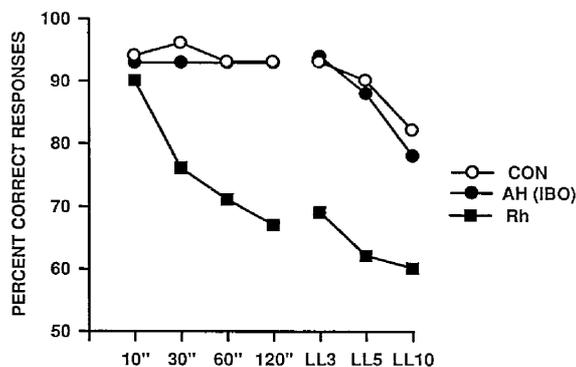


Overview

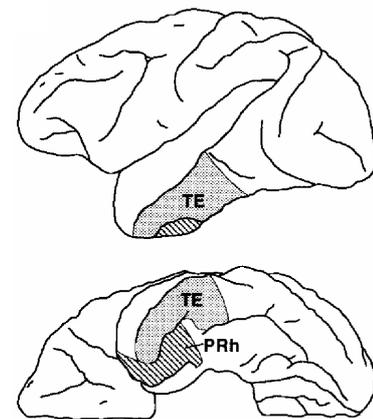
Last week we examined the effects of large medial temporal lobe lesions on memory in humans, together with attempts to model medial temporal lobe amnesia in animals, and we considered the nature of the information encoded by the hippocampus. Today we will consider in more detail the role of adjacent temporal cortex. We will examine the possibility that the hippocampus has a time-limited role in memory, considering models of consolidation, retrieval, and 'reconsolidation'. We will then discuss the structures implicated in procedural memory.

Contributions of rhinal cortex to memory and perception

We saw in the first lecture how inferior temporal cortex is at the anterior end of the ventral stream of visual information processing, and how 'mnemonic' effects are observed in the firing of inferotemporal (IT) cortex (areas TE and TEO in the monkey). We saw in the last lecture that rhinal (i.e. entorhinal + perirhinal) cortex lesions alone are sufficient to induce substantial delay-dependent (i.e. mnemonic) deficits in the delayed non-matching to sample (DNMTS) task (see figure).



Lesions of rhinal cortex impair DNMTS performance. Rhinal cortex data from Meunier et al. (1993), together with excitotoxic amygdala+hippocampus (AH) lesion data from Murray & Mishkin (1998). Alas, these rhinal cortex lesions were not excitotoxic, but — for once — excitotoxic lesions produce the same effect (Baxter & Murray, 2001; Malkova et al., 2001). (" 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 (Murray & Bussey, 1999). **Top:** lateral view (anterior to the left). **Bottom:** view of the inferior surface.*

So we know that TE/TEO contribute to visual object discrimination, i.e. perception (Ungerleider & Mishkin, 1982), and the rhinal cortex contributes to memory for visual objects. So does TE contribute to memory, and does perirhinal cortex contribute to perception?

Buckley *et al.* (1997) examined the effects of ablative lesions of perirhinal cortex and dorsal area TE. TE lesions impaired monkeys' ability to discriminate isoluminant colours, but had no effect on DNMTS performance; in contrast, perirhinal lesions impaired DNMTS but not colour discrimination. However, although this double dissociation of a perceptual and a mnemonic task is clear, this does not mean that the perirhinal cortex has no perceptual functions.

Perirhinal cortex and visual perception

Perirhinal cortex sits between the ventral visual stream and the putative medial temporal lobe memory system; it also receives multimodal inputs (e.g. from somatosensory regions of the insula and multimodal regions such as cingulate and orbitofrontal cortex) and is therefore the first polymodal cortical area in the ventral visual processing stream (Murray & Bussey, 1999). As we mentioned, lesions of perirhinal

cortex impair monkeys' performance on visual recognition memory tasks (Baxter & Murray, 2001; Malkova *et al.*, 2001) and visual associations (e.g. Goulet & Murray, 2001). Does it also contribute to visual *perception*? Buckley *et al.* (2001) provided evidence for such a role. They gave rhesus macaque monkeys 'odd-one-out' tasks of varying difficulty. None of these tasks required the subject to remember a stimulus, yet perirhinal lesions impaired discrimination, particularly when those discriminations were difficult.

Perirhinal cortex: representing conjunctions of features to resolve ambiguity.

