Memory

Learning and memory – structural correlates

Amnesia. Unilateral medial temporal lobe surgery has caused selective deficits in verbal memory (right) and visual memory (left); bilateral surgery leads to severe anterograde amnesia (H.M.). Weiskrantz (1987) summarized the evidence that patients with pure amnesic syndrome have lesions in two systems: **(a)** subiculum → hippocampus → fornix → mammillary body → anterior thalamus; **(b)** amygdala → medial dorsal and subependymal thalamus → frontal lobes. It may be that in man the fornix/mammillothalamic system is more important relative to the monkey.

Perception and Knowledge. PET scanning during visual tasks (Ungerlieder, 1995) shows that scrambled faces produce posterior activation. Identification of people by gender activates ventral posterior temporal cortex; identification of a unique individual activates a more anterior ventral temporal region; retrieving knowledge about an individual ("what's his job?") activates even more anterior regions in the parahippocampal gyrus and temporal pole. These results are consistent with the effects of lesions. Alexia is frequently associated with lesions of the left medial occiptotemporal cortex; this region is activated when people view words (as opposed to strings of random letters). "Object knowledge seems to be stored in a distributed cortical system in which information about specific features is stored close to the regions of the cortex that mediate the perception of those features."

Priming. As reaction time to visual stimuli improved, the activation of occipitotemporal cortex *declined* (fMRI, PET). It took novel objects to maintain the level of activation (but the cells were selective for stimuli and not just novelty detectors). Similar results for word stem priming. This is metabolically sensible. Animals studies support the view that (a) less cortex is needed to process familiar stimuli; (b) cortical activations shrink with familiarity because the neural populations that represent the familiar stimuli have become more selective.

[Squire, 1986] Priming effects may depend exclusively on intact cortical representations: they are reduced in early Alzheimer's disease, but not in amnesic patients or those with Huntingdon's dementia.

Cortical representations. But perceptual and motor skill learning leads to expansion of cortical representations (including expansion of somatosensory cortex, etc.). For example, learning a sequence of finger movements converts a patchy pattern of activation in the hand region of M1 into an expanded, more contiguous representation. This was selective for the trained sequence, and did not occur for the control sequence (the same finger movements in a different order).

It seems that the representation shrinks on the second trial (like the priming effect), then grows (within 30min). There may, then, be two stages in skill learning: an initial rapid stage in which activity b ecomes focused in a population of cells that best represents the stimulus (sensory cortex) or movement (motor cortex), and a later, slowly evolving stage in which additional cells are recruited into the critical network. The time course of this switch-over may depend on the nature of the task, etc.

Other structures; changes during learning. Activation of cerebellum and PFC, also thought to be important for learning, always diminishes over the course of short-term learning of motor sequences. This change occurs in the same time frame as the switch from reduced to enhanced activation in M1; it may be that cerebellum and PFC are preferentially engaged in tasks in which the initial learning is conscious and effortful, with the motor cortex gradually becoming predominant as the task becomes automatic. This same principle may apply to other tasks. For example, generating verbs in response to nouns is initially effortful (anterior cingulate cortex, left PFC, left posterior temporal cortex, right cerebellum) but becomes automatic (activation in those areas decline, and activation increases bilaterally in Sylvian insular cortex and in left medial extrastriate cortex).

Declarative memory; the hippocampus. Problems; imaging studies are a little difficult. There is evidence that it is active during encoding but not subsequent recognition of faces. It may be more active in memory tasks involving unfamiliar stimuli (geometric shapes, unfamiliar faces) than familiar (words). Or it may be only one part of a declarative memory system. The left PFC is commonly activated during encoding of information (verbal & visual) and the right PFC during retrieval (verbal & visual). Right PFC activity may reflect the conscious effort to retrieve information. Medial parietal lobe (precuneus or retrosplenial cortex or both) is activated during episodic but not semantic memory; it may be activated specifically in association with the visual imagery usually elicted by the retrieval of episodic memories. Why is the hippocampus involved, if cortical changes can occur without it (priming, skill learning)? It may be that priming/skill learning simply involve modification of an existing sensory/motor representation, whereas declarative memory requires associative links between different areas (the hippocampus is a convergence site)

