Overview

Memory is a complex topic. We will discuss the various forms of memory that exist from a theoretical and psychological perspective, and then examine the neural structures that are responsible for these different forms of memory (with some current controversies), beginning with medial temporal lobe and diencephalic structures. After we have covered this lecture and the next, you should appreciate the many different forms of 'amnesia', and how they implicate different neural systems specialized for processing different forms of information. It should also be clear how difficult it is to determine the necessary and sufficient neural substrates of these memory systems in humans, and how difficult it is to interpret some of the animal studies conclusively.

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. We won't discuss the dissociations between all these types (for that see R.A. McCarthy's lectures), but will introduce them as a background to considering their neural basis.

Individual versus phyletic memory; perceptual versus motor memory; activation

Before getting into the nitty-gritty, it's worth mentioning some points made by Fuster (1995), 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) (James, 1890; Broadbent, 1958; Norman, 1968; Baddeley, 1988).

STM appears to have a severely *limited capacity* — typically 7±2 arbitrary pieces of information (Miller, 1956), 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. STM has a very *short duration*: Peterson & Peterson (1959) 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. 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 (Atkinson & Shiffrin, 1968). 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. Jensen & Lisman, 1998). 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. (Shallice & Warrington, 1970), 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 Fuster, 1995, chapter 2). Declarative memory includes *episodic* and *semantic* memory (Tulving, 1972; Tulving & Markowitsch, 1998), 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 (Zola-Morgan & Squire, 1993); it includes *procedural* memory (Cohen & Squire, 1980) and *priming* (Tulving & Schacter, 1990). 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.' (Griffiths *et al.*, 1999). 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'), and has suggested that this may not be possessed by non-humans (Tulving, 1985; Tulving, 1995; Tulving & Markowitsch, 1998). 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 (1998) identify remembering *what, where,* and *when* an event occurred as key components of episodic memory, and show that scrub jays encode this information. Morris (2001) identifies some other episodic-like tasks, such as one-trial, scene-specific discrimination learning (that is, memory for particular *events*); he has developed a model of this in the rat.

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. Fuster, 1995; Baddeley, 2002), partly because they can be hard to define precisely (see also R.A. McCarthy’s lectures). One view (Squire, 1992a) is that semantic memories are episodic memories for which the detailed contextual information has disappeared, leaving only the generic features. Another (Tulving, 1989) 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.* (1996) 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 (Fuster, 1995). 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 (Cohen & Squire, 1980). 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 (Dickinson, 1980), 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. Dickinson & Balleine, 1994; Cardinal *et al.*, 2002) — 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 (Meyer & Schvaneveldt, 1971). 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 (Squire *et al.*, 1992); 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.

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.

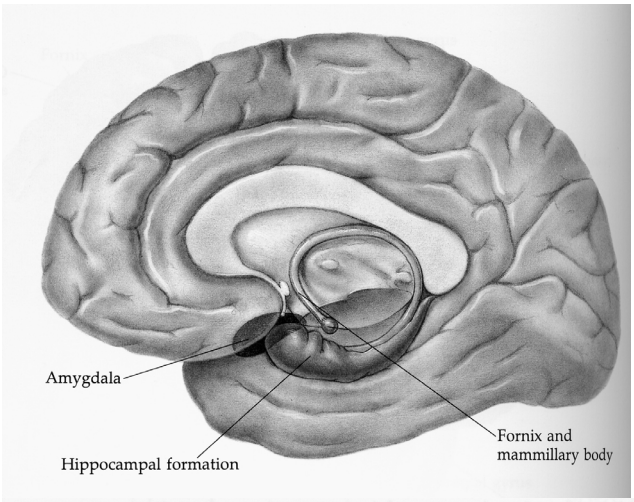
Medial temporal lobe amnesia

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 (Scoville & Milner, 1957; Corkin *et al.*, 1997). This resulted in a severe anterograde amnesia for many forms of material from different modalities (see also R.A. McCarthy’s lectures). 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!