If perirhinal cortex is involved in visual perception, and if it builds 'feature detectors' based upon *conjunctions* of features earlier in the ventral stream hierarchy, then lesions should impair discrimination performance particularly when stimuli share many common features (when 'feature ambiguity' is high) (Bussey & Saksida, 2002) (see also T.J. Bussey's lectures). Bussey *et al.* (2002) tested this hypothesis in monkeys. In accordance with their predictions, they found that aspirative perirhinal lesions had minimal effects when monkeys had to discriminate compound visual objects with little ambiguity (AB+, CD+, EF-, GH-, where '+' denotes a correct stimulus and '-' is incorrect), but subjects were impaired when the objects were moderately ambiguous (AB+, CD+, CE-, AF-), and dramatically impaired when the objects were very ambiguous (AB+, CD+, BC-, AD-). In this study there was no change in the number of objects to be discriminated (4 in each case). This hypothesis fits with previous findings that perirhinal lesions did not impair object discrimination when few stimuli were used, but did impair discrimination when many stimuli were used (Buckley & Gaffan, 1997) — the large stimulus set increased the feature overlap between the stimuli, and hence the ambiguity of individual features.

Conclusion

Perirhinal cortex appears to have roles in both perception (high-order object discriminations) and memory (Bussey *et al.*, 2002; 2003). In fact, Murray & Richmond (2001) suggest that it also has a wide role in associating polymodal information about objects. This view is right up Fuster's street (Fuster, 1995, p. 113) — the idea that memory and perception are largely inseparable in cortex.

Semantic memory: where? How?

There is debate not just about what semantic memories are (we discussed this briefly last time; see also Cognitive Neuropsychology lectures), 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 (Gadian *et al.*, 2000).

Conversely, there are patients who develop *semantic dementia* (Snowden *et al.*, 1989), characterized by progressive loss of conceptual knowledge about objects, facts, concepts, and word meanings (see Simons & Graham, 2000). 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 (Hodges *et al.*, 1992). 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 (Moss *et al.*, 2002). However, the relationship between semantic dementia and episodic memory is still controversial.

A time-limited role for the hippocampus?

Retrograde amnesia

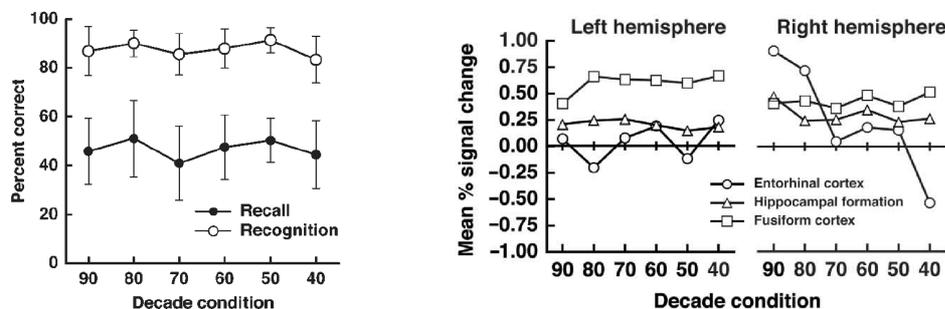
As we discussed last week, H.M. developed profound anterograde amnesia following his medial temporal lobe resection — but also a temporally-graded retrograde amnesia for events preceding the surgery (that is, old events were recalled better than recent ones). Indeed, such retrograde amnesia has been regularly noted in humans following medial temporal lobe lesions, or lesions apparently restricted to the hippocampal formation (see Squire *et al.*, 2001). This led to the hypothesis that the hippocampus is involved in consolidating memories held elsewhere (Scoville & Milner, 1957) — recent memories are vulnerable to hippocampal damage, but with time they become independent of the hippocampus. This view is highly popular.

The ‘multiple memory trace’ model

The major competing view is that of Nadel & Moscovitch (1997). They argue that the duration of retrograde amnesia for human autobiographical episodes following medial temporal lobe damage is extremely long (25–40 years), and may not even be temporally graded at all (‘flat’ retrograde amnesia; i.e. lesion → loss of memory, full stop). Even if the hippocampus does consolidate cortical memory, if it does so over 40 years then most humans throughout history would never have ‘fully’ consolidated a memory. They argue that it makes more sense to consider the hippocampus to be permanently involved in the storage of autobiographical memories. Nadel & Moscovitch also argue that autobiographical memory, personal semantic memory, and ‘general’ semantic memory (vocabulary, grammar, object recognition) are progressively less sensitive (in that order) to retrograde amnesia following medial temporal lobe lesions in humans. In their view, the hippocampus provides a permanent spatial/contextual ‘index’ that helps to retrieve a given memory. One-off (e.g. recent) autobiographical memories are dependent upon their index for retrieval, so are vulnerable to hippocampal damage. Semantic information is extracted from repeated episodic experiences; therefore, semantic information (and well-rehearsed, i.e. old, autobiographical memories) is supported by multiple memory traces, and is less dependent upon the hippocampal ‘contextual index’ for retrieval. See also Nadel & Bohbot (2001) and Rosenbaum *et al.* (2001) for recent statements of this hypothesis.