The PFC and working memory. Memory of a cue seems to endure by maintaining the activity of the cells that represent the cue. Ventral PFC is reciprocally connected with ventral visual stream; dorsal PFC with dorsal visual stream. The degree of maintained activity in PFC is greated than that in visual cortex, and is resistant to disruption (unlike temporal cortex). PFC cells may be the main originators of the delay activity and may activate sensory representations in posterior processing areas. Delay activity in posterior parietal cortex is indeed lower when PFC is deactivated. Confirmed in humans (delay activity clear in PFC, though the low levels of delay activity in posterior cortex not seen). It may be that explicitly instructing people to imagine a visual stimulus potentiates the maintentance of activity in visual cortex; this would explain PET data showing visual cortex activation during explicit imagery. If PFC is involved in WM, PFC cells may have an analagous role in retrieval of information from LTM. The question is how PFC cells

"know" which visual cells to activates ("esp. as representations in visual areas must change as a result of storage of new memories" – ?).

The Hippocampal Formation

Anatomy. Good picture of connections in "Computational models of the neural bases of learning and memory".

All major association cortex areas project reciprocally to the entorhinal cortex, which sends afferents via the subiculum to the molecular layer of the DG. This is known as the perforant path (as the fibres perforate the hippocampal fissure on their way). The DG sends mossy fibres to CA3. CA3 sends axons out along the fimbria, and also Schaffer collaterals to CA1. CA1 sends axons back to entorhinal cortex and subiculum. Note that the perforant path makes synapses with the apical dendrites of CA3 pyramidal cells, as well as those of DG cells.

Connections with the septum, via the fimbria-fornix bundle… The cholinergic cells of the medial septum innervate the whole hippocampus. CA3 cells project back to the lateral septum, where interneurons inhibit medial septal cells.

The hippocampus has reciprocal connections (via the subiculum and fornix) with the mammillary bodies, anterior thalamic nucleus and cingulate cortex (circuit of Papez).

Basket cells in the hippocampus might mediate forms of lateral inhibition.

Human amnesia. Patient RB has damage only to CA1 and only a limited retrograde amnesia; patients with additional damage to CA3 and other parts of the temporal lobe appear to have more profound retrograde amnesia. However, HM (widespread MTL damage) has mild retrograde amnesia. Korsakoff/Alzheimer's patients have profound retrograde defects.

"… hippocampus plays an important role in the initial binding of memories stored in neocortex …" – a current idea.

Consolidation in rats (one-trial passive avoidance) can be enhanced by boosting NA (esp. in amygdala), and DA in striatum; retrograde amnesia has been produced by interfering with those systems.

Spatial learning. Place cells (O'Keefe & Nadel, 1978) – not as daft as it looks, because the cells continued to fire when the lights were turned out. H cells also fire in relation to certain types of movement, and match/mismatch or in novel situations. H lesions can *improve* tasks which can be solved by local cues alone. Spatial learning depends upon the **dorsal hippocampus**, rather than the ventral; it impaired by dorsal lesions of CA fields, by NMDA antagonists and other things that block LTP (e.g. CaM kinase II knockout).

DNMTS. The effect of H lesions is much less than lesions of parahippocampal, perirhinal and hippocampal (PR+PH+H) lesions. The amgdala is *not* involved in visual recognition memory. Mishkin thought it was because he used aspiration lesions (suck out perirhinal cortex next to amygdala). Similarly, aspiration H lesions may damage area TE. Mishkin (unpublished) has found no DNMTS deficits at all with a combined A+H excitotoxic lesion (ibotenic acid). Lesions of perirhinal cortex (only) cause massive DNMTS deficits, but no defect of one-trial-a-day concurrent pattern discrimination learning (which is "habit" memory) (Gaffan & Murry, 1992).

Rats with **fimbria-fornix** lesions are grossly impaired on a radial 8-arm maze task (rat must visit each arm only once). Working memory? (Only useful within the context of the current trial.) Gaffan found that this lesion affects **scene memory** – the spatial relationships of objects in a scene.

Rats with H lesions can perform DNMTS with junk objects, but are impaired at DNMTP (P=position) or delayed response tasks, in a T-maze or operant chamber [a working memory test].

