activity or connectivity that are superimposed on the pre-existing brain, but that pre-existing brain is specific to our species and shaped by evolution — these specificities can be thought of as a *phyletic* memory. (2) Nervous systems take in sensory input and do things as a result; they have sensory and motor systems and complex processing in between; their memory systems are organized around this fundamental difference; we have *perceptual* and *motor* memories. (3) Both perceptual and motor memories may be *inactive* — a long-term condition — or become *active* in the short term.

Short- versus long-term memory

Traditionally, a distinction has been made between short-term memory (STM) and long-term memory (LTM) (*2-5*).

Incoming sensory information appears initially to enter a very short-term, high-capacity *sensory store*. Its existence was first shown by Sperling (*6*). He flashed a 4 × 3 matrix of letters for 50 ms. If participants were asked to report all the letters ('whole report'), they reported 4.32 letters correctly out of 12, but if they were cued by a series of tones, presented after the visual array, to report only the top, middle, or bottom row ('partial report'), they reported 3.04 out of 4 for each row. This implies that they had access to at least 9–10 out of 12 letters for a short time. It appears that this '*iconic* memory' lasts about half a second: if the tone was delayed for a second or so, participants were no better off than in the 'whole report' condition. The auditory version ('*echoic* store') last about 2 seconds (*3, 7, 8*).

From here, information appears to pass into a lower-capacity but slightly longer-lasting buffer, often known as short-term memory (STM). STM appears to have a severely *limited capacity* — typically 7±2 arbitrary pieces of information (*9*), though this can be increased by 'chunking' to impose structure on the stimuli; you can thereby remember seven arbitrary letters or numbers, or seven words, etc. If you are an expert in a particular domain, you may have more complex 'chunks' at your disposal and may therefore perform very well indeed; de Groot (*10*) showed that grandmasters had far superior short-term memory for valid chess positions than novices. If subjects hear or see a long list of items and must recall them (*free recall*)

there is better recall of early and late items (*primacy* and *recency* effects); the recency effect can be abolished by distractors. STM has a very *short duration*: Peterson & Peterson (*11*) found that if subjects memorized arbitrary patterns (e.g. 'XPJ'), performed a distractor task to prevent mental rehearsal, and were then asked to recall the pattern, they had forgotten 70% after nine seconds; obviously *rehearsal* can increase the effective duration. The *digit span* task is a popular test of STM.

According to early models of memory, some of the contents of STM can be passed on to LTM (*12*). The capacity of LTM appears effectively unlimited, and it is viewed as a permanent store. LTM can include spatial information about the world, motor skills, perceptual skills such as language perception, learned facts, etc.

Neurally, a concept of STM (or the related *working memory*, and *primary memory*) remains useful. It is likely, given its time-course and impermanence, that it reflects electrical activity; it has been hypothesized, for example, that the 7±2 limit reflects the number of neuronal ensembles that can simultaneously be 'bound' together by synchrony in the context of neuronal oscillations (e.g. *13*). Long-term memory storage is probably not dependent upon reverbatory patterns of electrical activity; it involves synaptic plasticity, and potentially the growth of new synapses. However, the concept of 'LTM' is not terribly useful, as it can be subdivided into many types of memory that can be dissociated neurally.

There have been theoretically important neural dissociations between STM and LTM; one such case was patient K.F. (*14*), who had a digit span of only 1–2 but apparently normal LTM, following a lesion of the perisylvian region of the left hemisphere (i.e. near / in auditory processing regions of cortex).

Dividing up long-term memory: declarative and nondeclarative memory

One way to begin is to divide LTM into *declarative* (or *explicit*) memory — memory for events and facts — and *nondeclarative (implicit)* memory — the rest (see *1, chapter 2*). Declarative memory includes *episodic* and *semantic* memory (*15, 16*), though whether these really reflect a different underlying neural process is less clear. Nondeclarative memory is a term that arose partly from the consideration of what was *not* lost from human amnesiacs (*17*); it includes *procedural* memory (*18*) and *priming* (*19*). The borderlines remain controversial.

Episodic memory

'The difference between episodic memory and semantic memory is often referred to in terms of remembering versus knowing: episodic memory is concerned with remembering specific personal experiences, whereas semantic memory mediates what one knows about the world. Remembering getting soaked in the London rain last Tuesday is an example of episodic memory, but knowing that it often rains in England is an example of semantic memory because it need not be acquired as a result of a personal experience of getting wet.' (*20*). Of course, semantic memory *can* be acquired as a result of personal experience.

An important problem in the study of episodic memory has been the lack of an *animal model.* In the absence of this, human lesion studies have provided a large proportion of the evidence regarding the structures that implement episodic memory, and these lesions tend to be either precisely demarcated but large (such as the neurosurgical lesion in H.M.) or difficult to define exactly (such as the damage caused by stroke, anoxia, or herpes simplex encephalitis). Tulving defines episodic memory as the memory of temporally defined events in subjective time, giving the possessor the ability to travel back in time to re-experience remembered events ('autonoetic consciousness', from Gr. *autos* self, *noetikos* pertaining to the mind, intellect, or process of perceiving or thinking), and has suggested that this may not be possessed by non-humans (*16, 21, 22*). It is difficult to know if animals 're-experience' past events, but the use of simpler definitions has allowed some remarkable capabilities of animals to be established. For example, Clayton & Dickinson (*23*) identify remembering *what, where,* and *when* an event occurred as key components of episodic memory, and show that scrub jays encode this information.

Semantic memory

Semantic memory can be thought of as *conceptual knowledge* or memory for *facts* (Bogota is the capital of Colombia; $i^2 = -1$). It does *not* necessarily include a representation of the episode in which the information was learned. In addition to such abstract pieces of information, semantic knowledge is usually taken to include categorical information about objects: 'a robin is a bird'.

There is considerable controversy about the nature of semantic memories (e.g. *1, 24*), partly because they can be hard to define precisely. One view (*25*) is that semantic memories are episodic memories for which the detailed contextual information has disappeared, leaving only the generic features. Another (*26*) is that they are two, truly separate systems.

Consider how semantic memory can be acquired associatively. Moggy, Felix, and Garfield are all conglomerations of stimulus features (elements). 'Moggy' can then be represented as the activation of a network of 'feature detectors' (neuronal assemblies) that is uniquely associated with Moggy. However, Moggy, Felix, and Garfield have *common* elements; these common features can be thought of as 'catness', could be associated with the word 'cat', and so on. This is one way in which semantic (categorical) information can be built up.

If this view is correct, then semantic information of this kind is intimately associated with perception — and indeed, action. Martin *et al.* (*27*) performed a PET study in which subjects identified line drawings of animals (which have to be distinguished by differences in visual form), tools (which can be distinguished by the use to which they are put), and nonsense objects. In addition to common areas of activation (animals and tools *versus* nonsense objects), there were regions that were specific to one category of information. Thus, animals (versus tools) activated an early visual processing area of occipital cortex, while tools (versus animals) activated a premotor area also activated by imagined hand movements. Semantic information, therefore, may be highly distributed across neocortex according to the perceptual and motor networks that it builds upon (*1*). Semantic dementia (loss of knowledge about meaning), agnosia, and apraxia can all follow damage to neocortical areas.

Procedural memory

Procedural memory means knowing *how* to do something (*18*). It is generally thought of as *skill* or *habit* memory. For example, patients with amnesia (see below) can have a preserved ability to learn a skill such as mirror-reading. More specifically, a procedural memory is one in which the structure of the memory's representation *directly* reflects the use to which the knowledge will be put in controlling the subject's behaviour (*28*), as opposed to declarative knowledge, which is to some degree independent of the use to which it is put.