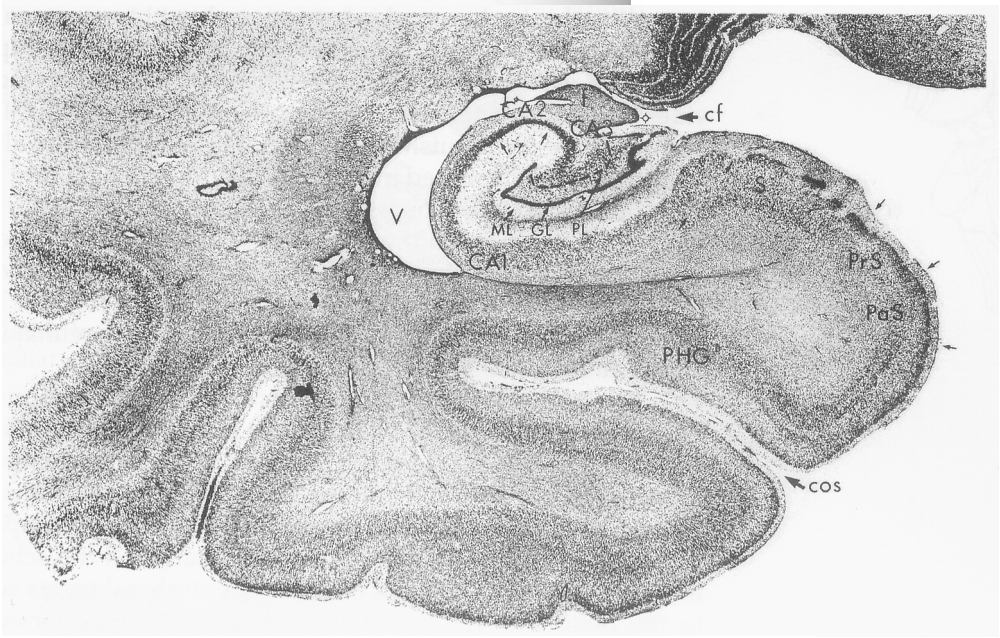
However, H.M. has not lost all forms of memory. His *digit span* and *visual immediate memory* is normal. He was able to learn new *motor skills*, such as mirror-writing, with practice (e.g. Corkin, 1968), though he was unable to remember having practised these tasks ever before! In similar fashion, he could learn the Tower of Hanoi *problem-solving* puzzle. *Priming* is also normal in amnesiacs such as H.M. (see Warrington & Weiskrantz, 1970; Graf *et al.*, 1984; Aggleton & Brown, 1999). 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; Claparède, 1911.) 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. We shall return to this issue in the next lecture.

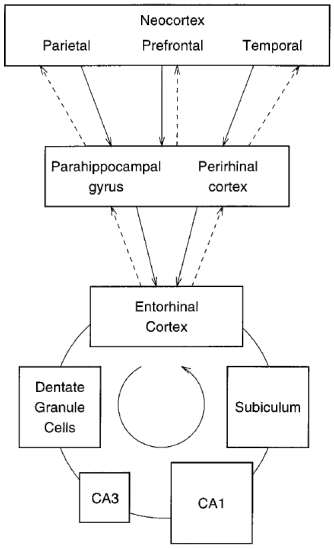
Basic anatomy of the medial temporal lobe; plasticity

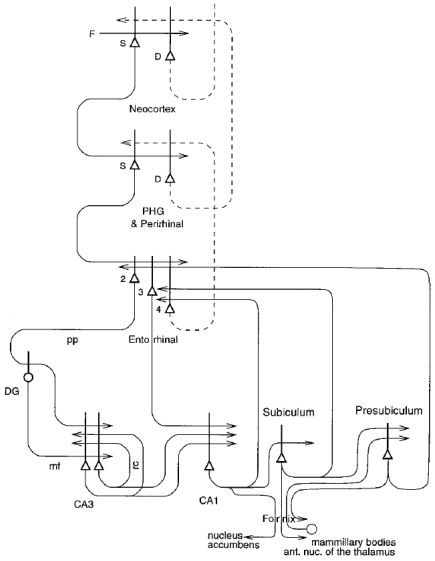
The term ‘hippocampus’ is usually taken to refer to CA1–4, the dentate gyrus, and the subiculum (Aggleton & Brown, 1999). ‘CA’ refers to the cornu ammonis, or Ammon’s horn. The hippocampus is archicortex; it has bidirectional links with adjacent entorhinal cortex (which itself communicates with perirhinal and parahippocampal cortex). The other main influx/efflux of information to/from the hippocampus is via the fornix, a fibre tract that starts with its ‘fimbriae’ (L. fringes) on the hippocampus, and terminates (mainly) in the mammillary bodies (part of the hypothalamus), and the anterior thalamic nuclei. The mammillary bodies themselves project to these thalamic nuclei via the mammillothalamic tract.