Functional imaging of remote versus recent memories

There have been many attempts to address the question of whether consolidation processes occur between neural structures. Here’s an example: Haist *et al.* (2001) showed famous faces from a range of decades to healthy 60–70-year-old adults in an fMRI scanner. Recall and recognition scores did not differ over the decades, yet activation in the (right) entorhinal cortex was temporally graded across decades (more for recent faces). On this timescale, no temporally-graded hippocampal activity was found (Haist *et al.* argued that the hippocampus only plays a part for a few years in humans, so their study was insensitive to a temporally-graded effect here). As a contrast, Ryan *et al.* (2001) found a lack of any temporally-graded activation in hippocampus or neocortex when subjects retrieved autobiographical memories.

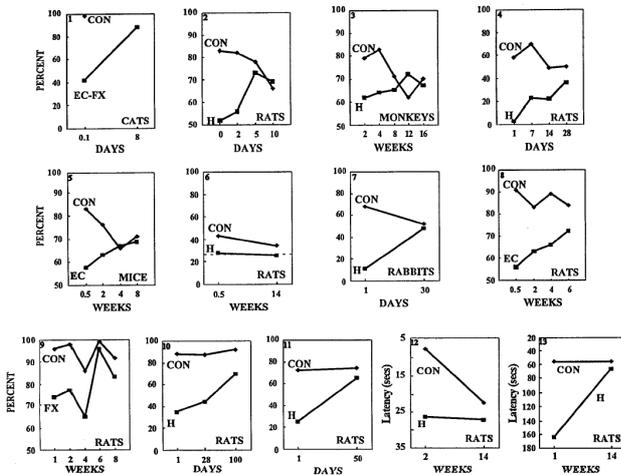


*Recognition and recall of famous faces from different decades (subjects were 60–70), from Haist *et al.* (2001). **Left:** behavioural results; **right:** fMRI activation.*

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, pro-

spective studies in animals have produced the most clear-cut results (see Murray & Bussey, 2001, for these and other important methodological issues). As shown below, the majority of such studies have shown temporally-graded retrograde amnesia following a variety of hippocampus, fornix, and entorhinal cortex lesions.

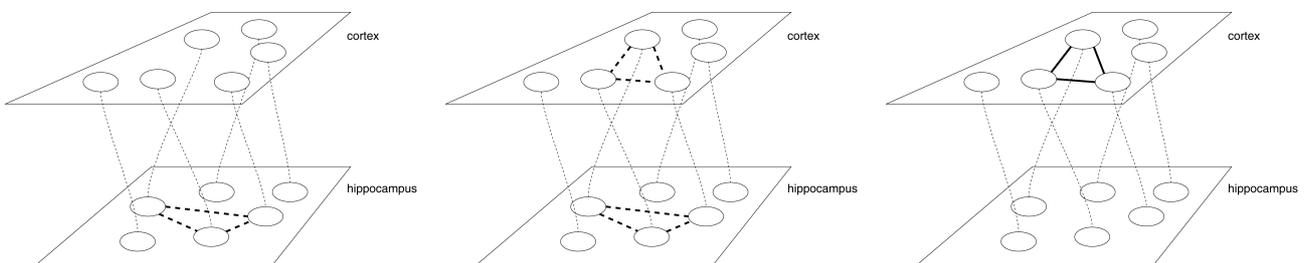


Summary of prospective studies, in several different labs using a range of tasks, of retrograde amnesia following hippocampus (H), fornix (FX), or entorhinal cortex (EC) lesions in a range of non-human species. From Squire *et al.* (2001). The studies include both excitotoxic and electrolytic/aspirative lesions, and between- and within-subject designs. The abscissa (x axis) is the training–surgery interval, so older memories are on the right; the ordinate (y axis) is performance (% or latency — arranged so that performance increases as you move up the y axis in all cases).

For example, we discussed briefly the involvement of the dorsal hippocampus in contextual conditioning last week; consistent with the human literature on temporally-graded retrograde amnesia, electrolytic or excitotoxic lesions of the hippocampus produce a time-limited retrograde amnesia for contextually-conditioned fear (see Anagnostaras *et al.*, 2001, who discuss some of the controversies in this area).

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. McClelland *et al.*, 1995): the figure below shows one. Incidentally, Maviel *et al.* (2004) have recently tackled the question of where memories that no longer depend on the hippocampus ‘go to’, if that is the right phrase, using a spatial memory task in mice. They used a combination of gene expression studies to localize time-dependent changes in neocortical activity and structure, together with inactivation studies to see if those changes were critical for memory retrieval.