Although many tasks have been considered to be learned by *habit* in amnesia research (see below), it's worth noting that few have proved their habits to be procedural in nature. What would do this? Dickinson and colleagues have developed a test for whether actions, such as lever-pressing by rats, are governed by declarative or procedural representations (see e.g. *29, 30*) — and they can be governed by either. If a rat presses a lever for food, and you then *devalue* (e.g. poison) the food, then you can assess the underlying representation. If the rat no longer presses the lever when you next test it, then it has integrated the knowledge of the food's value with the information that the lever produces the food; this requires declarative representations. If the rat presses the lever regardless, then its action is not controlled by the knowledge of the outcome, and is a stimulus–response habit. This level of psychological sophistication has yet to be applied to many of the 'procedural' tasks we will mention.

Priming

Priming is an increase in the speed or accuracy of a decision as a consequence of *prior exposure* to some of the information involved in the decision (*31*). It occurs in tasks where memory for the previous information is not required, and it may adversely affect performance, so it is assumed to be an involuntary and perhaps unconscious phenomenon. For example, the reaction time for 'doctor' is shorter if it has been preceded by 'nurse' than if it has been preceded by 'north' or the non-word 'nuber' (*semantic priming*). Repetition priming for visual stimuli is associated with reduced blood flow in occipital cortex (*32*); it is possible (but unproven) that (a) priming is a cortical effect in regions involved in processing the stimulus; (b) following presentation of a stimulus, less neural activity is required to process the same stimulus.

Encoding, forgetting and recall

Emotional effects on memory consolidation

We saw in the Emotion / Motivation handout (q.v.) that emotionally-arousing situations can improve memory consolidation, that this may be mediated by systemic adrenaline and glucocorticoids (and prevented by benzodiazepines), and that many of these effects appear to be modulated through the amygdala (see *33, 34, 35*).

Forgetting

Although the simple passage of time may be important in forgetting from STM, it is certainly important what happens *during* that time — perhaps that items are *displaced* rather than (or as well as) *decaying*. For example, recall can be better after sleep than after an equally long period of waking (*36*), though this effect might in principle be due to active consolidation during sleep than disruption by other activities during waking. If people attempt recall of an item in the middle of a list, their success depends more on the number of items that have followed than on the time that has elapsed (*37*).

Interference effects can be *retroactive* (new information interferes with previously-learned material) or *proactive* (previously-learned information interferes with new learning) — if you have to memorize list of numbers after list of numbers, you become progressively worse (proactive interference) but if you then have to learn a list of letters, you become better again (release from proactive interference) (*38*).

Cue- or state-dependence of recall

We may be unable to remember things not just because they are not encoded in our brain, but because we have the information but are unable to recall or retrieve it. Providing explicit cues (clues!) can assist recall (*39*). These cues can be *external:* if you learn material in one room, you recall it better if you're in the same room (*40*); if you learn material underwater, you recall it better underwater (*41*) — and this benefit was only for recall, not for recognition. The cues can be *internal*, known as *state dependence:* if you learn material drunk, there is a recall benefit to being drunk (*42*); recall is better when you're in the same mood as when you learned ('mood-dependent memory') (*43*) and mood affects recall in other ways — if you're happy, you're more likely to retrieve happy material ('mood-congruent memory') (*44*). This may be one reason why victims of violent crime have problems recalling details — recall occurs in a less emotionally-aroused state (*45*).

Schemata and memory distortion

Bartlett (*46*) introduced the idea that we interpret incoming information in terms of *schemata* (sing. schema), stored in LTM, and that this also influences our recollection. For example, Bartlett had subjects repeat an unusual short story to each other — by a process of Chinese whispers it became corrupted. These corruptions made the story *shorter, more coherent, more conventional*, and *more clichéd* — better fitting with the subjects' prior schema, perhaps. This is very important in the field of

eye-witness testimony, as it can lead to distortion. In 1947, Allport & Postman (*47*) briefly showed American subjects a picture of a white man threatening a black man with a cutthroat razor; one subject described the scene to another, who passed it on, for 6 rounds. Half of the final participants reported that the razor was held by the black man — subjects fitting the story to their prior schema (racial stereotype)? Later information can influence recall in a way that suggests memories are *reconstructed*, not simply recalled; for example, Loftus & Palmer (*48*) showed subjects a short video of a car crash. If they were asked for details of what happened when the cars 'smashed', participants estimated the cars to be going faster than if the question used the word 'hit' — and were more likely to invent the presence of broken glass.

Repression and false memories

False memories can be created, as we've seen, by combining actual memories with the content of suggestions from others, but it's very hard indeed to establish whether a *given* memory is false — a legal minefield. It's also hard to establish whether repression has occurred; this is a major problem with Freud's (*49*) repression hypothesis (was a memory repressed or was it never formed? If it's retrieved, is the retrieved memory false?). There have been some experimental attempts to demonstrate repression. Levinger & Clark (*50*) found that subjects generated free associations to negative words ('fear', 'quarrel', etc.) slower than to neutral words, and remembered them more poorly immediately afterwards — had they been repressed? — but this may be just an effect of emotional arousal: high arousal inhibits immediate recall but improves long-term recall (*51, 52*).

Human organic amnesia: evidence for multiple neural memory systems

Amnesia may be *retrograde* (failure to retrieve previously learned material) or *anterograde* (failure to learn new material). Amnesia can arise in humans from a variety of causes including anoxia / ischaemia, closed head injury, encephalitis, Korsakoff's syndrome (deficiency of thiamine, a.k.a. vitamin B1; usually due to dietary deficiency in alcoholics), and neurosurgery for epilepsy or tumours. It is also a prime symptom of progressive neurodegenerative disorders such as Alzheimer's disease.

Medial temporal lobe amnesia

Damage to the medial temporal lobes can follow surgical resection, anoxia, herpes simplex encephalitis, infarction, and sclerosis. The famous patient H.M. had his medial temporal lobes resected as an experimental treatment for epilepsy in 1953, when he was 27 (*53, 54*). This resulted in a severe anterograde amnesia for many forms of material from different modalities. His recall and recognition memory are severely impaired for lists, routes, and events. He has problems in learning about both autobiographical episodes and new facts — i.e. in both episodic and semantic memory (to use Tulving's distinction). He also has a mild retrograde amnesia for events from about 1942. The frequency of his seizures was, however, reduced!

However, H.M. has not lost all forms of memory. His *digit span* and *visual immediate memory* is normal. He was able to learn new *motor skills*, such as mirror-writing, with practice (e.g. *55*), though he was unable to remember having practised these tasks ever before! In similar fashion, he could learn the Tower of Hanoi *problem-solving* puzzle. *Priming* is also normal in amnesiacs such as H.M. (see *56, 57, 58*). His *IQ* is above average, and was not impaired by the surgery. Medial temporal lobe amnesia also spares *eyeblink conditioning* and *emotional conditioning*. (Famously, the Swiss psychiatrist Claparède once poked an amnesiac's hand with a pin while shaking hands; the next day, she would not shake hands but could not remember why; *59*.) These findings are important, as they indicate the scope of the memory systems that involve the medial temporal lobe — non-declarative memory systems appear to be preserved following medial temporal lobe lesions, implying *multiple memory systems* in the brain.