Jarrard (1993) finds that excitotoxic H lesions lead to more errors in acquiring place than cue tasks, but there are only minor errors on the place task if the lesion follows learning, i.e. storage elsewhere in the brain and working memory is fine.

So… O'Keefe & Nadel find impairment of spatial reference memory with H lesions. Olton *et al*. find impairment of non-spatial working memory. Both find impairment of spatial working memory. Neither find impairment of non-spatial reference memory.

The fornix and 'snapshot' memory (Gaffan & Harrison, 1989)

"When a monkey displaces a stimulus object in a certain place and finds a food reward underneath it, several memories are formed, some dependent on the fornix and others not. To classify them, we can regard the event in question as composed of 3 classes of stimulus item: the object displaced, the reward under it, and background items.

1. *A simple association is formed between the displaced object and the reward. This memory does not depend on the fornix. It can be used in tasks such as object-discrimination learning set, in which the background items, and the spatial position of the displaced object and the ward, are irrelevant.*
2. *A more complex association is formed among the background items, the object displaced, and the reward. This memory allows the animal to remember later that the event of this object revealing food occurred in the presence of teh door handle etc. This memory does not depend on the fornix. Unlike memory (1), it can be used in tasks in which reward can be predicted by the conjunction of the background items and the object displaced.*

3. *An even more complex memory stores not just the identity but also the spatial relations, in the scene as witnessed by the monkey, of the background items, the object displaced, and the reward. This memory allows the animal to remember later such things as: where was the reward in the scene; where was the door handle in the scene when object A revealed reward; where was this object when it was displaced; where was the monkey in relation to all these events. This memory depends on the fornix. Unlike memories (1) and (2), it can be used in: simple learning of the spatial position of the food reward in a single constant scene; learning the positions of food rewards in specific scenes which differ in their contents; learning that different spatial configurations of the background items predict different object-reward conjunctions; learning the significance of the monkey's own position in the scene.*

It would be wrong to conclude that fornix transection disrupts place memory. A better general conclusion is that the memory disrupted by fornix transection is like a snapshot memory, which stores not only the identity of visible stimulus items but also their spatial arrangement within the witnessed scene.

Gaffan & Harrison (1992) extended this result to complex naturalistic scenes (classifying stills from *Raiders of the Lost Ark*).

Spatial memory in rats (Barnes, 1988)

Post-lesion acquisition of spatial versions of reference and working memory tasks is disrupted after hippocampal formation damage, while the acquisition of cued versions reveals no impairment. [Working memory holds information within a trial, and reference memory holds information across trials. 'Cue' = e.g. visible water maze platform; 'spatial' = invisible.] Pre-lesion training results are more variable; the time between task acquisition and surgery is critical.

Old rats have dodgy hippocampi. The asymptotic levels of LTP do not decline, but the durability does, and this is related to the animal's performance on spatial tasks. NMDA antagonists block spatial learning, as does saturation of perforant path LTP.

Barnes on place fields. CA1 cells fire preferentially for a location in a maze (O'Keefe & Speakman, 1987). The characteristics of the cells' place fields were virtually the same on memory trials as on cue (perceptual) trials, as long as the animal chose the correct goal arm. If it confidently but incorrectly chose an arm as the goal, the place field of the cell was consistent in relation to where the animal thought the goal arm was located. Jones Leonard *et al.* (1985) showed that place fields in a familiar room were disrupted when the lights were out *only* if the animal was introduced into the room in darkness. The fields persisted beyong the time when the room lights were extinguished (for at least 30min) if the lights were turned out in the animals' presence.

Hippocampal cells have differential rates of firing in a place field depending on the direction the animal is facing, and the size of the place field scales when the animal is placed in a large or small cylinder in which the relative proportions of the visual features are preserved. The *local view hypothesis* suggests that animals form associations between local view of the environment and the body movements that link these representations; the *cognitive map* hypothesis is that there are two maps, of the controlled cues and of the fixed external cues, and that they are placed into register.

Mackintosh (lectures) cites evidence that rats do not have a 'map'. In particular, Sutherland *et al.* (1987): rats in a water maze only go directly to the goal if they have swum past the start point previously. See lecture notes.

Squire's (1992) summary: Memory and the Hippocampus

Humans.