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.

So is the hippocampus involved in encoding, consolidation, and retrieval?

Yes, it seems so — at least for certain classes of memory, and at certain times. A simple demonstration is that of Day *et al.* (2003). They presented rats with unique food/location (what/where) pairs in a *paired-associates* learning task. They found that blocking NMDA glutamate receptors in the hippocampus prevented encoding in this task, but had no effect on recall, suggesting that the hippocampus (and, likely, hippocampal plasticity) was involved in learning the task. However, blocking hippocampal AMPA glutamate receptors — intended to switch off neural transmission completely without affecting fibres of passage — prevented recall as well as encoding. If the pairs had been trained repeatedly, though, blocking hippocampal AMPA receptors had no effect on recall, suggesting that the role of the hippocampus declined with repeated training (or time). Finally, Riedel *et al.* (1999) have shown that infusion of an AMPA antagonist into the dorsal hippocampus *after* training impaired retrieval of a spatial memory, tested in a water maze, suggesting that the hippocampus is involved either in consolidation or long-term storage of this memory.

Decay of memories in the hippocampus

Finally, Villarreal *et al.* (2002) 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 was due to the drug's effect on the hippocampus.) Perhaps decay of LTP (or LTD, which also depends on NMDA receptors) 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 (Grossberg, 1982; McCloskey & Cohen, 1989). Rosenzweig *et al.* (2002) suggest that Villarreal *et al.* (2002) blocked exactly this loss of old memories.

Sleep and consolidation

If this model of hippocampal–cortical interaction (see figure above) 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 (Marr, 1971). Although it's an attractive idea that one function of sleep is to consolidate memory, the specific role of sleep in consolidation is somewhat controversial.

‘Replay’ of learned neural activity during sleep

Wilson & McNaughton (1994) 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. Similar effects have been found by Nádasdy *et al.* (1999): they found repeating patterns of spikes in the hippocampus of awake, behaving rats running in a wheel; these same sequences were observed to be ‘replayed’ at a faster timescale during subsequent SWS. Kudrimoti *et al.* (1999) observed reactivation of hippocampal discharge patterns during SWS, and also during periods of quiet wakefulness. Louie & Wilson (2001) have reported similar effects during rapid eye movement (REM) sleep — in this case, hippocampal ‘replay’ at the original timescale.

‘Procedural’ memory consolidation and sleep

Karni & Sagi (1991) 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 oc-

cur during practice, but at about 8 hours after the practice sessions (and these improvements are stable for years) (Karni & Sagi, 1993). This improvement requires sleep within 30 hours of training (Stickgold *et al.*, 2000). It is more controversial what type of sleep is important (Karni *et al.*, 1994; Gais *et al.*, 2000) — partly because techniques for disrupting SWS but not REM (or vice versa) are imperfect. There may be truth in the ‘sequential’ hypothesis of Giuditta *et al.* (1995; see Ambrosini & Giuditta, 2001), which suggests that you need SWS *then* REM.

Fischer *et al.* (2002) have shown that sleep improves subsequent performance of a sequential motor task (finger-to-thumb opposition in a particular sequence); the improvement was specific for the practised sequence and occurred whether subjects slept during the day or night. Sleep deprivation itself had no effect on performance.

‘Declarative’ memory consolidation and sleep

Wagner *et al.* (2001) found that declarative memory for a text (‘please memorize this text’) was enhanced by sleep. In particular, this effect was greater during the second half of the night, when rapid-eye movement (REM) sleep predominates, and it was greater for emotional texts than neutral texts; they suggested that REM sleep particularly consolidates emotional memories. There are obvious interpretative difficulties with this form of study, notably that the circadian time of deprivation is confounded with the REM versus non-REM factor. A related recent study by Marshall *et al.* (2004) found that applying frontal direct current stimulation to 19–28-year-old students during periods of sleep rich in SWS enhanced memory for word pairs (but did not improve mirror tracing skills, and did not improve word pair learning in the waking state).

‘Sleep inspires insight’

In a recent elegant study, Wagner *et al.* (2004) trained people in a sequence learning task. They saw a string of digits (e.g. 1 1 4 4 9 4 9 4). They began with the first two digits, and had to generate a new digit according to certain rules; they then combined their answer with the next digit in the sequence to produce another new digit; and so on. Their task was to come up with a ‘final’ digit at the end of the sequence. What they were not told is that the sequences were always generated such that the second digit they generated was always the same as the final answer. When people realize this, the time they take to complete the task plummets. Wagner *et al.* used this as a measure of who has developed ‘insight’ into the hidden rule. The number of people showing insight was dramatically increased in subjects who were allowed to sleep for 8 h after the first training session, regardless of the time of day they were tested.