Other patients showed similar patterns (though H.M.'s memory impairment is undoubtedly one of the most severe); sometimes, amnesia occurred after unilateral le-

sions, because of pre-existing pathology on the other side. What remains unclear from the study of these patients is the damage *necessary and sufficient* to produce full-blown anterograde amnesia. H.M. certainly has considerable damage to the main structures of the limbic system which underlie the temporal lobe, the hippocampus and amygdala; other patients have variable damage to these structures; are both implicated? Some answer to this question was provided by the discovery of patient R.B., who developed bilateral, complete, and (apparently) highly localized anoxic damage to the CA1 field of the hippocampus after a cardiac arrest following open-heart surgery; histologically, he had relatively minor damage elsewhere (*60*). He exhibited a marked anterograde amnesia and no intellectual deterioration, but overall his deficits were less severe than those of H.M.

Diencephalic amnesia

Patient N.A. was a 22-year-old technician in the US Air Force who was accidentally stabbed with a miniature fencing foil by a friend in 1960. The foil entered his right nostril, penetrated the cribriform plate, and damaged his medial diencephalon, including the mediodorsal nucleus of the thalamus, the mammillary bodies, and the mammillothalamic tract (*61*). He acquired a profound anterograde amnesia, but had no impairments of higher cognitive function.

Patients with Korsakoff's amnesia are frequently found on post mortem to have sustained damage to diencephalic structures including the medial thalamus, fornix and mammillary bodies. They have profound anterograde but also retrograde amnesia as well as other cognitive deficits resembling those seen after frontal lobe lesions (see *62*).

The Delay–Brion (or Papez) circuit

Thus, anterograde amnesia can result from damage to diencephalic structures, as well as the medial temporal lobe; do these form a common circuit? Delay & Brion (*63*) proposed that damage to a circuit from the hippocampus → mammillary bodies → anterior thalamic nuclei is sufficient to induce anterograde amnesia. The Delay–Brion circuit is sometimes called Papez's circuit; Papez (*64*) had previously suggested that a wider circuit including these structures and the cingulate cortex was involved in emotion. Whether diencephalic amnesia qualitatively resembles that of medial temporal lobe amnesia is unclear. Aggleton & Brown (*56*) argue that it does, in most key respects; 'pure' diencephalic amnesia is rare and some pathological processes affecting it (e.g. Korsakoff's) cause widespread damage elsewhere.

Effects of selective hippocampal and / or fornix lesions

This is a matter of enduring debate.

Spatial mapping

Following the discovery of cells in the rat hippocampus that increased their firing rate when the rat was at a particular location in its environment — 'place cells' (*65*), O'Keefe & Nadel (*66*) suggested that the hippocampus functions as a 'cognitive map', informing the rat where it is in the world (*67*).

Lesion studies appear to support the idea that the hippocampus is critical in navigation. For example, Morris *et al.* (*68*) showed that rats with hippocampal lesions were impaired at a task in which they had to learn the location of a hidden submerged platform in a tank full of opaque liquid — now known as the Morris water maze. The deficit appears to depend on navigating relative to a constellation of cues in the room, as hippocampal lesions do not impair the ability to head in a particular direction to a stimulus that bears a fixed relation to the platform (*69*).

Learning in the water maze can be blocked by the glutamate NMDA receptor antagonist AP-5, which blocks LTP (*70*); similar effects follow NMDA receptor subunit mutations. However, the effects of AP-5 can be almost completely blocked if

the rats are trained in a different water maze beforehand (*71*), so the role of the NMDA receptors may not be a specifically spatial one!

Using PET imaging, Maguire *et al.* (*72*) recently found that blood flow in the (right) hippocampus was activated when London taxi drivers (expert navigators) imagined navigating around London, compared to a control task in which they recalled famous landmarks in unfamiliar cities. The posterior hippocampus is larger, and the anterior hippocampus smaller, in taxi drivers compared to controls, and this effect is larger the longer the subject has been a taxi driver (*73*). The hippocampus is also activated when subjects navigate around the computer game Duke Nukem (*74*)!

More than a map

Morris, Eichenbaum and others argue that the hippocampus doesn't encode a *map* in the sense that we'd normally use the word (see *67*). Place cells tell you where you are, not where you want to go — if your place cells tell you that you're in position A, how do you decide to go to B and not to C? Furthermore, the arrangement of place cells doesn't seem to be very consistent — they certainly don't form a topographic map of space, they lose or change their properties when the environment expands, and so on. Rather, it appears that place cells encode the relationship between some subset of cues in the environment (independent of other cues). Furthermore, hippocampal neurons do not just encode space. Wood *et al.* (*75*) showed that hippocampal neurons encoded a range of nonspatial features of a odour-based nonmatching-to-sample task, independent of the spatial location of the stimuli.

Encoding episodes

Given the ambiguity of the AP-5 water maze experiments (see above), Morris & Frey (*76*) have updated their views and now see the hippocampus as vital for encoding *episodes* — that it encodes rapid, one-trial episodic memory (the 'automatic recording of attended experience'). The 'automatic' property is meant to capture the idea that the animal remembers things that are not relevant to the task at hand, but that may be recalled later. This is very much akin to human descriptions of episodic memory. Morris & Frey attempt to go some way down this path by examining water maze learning in a *one-trial* fashion; they find that the ability of rats to remember the most recent place they have visited in a familiar environment (one-trial delayed matching to position in a water maze) is exquisitely sensitive to AP5 in a delay-dependent manner. Is this an episode? Well, maybe. As we said at the outset, new animals models of episodic memory are being developed that may help the testing of this hypothesis. Day *et al.* (*77*) have recently shown that encoding of unique food / location (what / where) pairs requires hippocampal activity; this is progress towards the what / where / when triad of Clayton & Dickinson (*23*).

Encoding scenes

Gaffan (*78*) argued that the hippocampus is required for encoding scenes — that is, complex and arbitrary stimulus patterns. Gaffan & Harrison (*79*) examined the effects of fornix transection in the monkey. They gave the monkeys a series of object discrimination problems (A versus B), in which the correct object depended upon the position and / or visual environment of the monkey. The monkeys could learn normally if they saw different objects in the room when A was correct than when B was correct. However, if the two visual environments contained the same objects, but in a different configuration, then fornix-lesioned monkeys were impaired. Gaffan & Harrison suggest that at least three types of memory are formed when a monkey displaces an object and finds reward under it:

1. A simple association between the object and reward.
2. A more complex association, between the background items, the object displaced, and the reward. (This allows the monkey to solve problems of the kind 'if a door handle and a coat are visible, choose object X'.)
3. An even more complex memory that encodes the identity *and* the spatial relations of the background objects, the target object, and the reward. (This allows the monkey to solve 'if the radio is to the left of the tap, choose object X'.)