- Damage limited to the hippocampus is sufficient to cause easily detectable and significant memory impairment [R.B.]
- The additional severity of H.M.'s deficit probably resulted from damage to other medial temporal lobe structures.

Monkeys

- Simple object-discrimination tasks and concurrent object-discrimination tasks, which require several object pairs to be learned together, are among the tasks sensitive to H^+ lesions.
- Monkeys with H^+ lesions (hippocampus and underlying cortex) can succeed at certain skill-based or habit-based tasks.
- The most widely used task sensitive to H^+ lesions is DNMTS. Performance is good when the delay between presentation and task is short, and becomes poorer as the delay increases.
- Monkeys with ischaemis lesions (ISC, cell loss mainly in CA1 and somatostatin cells of DG) have impaired memory, though less severe than with the H^+ lesion. On DNMTS, ISC monkeys are impaired to the same degree as H^+. On object discrimination and eight-pair concurrent discrimination, ISC monkeys perform better than H^+ lesions.
- The H lesion (hippocampus, DG and subiculum, but underlying cortex spared) looks exactly like ISC.
- So even incomplete damage to the hippocampus can produce detectable impairments for monkeys, as for humans.
- The H^+A^+ lesion produces more severe memory impairment than the H^+ lesion. But monkeys with the A lesion perform normally on four tasks (DNMTS, retention of object discrimination, concurrent discrimination, delayed response); monkeys with H^+ or H^+A^+ were impaired on all four. Similarly, H^+A lesions are no worse than H^+. So

amygdala damage does not impair memory, nor does it exacerbate impairment caused by damage to the hippocampus.

- The H^{++} lesion (H^{+} and anterior entorhinal cortex and much of the perirhinal cortex) causes a deficit on DNMTS nearly as great as $H^{+}A^{+}$ and significantly more severe than H^{+} or $H^{+}A$. Thus, lesions of the cortex surrounding the amygdala, but not lesions of the amygdala itself, exacerbated memory impairment in monkeys following hippocampal lesions. The H^{++} monkeys were also as impaired as $H^{+}A^{+}$ monkeys on object-discrimination learning.
- Lesions of perirhinal cortex and parahippocampal gyrus, sparing the hippocampus, amygdala and entorhinal cortex (PRPH) caused an impairment similar to that after $H^{+}A^{+}$ and H^{++}. This was not due to impaired amygdala function (have to check; perirhinal cortex does project to amygdala).
- So the cortical structures adjacent to the hippocampus (entorhinal, perirhinal and parahippocampal cortex) appear to participate with the hippocampus in a common memory function. The entorhinal cortex, which projects directly to the hippocampus, receives input from a limited number of cortical areas. The perirhinal and parahippocampal cortices (and the other cortical regions that project to entorhinal cortex) talk to a much broader extent of neocortex.
- It seems likely that the medial temporal lobe memory system influences memory primarily through its reciprocal projections with widespread areas of neocortex. Damage to the major efferent system of the hippocampal formation, the fornix, and damage to the major diencephalic target of the fornix, the mammillary nuclei, had only mild effects on memory using the same tasks. So note that impairment after fornix section or mammillary nuclei lesions is less severe than after damage to the hippocampal formation.
- Medial thalamus lesions also cause amnesia. The areas most often linked to memory functions are the medial dorsal nucleus, the anterior nucleus, the internal medullary lamina, and the mammillothalamic tract. Most of these regions have connections to either the hippocampal formation or the perirhinal cortex.

Rats

- Lesions of hippocampus or related structures (fornix or entorhinal cortex) impair performance on a wide variety of memory tasks. These include spatial memory tasks, odor-discrimination learning, timing tasks, and discrimination tasks that require learning relationships between stimuli.
- It is certain that hippocampal lesions or lesions of anatomically related structures can produce an effect on memory where amygdala lesions produce no impairment and do not exacerbate the deficit. (There was one example of a visual Y-maze DNMTS that was not impaired by hippocampal lesions but was impaired by amygdala+hippocampus lesions; this might be because rats use a different strategy to monkeys.)
- The amygdala in rats and monkeys is important for other functions, including the acquisition of conditioned fear and the establishment of affective significance for neutral stimuli. It is possible that it also has a more general role in making associations across modalities, but that was Murray & Mishkin (1985), so they probably zapped cortex.
- Just as in monkeys, the deficits produced in rats by restricted hippocampal lesions can be increased by additional damage to anatomically related structures and fibre tracts (such as the subiculum or the alveus).