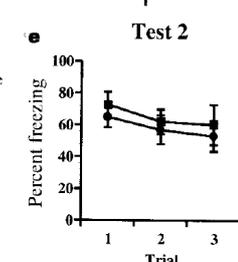
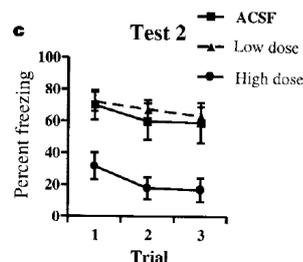
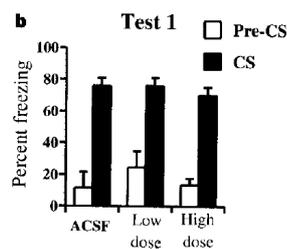
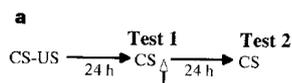
Debate about the relative roles of SWS and REM

There is now little doubt that sleep plays a role in the reorganization of some kinds of memories. There is much more debate about the relative contributions of different phases of sleep. Although many theories of sleep consolidation posited that REM sleep was critical for consolidation, the evidence for this is far from convincing; see Siegel (2001). 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 Siegel, 2001). The role of SWS is perhaps better established, for certain kinds of task (Stickgold *et al.*, 2001; 2002). However, a recent study showed that artificial enhancement of REM sleep improved later retention of a Y-maze task in rats (Wetzel *et al.*, 2003); the debate continues.

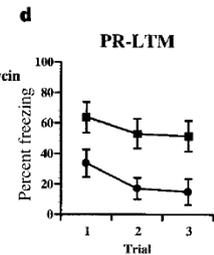
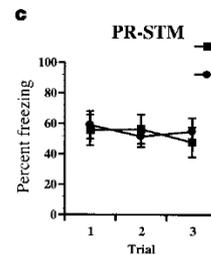
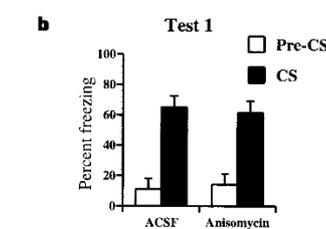
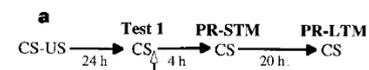
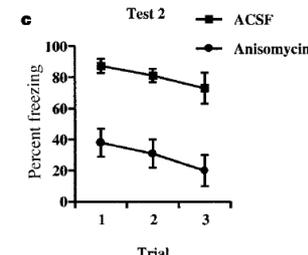
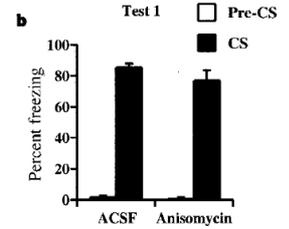
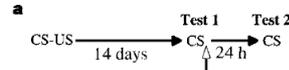
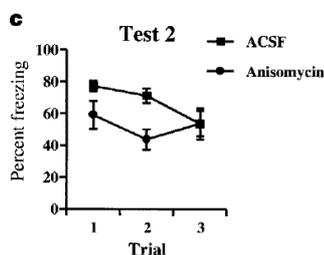
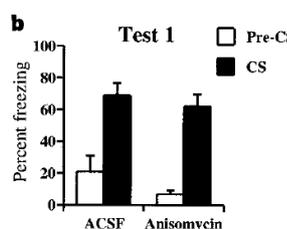
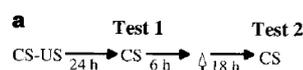
Reconsolidation

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, also known as 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 (Duncan, 1949). 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. Abel *et al.*, 1997; Kandel, 2001). 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 Beggs *et al.*, 1999).

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 (or other amnesic treatments) don’t disrupt stable memories, they should be able to disrupt old memories that have been reactivated. Indeed, this has been observed (Misanin *et al.*, 1968). Recently, Nader *et al.* (2000) found that infusions of anisomycin into the basolateral amygdala (a critical