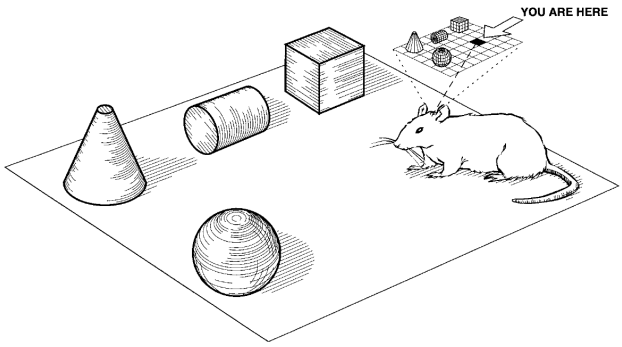
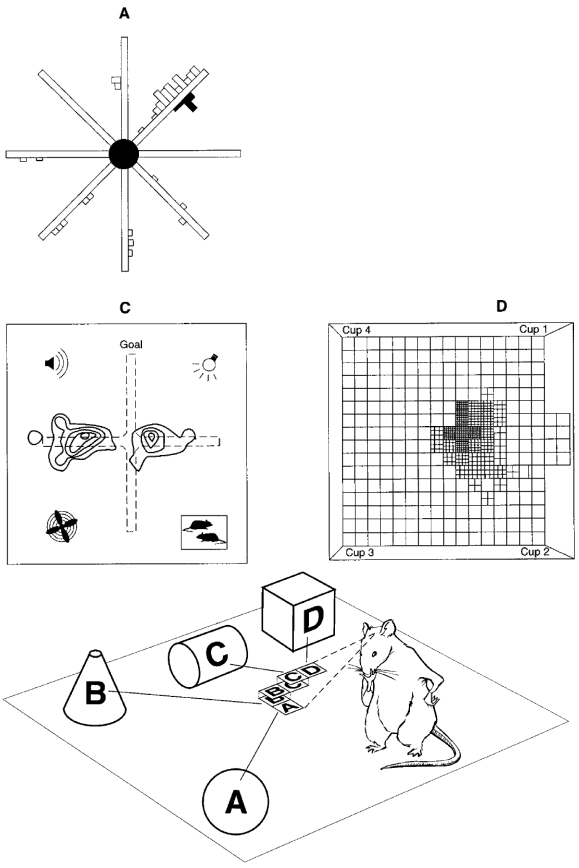
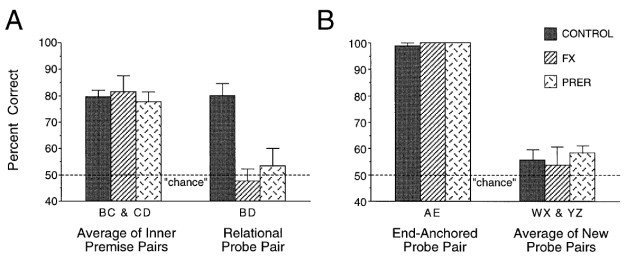


Figure 2. Cognitive Mapping
Conceptual model of hippocampal representation of a spatial environment according to the cognitive mapping hypothesis.



Top left: *the hippocampus as a cognitive map.* ***Top right:*** *place cells in the hippocampus.* ***Right:*** *encoding spatial relationships — a special case of encoding relationships.* ***Bottom right:*** *transitive inference — another, more abstract and non-spatial case of using information about the relationships between stimuli. The rat is trained on A>B, B>C, C>D, D>E. It is tested on A>E (easy — A has always been right, and E has always been wrong) and B>D (hard — the rat must infer that if B>C and C>D, then B>D; this is called transitivity).* ***Bottom left:*** *fornix transection and perirhinal/entorhinal cortex lesions impair the B>D probe test, but not the A>E test. Figures from Eichenbaum* et al. *(67)6} and Dusek & Eichenbaum (82)7).*

Figure 6. Relational Coding of Space
Representation of a spatial environment by cells that encode the spatial relations between a pair of the cues (AB, BD, or CD), plus nodal representations (dotted lines) for the cues that are common between some pairwise codings.



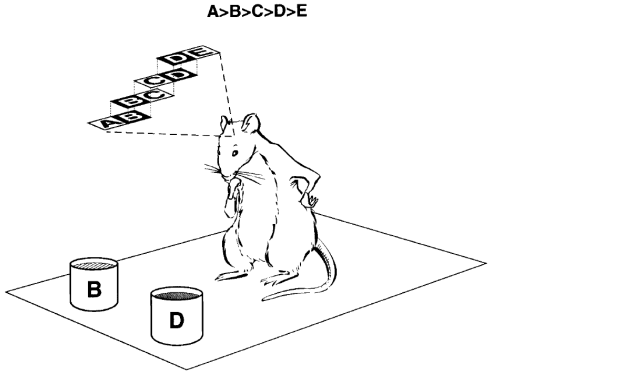


Figure 7. Transitive Inference in Serial Ordering
Representation of an odor series by cells that represent each trained odor pairing, plus nodal representations (dotted lines) of odors that are common between some of the trained pairings.

Gaffan & Harrison (*79*) argue that only the third type of memory — 'snapshot' memory — is disrupted by fornix lesions. Gaffan (*78*) extended this finding to show that fornix lesions impaired monkeys' ability to learn discriminations involving scenes from *Raiders of the Lost Ark!*

Representing context

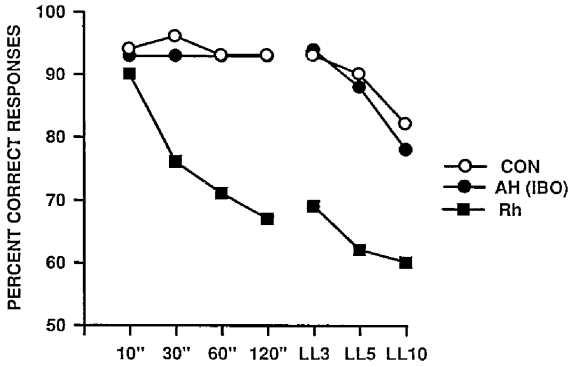
Both the hypothesis that the hippocampus encodes spatial relationships, and the hypothesis that it encodes scenes, predict that the hippocampus might, under some circumstances, be critical for *contextual conditioning*. For example, if a rat receives tone–shock pairings in a distinct environment, it may subsequently show 'fearful' reactions to the tone (discrete CS conditioning) and also the environment (contextual conditioning). Indeed, hippocampal lesions often interfere with contextual conditioning (*80*). However, animals may use contextual information in a variety of ways and many of these studies do not illuminate the exact contribution made by the hippocampus; an excellent review is provided by Holland & Bouton (*81*).

Relational information

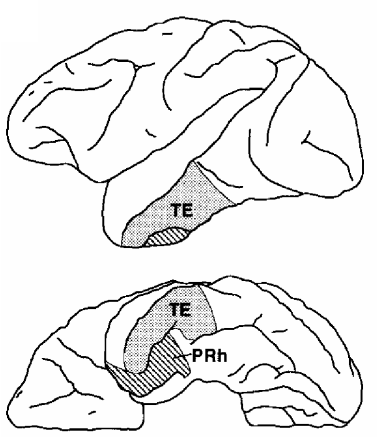
Eichenbaum *et al.* (*67*) argue that the hippocampus can encode spatial information because this is a special case of encoding the *relations* between stimuli. They suggest that these relations are useful for navigation when they are spatial relations, but that the memories encoded by the hippocampus can be used for other things. They give an example of a more abstract relationship: *transitive inference*. If a subject learns that B>C and C>D, then the logical property of *transitivity* should allow it to *infer* that B>D. Dusek & Eichenbaum (*82*) have shown that fornix transection and perirhinal / entorhinal lesions, both of which partially disconnect the hippocampus, impair transitive inference in rats (see figure).

Contributions of rhinal cortex to memory and perception

The rhinal cortex (i.e. entorhinal + perirhinal cortex), adjacent to the hippocampus in the medial temporal lobe, is certainly important for aspects of visual recognition memory (see figure). In fact, rhinal cortex is also at the end of the ventral visual processing 'stream', and is important for perception — it appears to be involved in discriminating complex conjunctions of visual stimuli (*83-85*), and perhaps in associating polymodal information about objects (*86*). This view is right up Fuster's street (*1*) — the idea that memory and perception are largely inseparable in cortex.