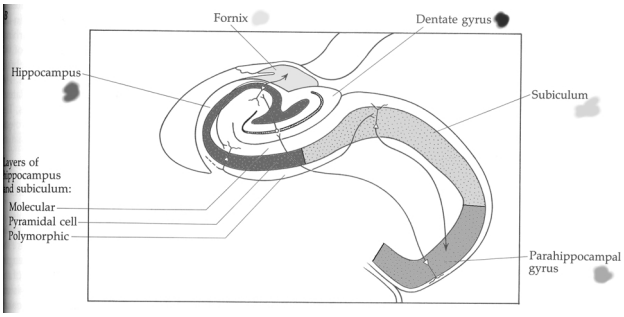


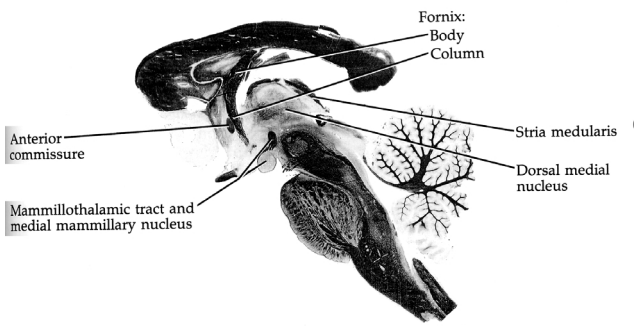
Left: major structures in the medial temporal lobe (medial view of right hemisphere). Below: cross-section of the human medial temporal lobe, showing the hippocampus and related structures. Below that: major extrinsic and intrinsic connections of the hippocampus, emphasizing its connections with adjacent cortex (the fornix, the other major output structure from the hippocampus, is given less emphasis in this diagram). Bottom left: schematic of the hippocampus again, simplifying the major connections. Bottom right: part of the Delay–Brion circuit (hippocampus → fornix → mammillary bodies → mammillothalamic tract → thalamus).











Within the hippocampus, there is a well-described *trisynaptic circuit*. All major association areas of cortex project reciprocally to the entorhinal cortex. (1) Entorhinal cortex cells project via the *perforant path* directly to the dentate gyrus, crossing the hippocampal fissure in the process. (2) Dentate gyrus cells (specifically, granule cells) project via so-called *mossy fibres* to CA3. (3) In addition to sending axons out along the fornix, CA3 cells project via *Schaffer collaterals* to the CA1 field. After this, CA1 axons project either back to the subiculum (and from there back to entorhinal cortex) or to the fornix. Inevitably, the full picture is more complex than this (see figure).

Acetylcholine. Another important set of connections is between the hippocampus and the *septum* (septal nuclei) in the basal forebrain. (The septum and the adjacent diagonal band of Broca provide much of the ACh input to the hippocampus; they are near the nucleus basalis, which provides ACh to neocortex.) Cholinergic cells of the medial septum project (via the fornix) to all regions of the hippocampus; in turn, CA3 projects back to the lateral septum, where inhibitory interneurons project to the medial septum. This projection is of considerable interest, since these cholinergic cells are lost early in Alzheimer's disease.

Plasticity. Various forms of synaptic plasticity have been described within the hippocampus; indeed, long-term potentiation (LTP) was discovered here (Bliss & Lømo, 1973). For example, the perforant path → dentate gyrus pathway (step 1 above) exhibits associative LTP; the same is true of the Schaffer collateral → CA1 pathway (step 3 above). The mossy fibre → CA3 pathway exhibits non-associative LTP (see e.g. Kandel *et al.*, 1991, chapter 65). This plasticity is the basis for learning in many theories of hippocampal function (see T.J. Bussey's lectures).

Other patients showed similar patterns (though H.M.'s memory impairment is undoubtedly one of the most severe); sometimes, amnesia occurred after unilateral lesions, 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 apparently 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 (Zola-Morgan *et al.*, 1986). 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 (Squire *et al.*, 1989). 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 Kessels *et al.*, 2000).