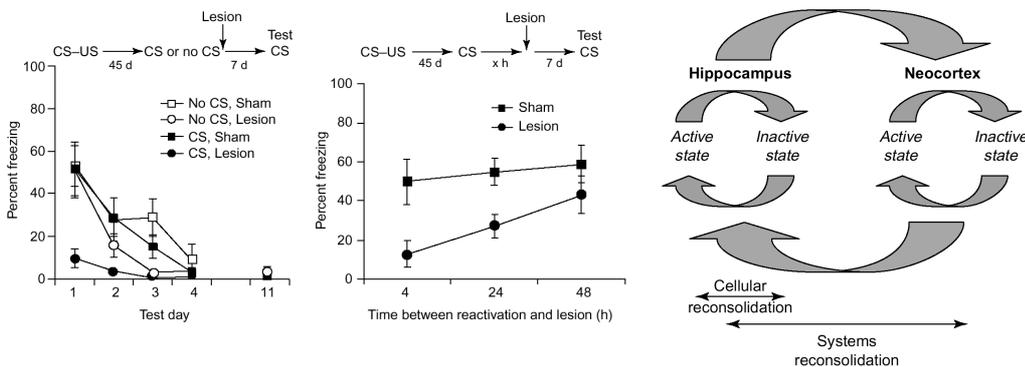


Reconsolidation in the amygdala (Nader et al., 2000). Top left: Rats experience CS(tone)–US(shock) pairings. They are later re-exposed to the CS. High-dose anisomycin (but not low-dose anisomycin or artificial cerebrospinal fluid) infused into the basolateral amygdala after this re-exposure disrupts conditioned freezing in a subsequent test 24h later (a, b, c). This does not happen if the CS is not presented before the infusion (d, e). Bottom left: if the anisomycin infusion is delayed by 6h, the memory is intact. Bottom middle: anisomycin has this effect even if 14 days elapse between conditioning and the re-exposure test. Bottom right: the memory is intact 4h after the infusion (‘post-reactivation short-term memory’), but not 20h after (‘post-reactivation long-term memory’).



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 (see figure). The molecular mechanisms of consolidation and reconsolidation are doubly dissociable (Lee *et al.*, 2004), so they are not exactly the same process.

The story so far has been termed ‘cellular reconsolidation’. A further phenomenon is ‘systems reconsolidation’ (Debiec *et al.*, 2002) — regarding the apparent movement of memory between neural systems. Debiec *et al.* gave rats CS–US pairings where the CS was a context and the US was shock; after 45 days, they then presented the CS on its own (or not) and lesioned the hippocampus (or not). In the absence of CS presentation, the memory was not hippocampus-dependent (no effect of the lesion); presentation of the CS caused the memory to depend on the hippocampus again, but only for ~48 hours. Debiec *et al.* suggest, based on these and other experiments, that a memory is formed, is initially hippocampus-dependent, and during this time it can undergo ‘cellular’ reconsolidation if activated. With time, the memory is consolidated in neocortex and no longer requires the hippocampus, unless it is reactivated, in which case it depends on the hippocampus for a while... and so on.



‘Systems reconsolidation’ (Debiec *et al.*, 2002). See text for details.

Is this important? Yes. One old case study (Rubin *et al.*, 1969) 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 her 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 (Rubin, 1976). The ability to ‘remove’ memories selectively might have enormous implications for the treatment of diseases including OCD, drug addiction, and so on.

Cautionary notes

The protein synthesis inhibitor puromycin was noted to disrupt memory forty years ago (Flexner *et al.*, 1963). However, protein synthesis inhibitors, even very selective ones such as anisomycin, have a range of side effects (e.g. when injected into the cerebral ventricles), and it is difficult to exclude the possibility that these side effects, rather than the inhibition of protein synthesis, have an effect on consolidation — or *retrieval* — of the memory (reviewed by Davis & Squire, 1984). These considerations are reduced by local infusion of the drug into one brain region, but they are not eliminated. In the case of puromycin, it turned out that the effect was caused by a metabolite of puromycin and not by its protein-synthesis-inhibiting properties; another protein synthesis inhibitor, acetoxycycloheximide, failed to affect memory formation (Flexner *et al.*, 1967).

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 (1970) 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.* (2001) point out that many forms of amnesia can be reversed by *reminder* treat-

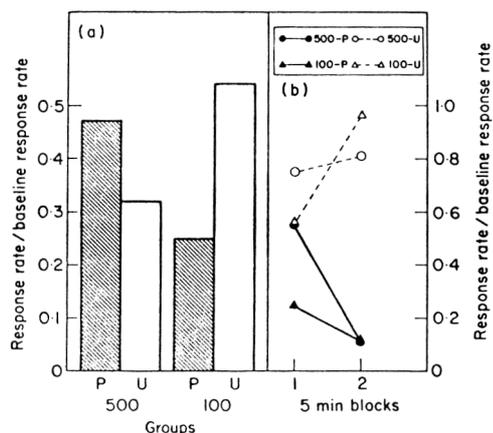
ments, indicating that the memories were present all along and the deficit was one of retrieval. Typical such studies used ECS to induce amnesia; subsequent exposure to the CS, the US, or the ECS have all been shown to reverse the amnesia (Miller & Springer, 1972; Springer & Miller, 1972; Miller *et al.*, 1974; see Millin *et al.*, 2001).