Multiple Memory Systems

- Amnesic patients show normal priming (the test must not use conventional memory instructions), and learn motor skills.
- The kind of memory that depends on the hippocampus and related structures has been termed *declarative* in humans.
- **Recall, recognition and feelings of familiarity.** Amnesics perform poorly on tests of recall and recognition, and have a diminished feeling of familiarity (low confidence in their recognition choices). Recall, recognition and feelings of familiarity seem to be tightly linked functions of declarative memory [recognition memory need not benefit from priming, for example]. Some reports found that recall can be disproportionately impaired in amnesia; it may be that frontal lobe damage affects recall more than recognition, because recall is affected more by impaired search strategies and impaired ability to organize incoming information. Perceptual fluency [priming] may sometimes contribute to recognition performance but its contribution is slight when explicit, conscious memory is readily available.
- **Spatial memory.** Hippocampal lesions impair nonspatial memory as well as spatial. Squire considers both to be aspects of declarative memory. Note that some tasks that purport to test spatial memory (object–place memory compared to visual recognition memory) may differ in that one requires recall and one just recognition… Performance is spared on some nonspatial tasks (in rats, monkeys and humans) not because they are nonspatial but because performance on these tasks depends on a broader class of (nondeclarative) memory.
- **The role of the hippocampal formation: establishing conjunctions.** A device for forming conjunctions between ordinarily unrelated events? LTP. [Psychological examples: stimulus–spatiotemporal conext = new episode; fact–semantic context = new concept.]
- **Configural associations,** as opposed to simple associations. Best example: rats with hippocampal lesions cannot learn a negative pattern discrimination (L+, T+, LT–). But it's hard to define which tasks require a *configural* strategy (when is a stimulus unitary?).