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 circuitry? Delay & Brion (1969) 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 (1937) 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 (1999) 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.

Early animal models of medial temporal lobe amnesia; controversies

In 1978 it was reported that large temporal lobe lesions in monkeys, intended to mimic the surgical damage sustained by H.M., caused severe memory impairment — for example, an inability to recognize recently seen (or recently touched) objects (Mishkin, 1978). Originally it appeared that the impairment following hippocampal lesions was not as profound as that following combined lesions of the hippocampus and amygdala; on the basis of these and related results, Mishkin proposed that global anterograde amnesia, akin to that seen in human medial temporal lobe resection, was the consequence of combined bilateral lesions of the hippocampus and amygdala (there's a nice account in Mishkin & Appenzeller, 1987).

However, it is very important to bear in mind the lesion technique. Mishkin's early lesions were very like H.M.'s — cutting out or aspirating tissue. This removed neuronal cell bodies in the target area, destroys axons travelling through this area from distant regions ('fibres of passage'), and inevitable damages adjacent tissue. Later lesions were performed stereotaxically, typically by radiofrequency ablation (heating up a probe to destroy tissue). Though this doesn't necessarily damage adjacent tissue to the same extent, it certainly destroys fibres of passage. Finally, permanent lesions can be made by injecting excitotoxins; these kill neurons whose cell bodies are in the target area but spare fibres of passage (which tend not to have receptors for the excitotoxin). Excitotoxic lesions are the current 'gold standard', but ultimately, it is less important to use a perfect technique than to understand the consequences of the technique you have used! Initially, the significance of the inadvertent damage to adjacent cortex following aspirative lesions was not appreciated. So let's evaluate Mishkin's results with hindsight (see Squire, 1992b).

Hippocampus, amygdala, adjacent cortex

Mishkin's combined lesion included the amygdala, hippocampus (including the dentate gyrus and subiculum), and adjacent cortex; it has been termed the H^+A^+ lesion (the '+' refers to damage to adjacent cortex). Since the human literature suggested that damage to the hippocampus might be especially important, the effects of a more restricted lesion (H^+) were subsequently investigated — the impairment was less severe, but both these lesions impaired a number of tasks, including the following:

- *simple object discrimination* (present two objects; reward the subject consistently for choosing one of them)
- *concurrent object discrimination* (present lots of pairs of objects; reward the subject consistently for choosing one of each pair)
- *delayed nonmatching to sample* (DNMTS: present one object; wait; present the previous object and a new object; reward the subject for choosing the new object) — usually performed in a *trial-unique* fashion, with new stimuli for each trial

The trial-unique DNMTS task (Delacour & Mishkin, 1975), a test of recognition after a delay, has featured heavily in animal studies of amnesia. This is partly because a loss of recognition is a striking and core feature of anterograde amnesia in humans (Aggleton & Brown, 1999). Significantly, the lesioned monkeys' performance on DNMTS was found to be *delay-dependent* (see Squire, 1992b), suggesting that an aspect of memory was impaired, and not simply the subject's ability to discriminate the stimuli or learn the task rules.

Remember that R.B. sustained CA1 damage following global anoxia; the CA1 cells are among the most sensitive in the brain to ischaemia. Monkeys with global is-

chaemia similarly lose CA1 cells, and they exhibit deficits on DNMTS (but were less impaired on simple and concurrent object discrimination tasks). Monkeys with selective (stereotaxic) lesions to the hippocampus ('H') were similar to those with global ischaemia. In contrast, monkeys with amygdala ablations ('A') were unimpaired on these mnemonic tasks. Monkeys with hippocampal lesions and extensive adjacent cortical damage sparing the amygdala ('H^{++}') were as impaired as the $H^{+}A^{+}$ monkeys. It therefore appeared that the adjacent cortical damage was the critical factor — and indeed, lesions of the perirhinal cortex and parahippocampal gyrus ('PRPH') produced severe impairments on DNMTS, object discrimination, and concurrent discrimination, much like the effects of $H^{+}A^{+}$ and H^{++} lesions (Zola-Morgan *et al.*, 1989).