Lesions of rhinal cortex impair delayed non-matching-to-sample (DNMTS) performance (87-90): the monkey sees an object, then there's a delay, then it sees two objects and must pick the one it hasn't seen before. Rh = rhinal cortex lesion; AH = amygdala+hippocampus lesion; CON = controls. (" means seconds, using a single object for DNMTS; LL means list length, i.e. multiple objects, and in this situation the minimum retention interval for each trial was 20 s × list length.)



Location of area TE (part of inferotemporal cortex) and perirhinal cortex in the rhesus macaque monkey (91). ***Top:*** *lateral view (anterior to the left).* ***Bottom:*** *view of the inferior surface.*

Semantic memory: where? How?

There is debate not just about what semantic memories are, but how they are established. Do they begin as episodic memories but become independent of the episodic memory system with repetition and additional association? Perhaps not. There are intriguing reports of patients who suffered perinatal hypoxia (with consequent severe hippocampal atrophy visible on MRI) who have severe episodic memory deficits. In spite of this, they showed relatively normal semantic memory for facts and were able to attend mainstream schools (*92*).

Conversely, there are patients who develop *semantic dementia* (*93*), characterized by progressive loss of conceptual knowledge about objects, facts, concepts, and word meanings (see *94*). It has been suggested that episodic memories appear to suffer a *reverse* temporally graded retrograde amnesia in semantic dementia — old memories are remembered less well than recent ones. Structurally, this disorder is associated with atrophy of the anterolateral temporal lobes (*95*). The pattern of semantic memory loss is perhaps explicable in terms of random damage to a distributed cortical associative memory that represents associations between features (and as a consequence, conceptual information) according to simple statistical principles (*96*).

However, the relationship between semantic dementia and episodic memory is still controversial.

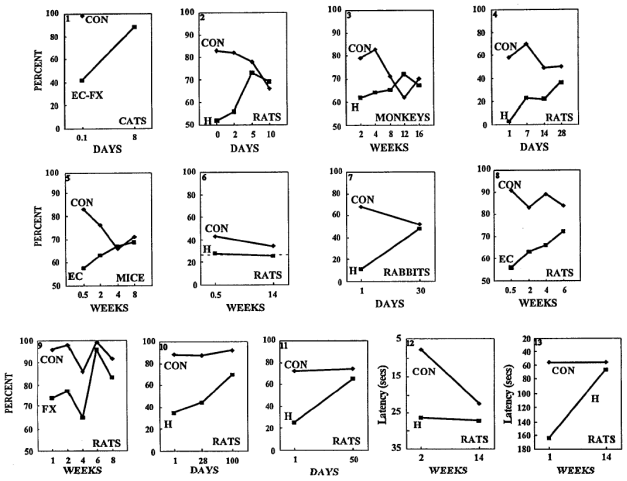
A time-limited role for the hippocampus?

Retrograde amnesia

As we saw earlier, H.M. developed profound anterograde amnesia following his medial temporal lobe resection — but also a temporally graded retrograde amnesia for events preceding the surgery (that is, old events were recalled better than recent ones). Indeed, such retrograde amnesia has been regularly noted in humans following medial temporal lobe lesions, or lesions apparently restricted to the hippocampal formation (see *97*). This led to the hypothesis that the hippocampus is involved in consolidating memories held elsewhere (*54*) — recent memories are vulnerable to hippocampal damage, but with time they become independent of the hippocampus. This view is highly popular, althought not the only view (*98*).

Prospective animal studies of retrograde amnesia

Retrograde amnesia is difficult to study in humans, because it is necessarily done retrospectively — the experimenter must assess the subject's memory for recent and ancient experience after the onset of amnesia, but it is difficult to sample memory equivalently from different past time periods, and to know that these memories were of comparable 'strength' before the event that caused amnesia. Consequently, prospective studies in animals have produced the most clear-cut results (*99*). As shown below, the majority of such studies have shown temporally-graded retrograde amnesia following a variety of hippocampus, fornix, and entorhinal cortex lesions.



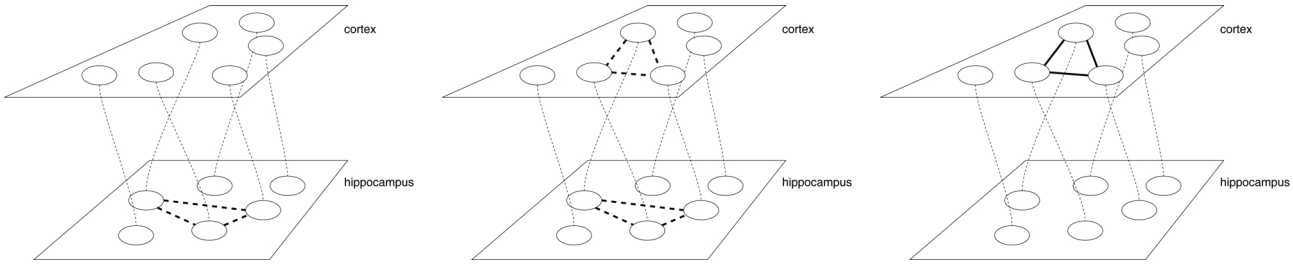
Summary of prospective studies, in several different labs using a range of tasks, of retrograde amnesia following hippocampus (H), fornix (FX), or entorhinal cortex (EC) lesions in a range of non-human species. From Squire et al. (97). The studies include both excitotoxic and electrolytic/aspirative lesions, and between- and within-subject designs. The abscissa (x axis) is the training–surgery interval; the ordinate (y axis) is performance (% or latency — arranged so that performance increases as you move up the y axis in all cases).

Encoding and consolidation: the relationship between hippocampus and neocortex

The data reviewed above suggest that memories (of a certain kind) are initially dependent upon the hippocampus but with time they become independent of the hippocampus. This might suggest that the memory *moves* with time. We should be wary of interpreting this too literally, if for no other reason than it is not clear that the brain can store memories in a manner that is independent of the specific neurons that take part in that memory (unlike digital computers, in which the information is independent of the storage medium) — the brain may not be able to 'move' memories to arbitrary locations within it. However, there are perfectly plausible ways in which a memory might depend on a structure only temporarily (e.g. *100*): the figure below shows one.

Decay of memories in the hippocampus

Finally, Villarreal *et al.* (*101*) have shown that systemic administration of the drug CPP, a glutamate NMDA receptor antagonist, blocks decay of hippocampal LTP. If given between training and testing of performance in a radial 8-arm maze task, the CPP *improved* the retention of the memory. (Note: it has yet to be shown that this



Left to right: schematics of how the hippocampus might interact with cortex to consolidate memories 'held' elsewhere, without the memory really 'moving' in a physical sense. If the hippocampus exhibits rapid synaptic plasticity (but this is transient or easily disrupted) and the cortex exhibits slower but more stable plasticity, we might proceed as follows. ***Left:*** *hippocampal neurons have permanent connections to regions of neocortex (vertical dotted lines). A memory is formed by the hippocampus rapidly associating a number of active neurons, via synaptic plasticity (horizontal dashed lines). The memory is dependent upon the hippocampus.* ***Centre:*** *subsequent hippocampal activity promotes the firing of a cortical network that corresponds to the group of associated hippocampal neurons. As a direct result, this promotes an increase in the connectivity between the cortical neurons.* ***Right:*** *with time, the cortical links become strong enough not to require further hippocampus-driven consolidation. The memory is now independent of the hippocampus.*

was due to the drug's effect on the hippocampus.) Perhaps decay of LTP (or LTD, which is also NMDA-receptor-dependent) is required to allow the hippocampus to acquire new memories, at the expense of old ones. For if a rapidly-associating network does not have the ability to lose old memories, there is *catastrophic interference* when new memories are laid down. This is the *stability–plasticity dilemma* familiar to connectionist modellers (*102, 103*). Rosenzweig *et al.* (*104*) suggest that Villarreal *et al.* (*101*) blocked exactly this loss of old memories.