- **Relational and flexible memory.** But it's difficult to predict which system will be used; humans are declarative and will use hippocampus-dependent memory, where rats will readily adopt a simple associational strategy. When stimuli are recombined (so A+B– and C+D– become A+D– and C+B–), fornix- or hippocampus-lesioned animals cannot use the information acquired previously about the value of the two elements that comprised each combination. They behave inflexibly, as if the recombined stimuli constitute new problems.
- **Nondeclarative memory.** Includes skillful behaviour or habits (perceptuo-motor, perceptual and cognitive skills), simple conditioning (including emotional learning), priming, and other instances where experience changes the facility for operating in the world but without affording conscious access to past episodes. Whereas declarative memory concerns recollection, nondeclarative memory concerns behavioural change. In nondeclarative memory, information is acquired as changes within specific perceptual or response systems, independently of memory for the prior encounters that led to behavioural change.
- Different brain systems appear to be involved in these kinds of learning. Skill learning and habits depend on the integrity of the **neostriatum**; conditioning of skeletal musculature depends on the **cerebellum**; emotional conditioning depends on the **amygdala**; some kinds of priming depend on early-stage proocessing systems in posterior neocortex.
- **Skills and habits.** Skills in humans are typically acquired gradually and without conscious memory of what kind of information has been acquired. (Amnesics are useful: if they perform OK, a given task doesn't depend on declarative memory [but beware the potential for circularity!].) Examples: motor skills, perceptuo-motor skills, perceptual skills, early-stage cognitive skills… experience of lifting weights affects future performance [amnesics perform normally, as do AlzD but not HD patients], reading skill for regularly repeating non-words, mirror-writing…
- *Habits.* Some habitlike tasks that are intact in animals with hippocampal lesions are impaired by lesions of the caudate (the win-stay task, the 24-hr concurrent task). For example, in the monkey, inferotemporal cortex (area TE) is necessary for visual recognition memory and for the 24-hr concurrent task; recognition memory depends on TE and the hippocampus, while the 24-hr concurrent task (a test of habit memory) depends on TE operating with the caudate.
- *Classification learning.* Amnesics can learn to classify letter strings according to an artificial grammar as well as controls. But they were impaired at recognizing the exemplars that had been used to teach these rules. So classification judgements do not occur only by direct and explicit comparison with stored exemplars. Instead, it seems likely that two systems are involved in classification learning: one stores exemplars (hippocampus and related structures), the other allows for the gradual development of rule-based behaviour (neostriatum?).
- *Conditioning.* Without a hippocampus, subjects can learn eyeblink conditioning, heart-rate conditioning and skeletal measures of conditioned fear. But the hippocampus is important for effects of context.
- *Priming:* an increased facility for detecting/identifying stimuli as a result of their prior presentation. Priming can involve the acquisition of new knowledge, not simple the activation of preexisting knowledge. Amnesics show priming. One kind of priming ('direct' or 'repetition' priming) has been shown to be associated with reduced blood flow in posterior sensory cortex. For example, right extrastriate cortex blood flow is reduced in word-stem completion priming. Aand following central presentation of words, the right hemisphere shows a priming advantage [words shown to one visual field], but only when the items were presented in the same modality and in the same letter case as the initial presentation. It has been suggested that priming of words occurs in a LHS word-form system, specialized for the abstract processing of words, and that priming of visual objects might occur in a RHS structural description system. (Word-completion priming by LHS was not affected by changes in letter case, while RHS priming was diminished, *t. ex.*) Priming is quite specific compared with declarative memory; priming effecgts are readily diminished by altering the physical features of the orginal items. Declarative memory is much less sensitive to this. Yet you don't need to present precisely the same word form or object to see full priming. This suggests that priming occurs in systems that have extracted some surface, physical features and that are already processing a somewhat abstract version of the stimulus. Nevertheless, priming effects are strongly determined by structural featres of the perceptual obejcts that was originally presented.
- Nondeclarative memory can support learning of specific information (one- and multiple-trial learning), novel information (one- and multiple-trial) and new associations (multiple-trial learning only). One-trial acquisition of new associations probably requires declarative memory. Priming of new associations, although dissociable from other measures of declarative memory in normals, is impaired in amnesics, suggesting that a significant part of this effect depends on declarative memory. To exhibit priming of new associations between semantically unrelated words may require subjects to access a link that was formed declaratively.
- **So** nondeclarative (implicit) memory is specialized for incremental, cumulative change: new associations can be formed but require multiple presentations. The acquired knowledge is relatively inflexible, and the confidence rating assigned to patients' choices should be low. The hippocampus is specialized to form associations rapidly between arbitrary elemtents. Taste aversion may be an exception: this can occur in one trial and (probably; controversy) does not require the hippocampus.
- **Scanning techniques.** At the time of encoding, ERPs to words that were subsequently recalled (Paller, 1990) were more positive than ERPs to unrecalled words; the difference was most anteriorly. In contrast, ERPs to words that were subsequently primed were not significantly different from ERPs to words that were unprimed (and the small difference was greatest posteriorly). Similarly, using PET (Squire *et al.*), when word stems are

presented with instructions to form the first word that comes to mind (priming instructions), there was reduction in blood flow in right extrastriate cortex. If subjects were instructed to complete word stems with study words (memory instructions), there was an increase in blood flow in the right hippocampal region.