The same question can be applied to reconsolidation (Millin *et al.*, 2001): 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 (Judge & Quartermain, 1982; Mactutus *et al.*, 1982). Nader and colleagues now acknowledge this possibility (Debiec *et al.*, 2002).

Habit learning: the dorsal striatum

The amnesia exhibited by H.M. was originally labelled ‘global anterograde amnesia’ — yet, as you recall, a number of learning abilities were preserved in H.M. One of these was the ability to learn the skill of mirror-drawing (Milner, 1962). 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 (Mishkin *et al.*, 1984). What are habits?

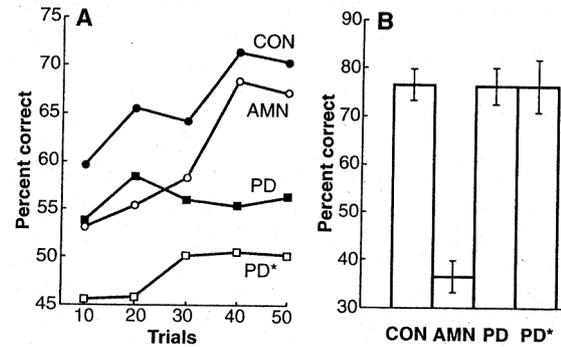
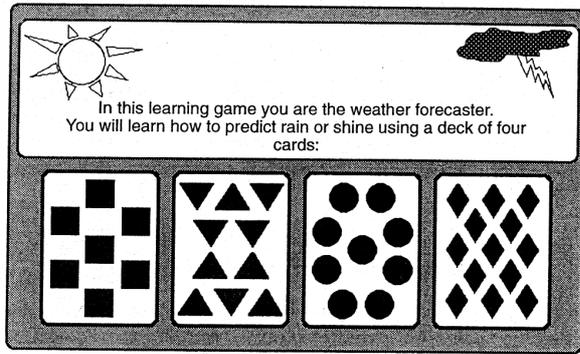
Habits are the archetype of procedural memory. They are direct stimulus–response (S–R) links that are acquired as the result of reinforcement occurring when an animal makes a response in the presence of a stimulus (Thorndike, 1911). Do animals have a habit system? Yes. We can test for it in rats using the *reinforcer devaluation* procedure that we mentioned last week. 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 (Adams, 1982). 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 Dickinson, 1985). It appears that S–R links develop slowly through training until, under some circumstances, they dominate behaviour.



Overtraining an instrumental behaviour renders it habitual, and resistant to devaluation of the reinforcer (Adams, 1982). Rats were trained to press a lever for food under a fixed-ratio-1 schedule for either 100 or 500 reinforcers. They then received food–LiCl pairings to induce a conditioned taste aversion to the food (group P) or, for a control group, unpaired presentations (group U). In an extinction test (a), the groups that had been trained with only 100 reinforcers reduced their lever pressing following devaluation (devaluation effect: group 100-P < 100-U) but the overtrained group did not (group 500-P versus 500-U), indicating that their behaviour was habitual following training with 500 reinforcers. In a subsequent reacquisition test (b), when reinforcers are delivered once more, it is now clear that the reinforcer is aversive and capable of suppressing responding in both the nausea-conditioned groups (500-P and 100-P).

So what neural structures subserve habit learning? Mishkin *et al.* (1984) originally suggested that a cortico-striatal system subserved habit formation. Much of the subsequent work on this issue proved controversial (see Wise, 1996; Wise *et al.*, 1996); a recent review is provided by White (1997).

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

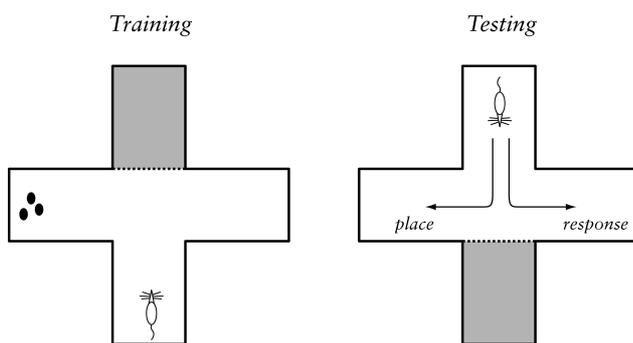


Left: two tasks in one. In this computerized probabilistic classification task, one to three cards are shown and the subject must predict sunshine or rain. Feedback is provided as to whether the subject predicted correctly or incorrectly. One cue is associated with sunshine on 25% of occasions; one on 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.* (1996).

puzzle (Butters *et al.*, 1985; Saint-Cyr *et al.*, 1988). Knowlton *et al.* (1996) 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).