Thus, it appeared that selective hippocampal lesions induced mnemonic deficits, additional damage to adjacent cortex produced further deficits in object discrimination, and amygdala lesions did not contribute to the amnestic syndrome. (On the other hand, amygdala lesions do produce profound deficits in processing the emotional significance of stimuli; see Aggleton, 2000.) However, even these findings regarding the hippocampus have recently been called into question: bilateral *excitotoxic* combined lesions of the amygdala and hippocampus do not impair DNMTS performance in monkeys (Murray & Mishkin, 1998). Instead, the perirhinal cortex is vital for this task (Malkova *et al.*, 2001). So what does the hippocampus really do?

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' (O'Keefe & Dostrovsky, 1971), O'Keefe & Nadel (1978) suggested that the hippocampus functions as a 'cognitive map', informing the rat where it is in the world (recently reviewed by Eichenbaum *et al.*, 1999a).

Lesion studies appear to support the idea that the hippocampus is critical in navigation. For example, Morris *et al.* (1982) 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 (Pearce *et al.*, 1998). Water maze performance is damaged by dorsal, not ventral hippocampal lesions (Moser *et al.*, 1995).

Learning in the water maze can be blocked by the glutamate NMDA receptor antagonist AP-5, which blocks LTP (Morris *et al.*, 1986); 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 (Bannerman *et al.*, 1995), so the role of the NMDA receptors may not be a specifically spatial one!

Using PET imaging, Maguire *et al.* (1997) 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 (Maguire *et al.*, 2000). The hippocampus is also activated when subjects navigate around the computer game Duke Nukem (Maguire *et al.*, 1998)!

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 Eichenbaum *et al.*, 1999a). 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.* (1999) 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 (1997) 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.

Encoding scenes

Gaffan (1992) argued that the hippocampus is required for encoding scenes — that is, complex and arbitrary stimulus patterns. Gaffan & Harrison (1989) 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'.)

Gaffan & Harrison (1989) argue that only the third type of memory — 'snapshot' memory — is disrupted by fornix lesions. Gaffan (1992) 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 (Phillips & LeDoux, 1992). However, animals may use contextual informa-

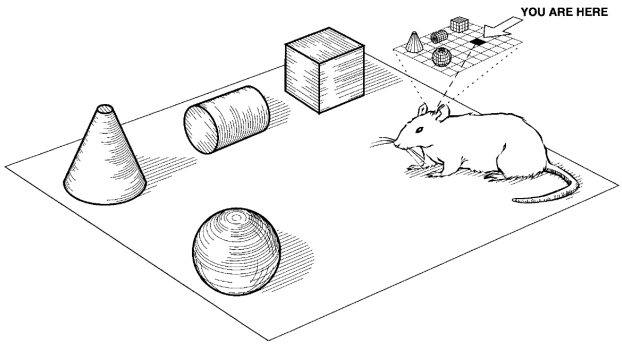
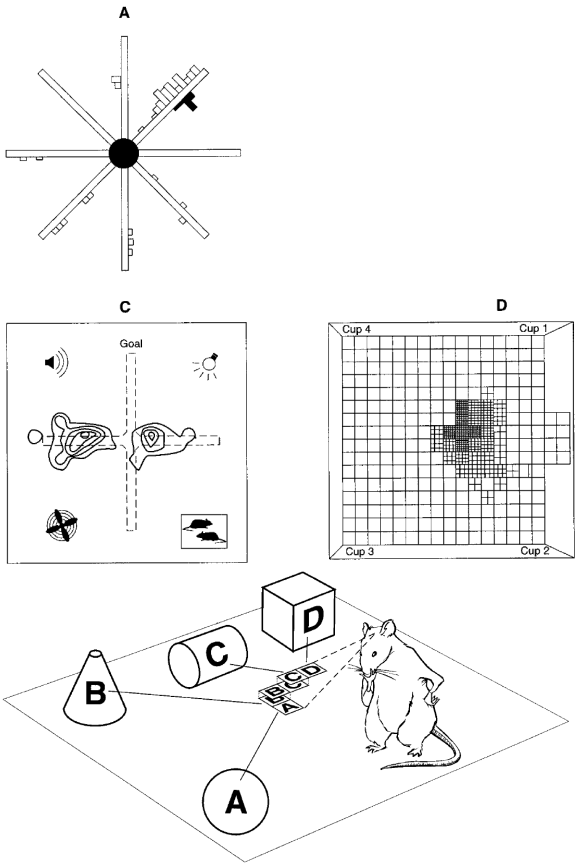
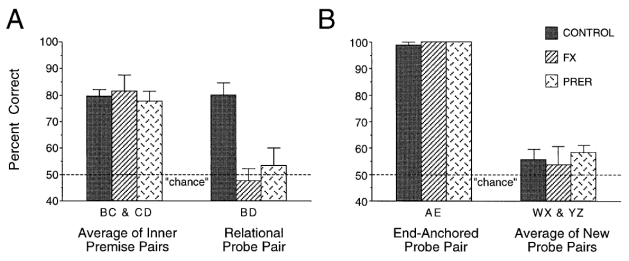