Sleep and consolidation

If this model of hippocampal–cortical interaction is correct, there should be times when the hippocampus 'replays' patterns of activity in order to teach the cortex. This is an old idea, and a favourite theory has been that this replay occurs during sleep (*105*). Although it's an attractive idea that one function of sleep is to consolidate memory, the role of sleep in consolidation is somewhat controversial.

'Replay' of learned neural activity during sleep

Wilson & McNaughton (*106*) recorded from large numbers of hippocampal 'place cells' during a spatial task, and during slow-wave sleep (SWS) before and after the task. They found that cells that fired together when the animal was in a particular location during the task were more likely to fire together in subsequent sleep, in comparison to sleep episodes preceding the behavioural task. There have been a number of similar demonstrations.

Memory consolidation, insight, and sleep

Karni & Sagi (*107*) developed a visual texture discrimination task in which human subjects have to detect a brief pattern of oriented lines. They found that subjects improve on this task (but only in the trained eye and only in the trained retinotopic quadrant of that eye). More interesting is the fact that the improvement does not occur during practice, but at about 8 hours after the practice sessions (and these improvements are stable for years) (*108*). Overnight improvements on this task follow a normal night's sleep, or a night's sleep in which SWS is disrupted, but no improvement followed a night's sleep in which REM is disrupted (*109*) — suggesting that REM is required for consolidation. Stickgold *et al.* (*110*), controlling for the effects of sleep deprivation on performance, have since found that improvement on this task requires sleep within 30 hours of training. However, there is debate about the SWS / REM issue; there may be truth in the 'sequential' hypothesis of Giuditta *et al.* (*111*, see *112*), which suggests that you need SWS *then* REM.

Fischer *et al.* (*113*) have shown that sleep improves subsequent performance of a sequential motor task (finger-to-thumb opposition in a particular sequence); the im-

provement was specific for the practised sequence and occurred whether subjects slept during the day or night. Sleep deprivation itself had no effect on performance.

Recently, Wagner *et al.* (*114*) have found that 'insight learning' — in their experiment, the ability to spot a hidden simplifying rule in a complex task — is hugely facilitated by sleep.

Criticisms

Although many theories of sleep consolidation posited that REM sleep was critical for consolidation, the evidence for this is far from convincing; see Siegel (*115*). There is no clear evidence that REM sleep duration increases following learning; the duration of REM sleep is not obviously correlated with intellectual ability across species — dolphins, for example, have very little REM sleep — and many studies of REM sleep disruption are subject to confounds (e.g. not controlling for stress or total sleep deprivation). There are case reports of humans who have lost most or all REM sleep (e.g. following brainstem injury) but have no apparent memory deficits; one subsequently went through law school and edited a puzzle section of a local newspaper (see *115*). The role of SWS is perhaps better established, for certain kinds of task (*116, 117*). However, a recent study showed that artificial enhancement of REM sleep improved later retention of a Y-maze task in rats (*118*); the debate continues.

Reconsolidation

A 'standard' view of consolidation would be that memories are created in a labile state (sometimes thought of as STM), and with time, they are consolidated into a stable state (LTM). For example, electroconvulsive shock (ECS, a.k.a. electroconvulsive therapy, ECT), which disrupts all ongoing electrical activity in the brain, induces amnesia if given shortly after training, but not if given a long time after training (*119*). While the formation of new memories does not require protein synthesis, the consolidation of memories does; thus, administering the protein synthesis inhibitor anisomycin during contextual fear conditioning does not impair the memory of mice if they are tested one hour later, but that memory fades by 24 h as compared to a control group (see e.g. *120, 121*). Incidentally, the same is true (at a cellular level) of hippocampal LTP: 'early' LTP is not dependent upon protein synthesis, but it fades; normally, it is made long-lasting by a second phase, 'late' LTP, which requires protein synthesis (see *122*).

Reconsolidation, a long-forgotten and interesting phenomenon of memory has recently been thrown into the limelight. As before, this hypothesis suggests that memories are created in a labile state and are consolidated into a stable state. However, in this theory, recalling a memory *returns it to the labile state*. Therefore, although protein synthesis inhibitors don't disrupt stable memories, they should be able to disrupt old memories that have been reactivated. Indeed, this has been observed (*123*). Recently, Nader *et al.* (*124*) found that infusions of anisomycin into the basolateral amygdala (a critical site of plasticity for CS–US associations involved in conditioned freezing in the rat) disrupted memory for a CS–US association that had been 'retrieved' by presenting the CS. Appropriate controls demonstrated that this only happened when the memory had been 'retrieved' in this way.

Is this important? Yes. One old case study (*125*) made use of the idea of reconsolidation. A patient had obsessive–compulsive disorder (OCD) that took the form of an obsession to kill her mother with a butcher's knife. She had previously received 22 sessions of ECS under anaesthetic (this is the normal way of doing it!). Rubin *et al.* made her act out her compulsion (N.B. reactivation of the memory in question) and gave here one session of ECS whilst awake. She was subsequently symptom-free for the two years before publication of the study. This technique was effective, for varying periods (3 months to ≥10 years), in all 28 patients tested (*126*). The ability to 'remove' memories selectively might have enormous implications for the treatment of diseases including OCD, drug addiction, and so on.

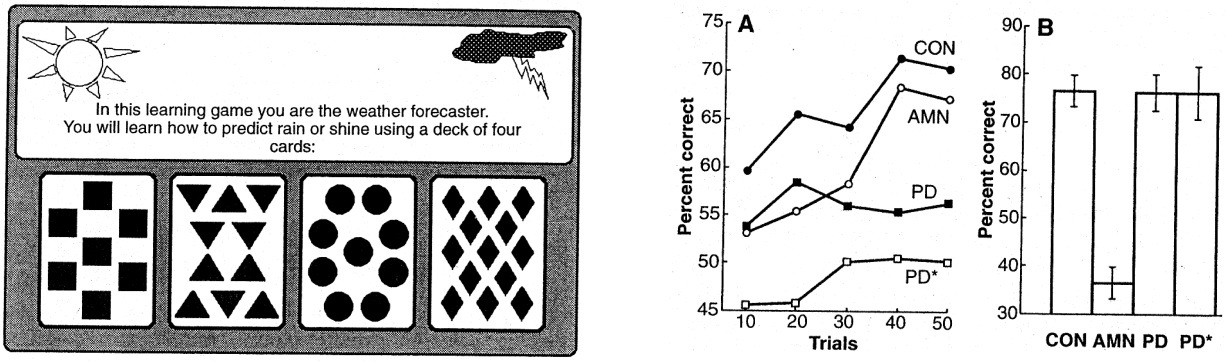
Interference with (re)consolidation, or interference with retrieval?