- **Time-limited role of the hippocampus.** The hippocampus has only a temporary role in memory storage.
- In humans, there seem to be two levels of memory impairment: a moderately severe anterograde amnesia and limited retrograde amnesia with damage to CA1 only, and more severe anterograde and retrograde amnesia associated with more extensive damage to the hippocampal region.
- Retrograde amnesia following hippocampal lesions shows a temporal gradient. It is stable. It is not the case that retrograde amnesia can be mitigated by changing the test procedure (Warrington & McCarthy, 1988, shot down in flames. They had redesigned a remote memory test as a semantic memory test and used one patient).
- Autobiographical and factual retrograde amnesia are associated. Usually temporally graded with sparing of very remote memory.
- Severe and ungraded [no temporal gradient] retrograde amnesia requires damage in addition to (or different from) the medial temporal lobe and midline ediencephalic structures usually associated with circumscribed amnesia. Cortical damage will do (AlzD, encephalitis, head trauma left temporal lobectomy, HD, some cases of diencephalic amnesia). This amnesia need not be associated with severe anterograde amnesia (left temporal lobectomy: only mild anterograde amnesia but extensive and ungraded retrograde).
- Memories *are* reorganized or consolidated with time after learning (was difficult to distinguish from differential attrition of memories, see p221). Sparing of remote memory in amnesia is not based on greater rehearsal or repetition.
- The retrograde amnesic gradient varies with species: mice (1–3 weeks), monkeys (2–12 weeks), humans (1–3 years). Consolidation in slower in more complex nervous systems; it is likely that neuroplasticity develops more slowly in more complex nervous systems (e.g. seconday 'mirror' epileptic foci develop more slowly in cats/monkeys than in frogs/rats/rabbits; Wilder, 1972).
- When damage is limited to CA1 in humans, retrograde amnesia is limited to 1 or at most 2 years. If damage to the hippocampal formation is more complete, retrograde amnesia can be extensive and temporally graded across a decade or more.
- Very plausible that the hippocampal formation temporarily binds together (LTP) the areas in neocortex that originated the convergent input. Adjacent cortex is probably also a site of plasticity. In this view, simultaneous and coordinated neocortical activity is sufficient for perception and STM. When one shifts one's attention to something else and tries to retrieve the original memory, a partial cue that is processed through the hippocampus may reactivate all of the bound sites. Consolidation occurs, so the role of the hippocampus diminishes. In the neocortex, first, forgetting occurs as new connections interfere with old, as well as actual weakening of existing connections. Second, the distributed networks that constitute a memory develop greater coherence, perhaps by developing functional corticocortical connections or by representing information in a more efficient form.

Functions of adjacent cortex (Suzuki, 1996; Murray, 1996)

Perirhinal cortex – prominent input from unimodal visual areas TE, TEO: important in visual object memory.
Parahippocampal cortex, area TF – input from visuospatial areas: important for spatial memory?
Parahippocampal cortex, area TH – auditory memory?
Entorhinal cortex – receives from perirhinal and parahippocampal cortex: higher-order or integrative memory?
These systems also have substantial interconnections with other systems important for nondeclarative memory.
Very good simple diagram of connections (p11).
The rhinal cortex (but not A or H) is critical for the learning of (visual) stimulus–stimulus associations.
The amygdala is *not* critical for cross-modality S–S associations.

Incremental and decremental responses in temporal cortex (Brown, 1996)

Decrements and increments in response in anterior inferior temporal and perirhinal cortex.

Decrements are specific to a stimulus (➔ decrement is specific to a subset of synapses onto the cell). They survive distractors. They are insensitive to reinforcement value.

The "synapse specificity" argument is supported by Ringo *et al.* (1994). Monkeys with sectioned optic chiasm and partially sectioned corpus callosum. Stimulus presented to one eye, then the other. Cells which showed decrements to the stimulus when it was presented twice to one eye didn't show it in this case (suggests visual signals from the two h'sphere converge on the cell through two sets of synapses, commissural and associational). But no "second-order" cells showing response decrements were found in inferior temporal cortex, as might be expected if the first cell projected to another. So either such cells exist elsewhere or another mechanism is used, because the animal can perform the delayed matching task [though worse if the second presentation was to the other eye].

They are up to 50% from first to second stimulus presentations, even with novel stimuli.

Many nearby neurons show no such changes.

Why? (1) Attention to novelty pays. (2) Novel stimuli require more processing; conversely, familiar stimuli may be processed faster. (3) Most stimuli are familiar; energy usage minimized, processing capacity maximized.

Memory spans of these cells vary: 1min to 24h (with >100 distractors).

There are *recency neurons* (respond less when a stimulus is seen a second time, insensitive to relative familiarity) and *familiarity neurons* (respond less to familiar stimuli regardless of whether a stimulus has been presented recently).

The responses are probably generated locally, based on the lack of earlier such responses elsewhere. They are probably not dependent on hippocampal input (1– while some decremental responses are seen there, hippocampal neuron memory spans too short; 2 – perirhinal/TE latencies are shorter; 3 – excitotoxic H lesions do not impair DNMTS while perirhinal lesions do.)