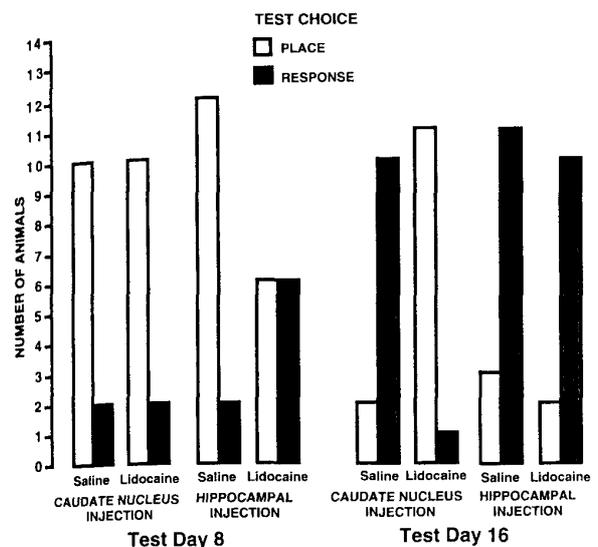
This double dissociation clearly shows that the impairments in PD and hippocampal/diencephalic amnesia are qualitatively different. However, it does not show that what the PD patients couldn't do was learn a habit (or, for that matter, that the deficit was due to striatal dysfunction, rather than — say — 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 thought to test 'habits' actually do so. Tasks have even been described as non-habit-based on the grounds that human amnesiacs cannot learn them (Hood *et al.*, 1999).

For years, the best demonstration of a striatum-dependent habit was an elegant study by Packard & McGaugh (1996), illustrated below. It shows that a stimulus-to-motor-response mapping develops slowly during reinforced training, and comes to domi-



Design and results of Packard & McGaugh (1996). **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'.



nate 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. However, it should be noted that even this study does not fulfil the definition of a ‘habit’ given above in the context of instrumental behaviour; for example, the effect of reinforcer devaluation on performance of the presumptive habit was not tested. More recently, Yin *et al.* (2004) have shown that the dorsolateral striatum is necessary for the formation or expression of a habit, as judged by reinforcer devaluation.

Summary

We have considered the role of inferior temporal lobe cortical regions in visual memory and semantic memory, and their relationship to the hippocampus. We have considered hypotheses concerning the manner in which the hippocampus may acquire certain kinds of memory rapidly and consolidate them in other structures. We have considered sleep as a time of memory consolidation, discussed the phenomenon of reconsolidation, and examined the evidence for striatum-dependent habit learning. Next time, we will look at the prefrontal cortex.

Topics that we haven’t covered

Since ‘memory’ is such a vast subject, it may be useful for you to know what topics we haven’t covered at all! Obviously, we’ve concentrated on systems-level neuroscience and haven’t discussed cellular mechanisms of memory (for which, see Beggs *et al.*, 1999). Neither have we paid much attention to anything except mammalian learning. Even within mammals, we haven’t looked at several well-defined learning systems. These include associative learning in the *cerebellum*, which 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 (Steinmetz, 2000; Thompson *et al.*, 2000). They also include ‘emotional’ conditioning — value representations — in the *amygdala* and related limbic structures like the *orbitofrontal cortex*, though we will mention the orbitofrontal cortex next time. Finally (?), we haven’t talked about *neurochemical modulation* of memory — such as the mechanisms by which emotionally arousing situations enhance memory (Cahill, 2000; McGaugh *et al.*, 2000).

Sample essay questions

- How convincing is the psychological and neural evidence for the ‘declarative/procedural memory’ distinction?
- What is the significance of the relationship between anterograde and retrograde amnesia?
- Compare the roles of the hippocampus and prefrontal cortex in memory encoding and retrieval.
- What is known about the neural basis of reconsolidation? Is reconsolidation a defensible concept?

Suggested reading

- Bussey *et al.* (2002) — perirhinal cortex; see also Murray & Richmond (2001) for an excellent review.
- Squire *et al.* (2001) — retrograde amnesia; see also Nadel & Moscovitch (1997) or Nadel *et al.* (2000) for their ‘multiple memory trace’ theory; Murray & Bussey (2001) for a clear approach to methodology in this field.
- Stickgold *et al.* (2002) — ‘sleep vital for consolidation’; Siegel (2001) — ‘REM sleep isn’t’; Ambrosini & Giuditta (2001) — ‘need SWS then REM’. A flavour of the debate!
- Nader (2003) — reconsolidation; Millin *et al.* (2001) — interpreting reconsolidation
- Wise (1996) — critique of the ‘basal ganglia = habit’ hypothesis. Compare Packard & McGaugh (1996). The article by Wise is in a special issue of *Seminars in the Neurosciences*, much of which you may find interesting.

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

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