It has been a matter of enduring debate whether amnesia is a result of a *storage deficit* or a *retrieval deficit.* For example, Warrington & Weiskrantz (*58*) interpreted the normal performance of amnesiacs on memory as assessed by priming or word-completion tasks as indicating that their deficit was one of retrieval. Millin *et al.* (*127*) point out that many forms of amnesia can be reversed by *reminder* treatments, indicating that the memories were present all along and the deficit was one of retrieval. Typical such studies used ECS to induce amnesia; subsequent exposure to the CS, the US, or the ECS have all been shown to reverse the amnesia (see *127, 128-130*). The same question can be applied to reconsolidation (*127*): is it correct to say that the reactivated memory is not stored again (reconsolidated) correctly, or can a retrieval deficit explain these results? Well, again, 'reminder' effects occur, implying a retrieval deficit (*131, 132*). Nader and colleagues now acknowledge this (*133*).

Habit learning: the dorsal striatum

The amnesia exhibited by H.M. was originally labelled 'global anterograde amnesia' — yet a number of learning abilities were preserved in H.M. One of these was the ability to learn the skill of mirror-drawing (*134*). The distinctions between the forms of memory that are impaired in medial temporal lobe amnesiacs and those that aren't has been described as recognition / associative, episodic / semantic, working / reference, declarative / procedural, and memories / habits (*135*).

Habits are the archetype of procedural memory. They are direct stimulus–response (S–R) links that are acquired as the result of reinforcement occurring when an animal makes a response in the presence of a stimulus (*136*). Do animals have a habit system? Yes. We can test for it in rats using *reinforcer devaluation*. Rats are trained to press a lever for food, and then they are given food and poisoned (to induce a conditioned taste aversion to that food) in the absence of the lever; after they have sampled the poisoned food, they are returned to the operant chamber and their lever-pressing is assessed (in extinction, to prevent delivery of the now-aversive food from having a direct punishing effect on behaviour). Although under certain conditions, rats press the lever less than if the food had not been poisoned (indicating *declarative* knowledge — the effect of poisoning on lever-pressing was mediated through an internal representation of the food), this is not always the case. If rats are *overtrained* on the lever-pressing task beforehand, reinforcer devaluation does not suppress their lever-pressing (even though they won't eat the food subsequently) (*137*). This indicates that a *procedural* representation has come to govern behaviour — a stimulus–response link that does not include a representation of the food (see *138*). It appears that S–R links develop slowly through training until (under some circumstances) they dominate behaviour.

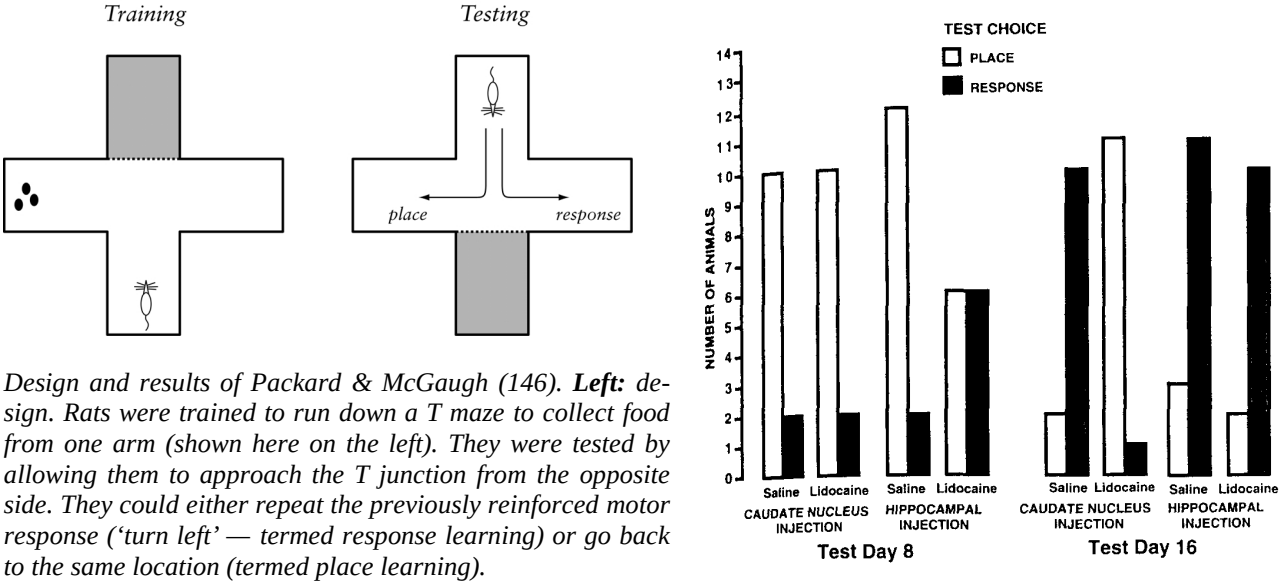


Left: *two tasks in one. In this computerized probabilistic classification task, one to three cards are shown and the subject must predict sunshine or rain. Feedback is provided (whether the subject predicted correctly or incorrectly). One cue is associated with sunshine on 25% of occasions; one on 43% of occasions; one 57%; one 75%. The subject must use this feedback to predict successfully (chance performance is 50%). In a subsequent second, declarative task, subjects' memory for features of the same game (screen layout, cues, etc.) is tested with four-way multiple-choice questions (chance performance is 25%).* ***Right:*** *results. Amnesiacs learned the classification task, but couldn't remember details of it; patients with PD couldn't learn the classification, but remembered the task. (PD* = a subgroup of the PD group with severe PD.) From Knowlton et al. (139)3).*

So what neural structures subserve habit learning? Mishkin *et al.* (*135*) originally suggested that a cortico-striatal system subserved habit formation. Although much of the subsequent work on this issue has proved controversial (*140-142*), he was probably right. For example, patients with Parkinson's disease (PD) or Huntington's disease (HD) are impaired on supposedly procedural tasks such as learning the Tower of Hanoi puzzle (*143, 144*). Knowlton *et al.* (*139*) demonstrated a double dissociation between performance on a probabilistic classification task (impaired in PD, but not in patients amnesic secondary to hippocampal or diencephalic damage) and declarative memory for the same task (impaired in amnesiacs but not in PD patients) (see figure).

This double dissociation clearly shows that the impairments in PD and hippocampal / diencephalic amnesia are qualitatively different. However, it does not show that what the PD patients couldn't do was learn a habit (or, for that matter, that the deficit was due to neostriatal dysfunction, rather than — say — prefrontal cortical dopamine dysfunction). Unfortunately, while the learning theory definition of a habit given earlier is widely quoted, the learning theory methods to determine whether behaviour is habitual (such as reinforcer revaluation) have not adopted widely. There is no clear evidence that many of the tasks though to test 'habits' actually do so. Tasks have even been described as non-habit-based on the grounds that human amnesiacs cannot learn them (*145*).

Until 2004, probably the best demonstration to date of a striatum-dependent habit was an elegant study by Packard & McGaugh (*146*), illustrated below. It shows that a stimulus to motor response mapping develops slowly during reinforced training, and comes to dominate behaviour in this task; its performance depends upon the caudate (with the caveat that local anaesthetics such as lignocaine can inactivate fibres of passage as well as cell bodies). In contrast, a hippocampus-dependent place-based memory develops rapidly and is superseded by the S–R memory under normal circumstances. Similar results using a more rigorous demonstration of a 'habit' have recently been obtained (*147*).