Increments are rare to simple presentation. But incremental responses are more frequent when a monkey must discriminate repeated presentations of a rewarded and an unrewarded stimulus. 1/3 of the cells which respond to the rewarded stimulus show an increment; 2/3 decrement. The cells that decrement also decrement to non-target stimuli. The cells that increment show no change to repeated non-target stimuli.

Other places, including basal forebrain.

The responses observed would be sufficient to enable solution of all the behavioural tasks.

Scopolamine (impairs recognition memory) has no effect on the responses (affects PFC?) but lorazepam, a BZ that impairs recognition memory and priming, abolished decremental responses in TE and perirhinal cortex.

Recognition memory has been doubly dissociated from priming, but recency memory hasn't. "Recency neurons" may support recency memory and priming.

Memories and habits (Gaffan, 1996)

Rhinal cortex is specialized for identifying individual stimuli. Lesions impair trial-unique matching/nonmatching, but if two stimuli are used repeatedly in concurrent discrimination, monkeys can cope.

Visual learning for a visual or auditory secondary reinforcer requires only the link between visual association cortex and the corpus striatum. It survives lesions of the amygdala, fornix and uncinate fascicle [no association cx–PFC link]. It is not well described as a habit: the monkey makes a careful long-latency choice, based on events of a few seconds ago.

While PFC lesions may impair reward-association learning and recognition memory, lesions of the uncinate fascicle, which links visual association cortex with PFC, do not. The PFC, then, exerts its influence by a convergent projection into the corpus striatum alongside that from the visual association cortex of the temporal lobe.

Associating stimuli with primary reinforcement involves the amygdala. However, the amygdala may do this through its projections to the corpus striatum. However, visual learning for primary reinforcement recovers somewhat after amygdalectomy; the amygdala may act in this case as an adjunct to a basic corticostriatal learning mechanism.

What motor control needs to be exerted by a corticostriatal pathway? Visual fixation of the rewarding stimulus may be enough, other actions following from it.

The basal ganglia and procedural memory (Wise, 1996)

"The basal ganglia (pallidum, striatum and catecholaminergic input from the midbrain) are among the oldest and most conservative features of the vertebrate brain." [But see below!]

"Habits": stored S–R associations that are (a) slowly learned; (b) relatively stable over time, except under extinction conditions; (c) transferred poorly among effector systems and behavioural contexts; (d) unavailable to consciousness.

HD and/or PD patients have had deficits in: mirror reading, rotary pursuit, Tower of London, serial reaction-time tasks (speeding reactions based on repeated movement sequences). What distinguishes HD patients from control is a rapid plateau in acquisition; initial learning is normal. Wise doesn't believe the clinical data supports the habit tasks. Basal ganglia does not disrupt the most automatic and well-learned behaviours. The impairments might be interpreted as resulting from the persistence of automatic behavioural routines rather than a deficiency in them. (Mirror reading = persistence of normal reading habits; rotary pursuit = persistence of old motor skills; etc.) The data are as consistent with the **basal ganglia mediating changes from prevailing response rules**. For example, HD patients couldn't use experience of weight lifting to influence their perception about weight; this is an inability to modify programmed movement parameters.

Much of the basal ganglia system, especially those parts that receive the most direct from extrastriate visual areas, is thought to lack direct access to motor or premotor cortical areas and to send its output instead to the PFC. Thus, the basal ganglia would not appear to be privileged sites for sensorimotor associations.

There is no sound reason to believe the striatum is phylogenetically older than either the cerebral cortex [but it's older than neocortex] or the limbic system. So there is no basis there for assigning habit formation to the basal ganglia as opposed to archicortex or paleocortex.

Models. Houk & Wise (1995) proposed a model in which motor outputs are determined by the input-output processing of a number of distributed neural modules, many of which involve the corticocortical connections of the frontal cortex. They proposed that learning in frontal networks may be guided by forcing functions provided by its main subcortical inputs, in partucular those from basal ganglia and cerebellum, as those signals are transmitted through thalamic relays. The basal ganglia and cerebellar inputs would alter synaptic weights in the cortical network to gradually produce a particular input-output function, until the cortical network is efficient and automatic. This is the mirror-image of the habit hypothesis (in which higher order cortical areas train the basal ganglia)!