Figure 2. Cognitive Mapping
Conceptual model of hippocampal representation of a spatial environment according to the cognitive mapping hypothesis.



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 B 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. *(1999a)6} and Dusek & Eichenbaum (1997).*

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.



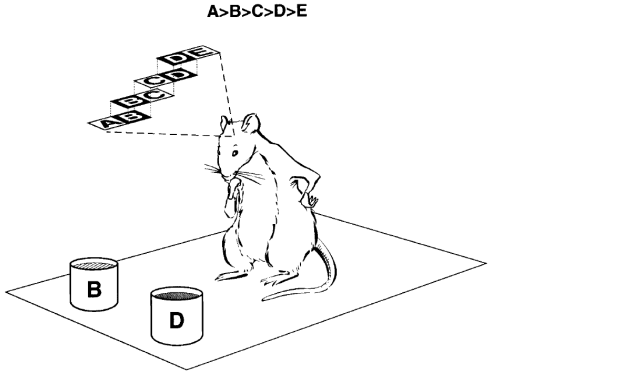


Figure 7. Transitive Inference in Serial Ordering
Representation of an odor series by cells that represent each trained odor pairing, plus nodal representations (dotted lines) of odors that are common between some of the trained pairings.

tion 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 (1999).

Relational information

Eichenbaum *et al.* (1999a) 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 (1997) have shown that fornix transection and perirhinal/entorhinal lesions, both of which partially disconnect the hippocampus, impair transitive inference in rats (see figure).

Summary

We have seen that there are multiple psychologically distinct memory systems. Damage to medial temporal lobe and diencephalic structures impairs episodic memory in humans, sparing a wide variety of other types of memory. Modelling this deficit in animals has been fraught with interpretative difficulty due to both the lesion techniques and the complexity of the tasks used. Considering the hippocampus on its own, as a major part of the medial temporal lobe memory system, has revealed that it has both spatial and non-spatial roles; perhaps the theme common to most theories (spatial, context, scenes, episodes, relations) is that it rapidly encodes the relationship between complex stimuli, and this is important in a variety of tasks. Next week we will look at some of the roles of adjacent cortex, examine the evidence for distinct procedural memory systems, and consider the process by which memories are consolidated and retrieved.

Sample essay questions

- Which aspects of the human organic amnesia syndrome do experiments with brain damaged monkeys fail to capture?
- Critically analyse the proposition that the mammalian hippocampus is implicated specifically in spatial memory, considering carefully any evolutionary implications.
- 'Any one theory of hippocampal function is doomed to failure.' Discuss.
- What is the current status of the hypothesis that NMDA receptors play essential roles in particular forms of learning? *(This would require integration of material from several lectures.)*
- How has recent evidence changed our views about the functions of different regions of the temporal lobe in memory?

Suggested reading

- Eichenbaum *et al.* (1999b) — chapter 56 in *Fundamental Neuroscience*
- Fuster (1995) — chapter 2, summarizing types of memory. The whole book is excellent, however.
- Griffiths *et al.* (1999) and Morris (2001) — animal models of episodic memory.
- Squire (1992b) — a chronicle of the medial temporal lobe story
- Eichenbaum *et al.* (1999a) — memory functions of the hippocampus (animal view)
- Good (2002) — excellent and thoughtful review of hippocampal function

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Don't read all these! Concentrate on the *Suggested Reading* list.

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