Design and results of Packard & McGaugh (146). ***Left:*** *design. Rats were trained to run down a T maze to collect food from one arm (shown here on the left). They were tested by allowing them to approach the T junction from the opposite side. They could either repeat the previously reinforced motor response ('turn left' — termed response learning) or go back to the same location (termed place learning).*
Right: *results (number of rats displaying each type of behaviour). If rats were tested on day 8, they exhibited place learning (see 'saline' groups). This was blocked by pre-test injections of lidocaine (lignocaine), a local anaesthetic, into the dorsal hippocampus; these rats performed at chance. Intra-caudate injections had no effect. On day 16, rats exhibited response learning. This was not blocked by inactivation of the hippocampus, but it was blocked by inactivation of the caudate, which reinstated 'place responding'.*

Incidentally, the cerebellum is another structure that appears to implement procedural memories: it mediates conditioning when the UR is a simple motor response, the CS–US interval is shorter than ~4 seconds, the US is aversive and activates the inferior olive, the 'teaching system' for cerebellar learning (*148, 149*).

Encoding, retrieval, and the prefrontal cortex

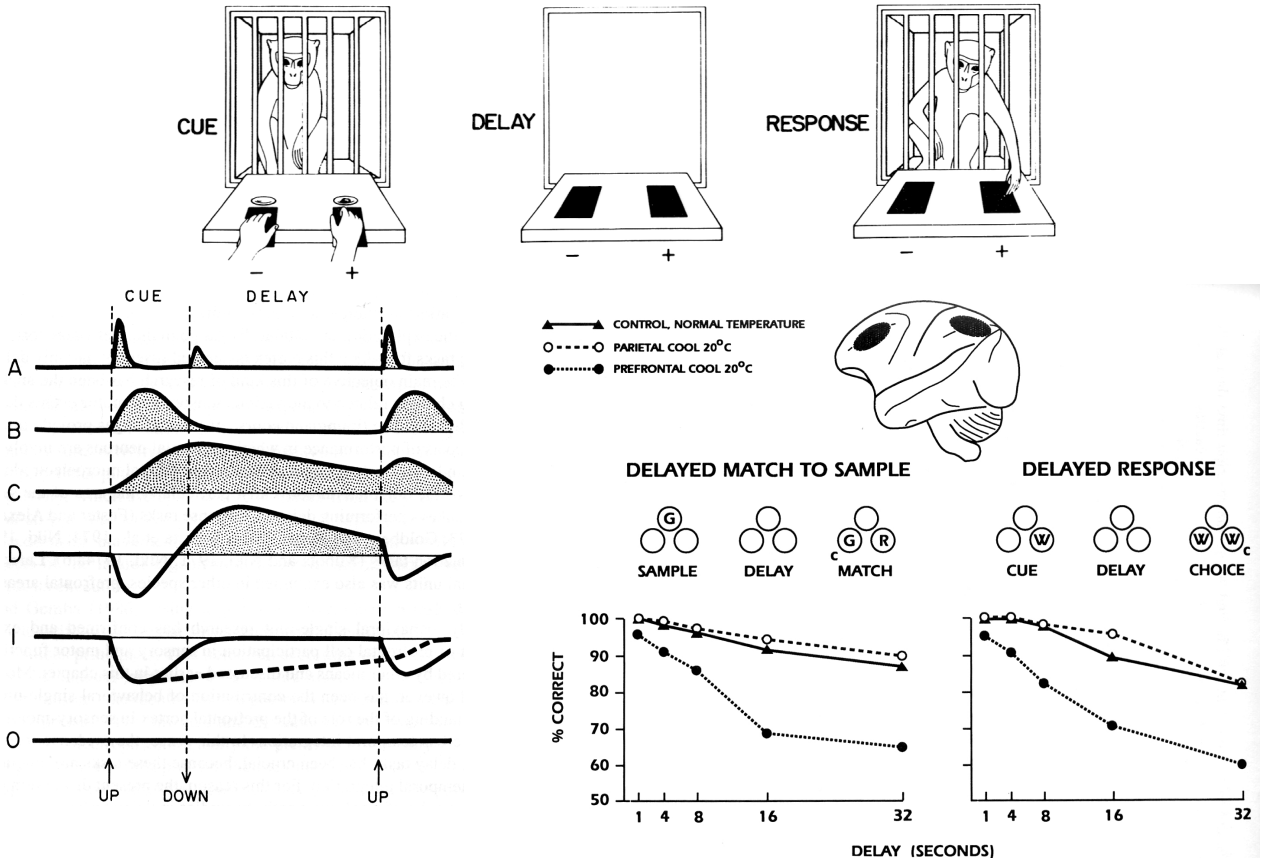
The prefrontal cortex (PFC) may contribute to memory encoding and/or recall, probably via its extensive back-projections to posterior neocortex. For example, humans with PFC lesions are profoundly impaired on *verbal fluency* tests (*150*) — e.g. 'please say as many words beginning with S as you can in the next minute'.

Many of the data regarding this function of the PFC come from neuroimaging studies (see e.g. *151, 152*). Tulving *et al.* (*153*) proposed a *hemispheric encoding/retrieval asymmetry (HERA)* model on the basis of PET studies of memory tasks; they suggested that the left PFC is more involved than the right in encoding episodic memory (and retrieving semantic memory), whereas the right PFC is differentially more involved in episodic memory retrieval. As an example, left PFC activity at the time of processing verbal material ('is this word abstract or concrete?') predicts how well people subsequently remember that material ('did you see this word earlier?') (*154*). It has been suggested that the nature of the material also determines the degree of left versus right activation (*155*).

These studies are vulnerable to a number of criticisms. One relates to whether the memory processes being observed in the scanner are episodic, semantic, both, etc. A more serious criticism is that this imaging-based model is purely *correlative*; what process the PFC is playing in these tasks is hard to fathom.

Dorsolateral prefrontal cortex and working memory

Jacobsen (*156*) was the first to demonstrate an impairment in monkeys with frontal lobe lesions on a *delayed response* task. In this, a monkey is shown a peanut in one of two locations; a screen then comes down for a delay period, and the monkey then has to respond to the previous location of the peanut. The suggestion is that the frontal lobes contribute to *working memory* — holding the relevant stimulus 'on line' during the delay.



Top: *Delayed response task.* ***Bottom left:*** *types of neuronal response in DLPFC during delayed-response tasks.* ***Bottom right:*** *Cooling DLPFC (but not parietal cortex) produces delay-dependent deficits on DMTS and delayed response tasks (figure from 157, p. 93)3). Note that cooling may affect fairly large areas of cortex; irreversible lesion studies have shown that the DMTS deficit depends upon lesions of the inferior convexity, while the DR deficit depends upon principal sulcus lesions (158, 159)2).*

This deficit has since been localized to the sulcus principalis (i.e. DLPFC) in monkeys. Neurons here respond during the delay (*160*); cooling (*161*) or lesions (*162*) of the DLPFC impair delayed-response performance (see figure).

There are several lines of evidence that the PFC implements working memory via its *back projections* to posterior cortex. Fuster and colleagues have shown that cooling of either DLPFC or inferotemporal cortex impair visual delayed matching-to-sample. There is a robust projection between these two regions. Furthermore, cooling one region affects the responses of neurons in the other (*163*); for example, DLPFC cooling diminished the discrimination shown by IT neurons in the delay, perhaps suggesting that the PFC is *maintaining* the response of the posterior cortical region during the delay (*157*, *164*, *165*). Ruchkin *et al.* (*166*) argue along similar lines based on event-related EEG work in humans. There is a functional argument to be made here: it is implausible that the PFC 'contains' the memory being held online, for it would have to duplicate all the perceptual capabilities of (e.g.) visual cortex in order to 'hold' a visual memory. Rather, by maintaining activation in visual processing areas, working memory is achieved without duplicating perceptual systems.

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