

REVIEW ARTICLE

Elements of a neurobiological theory of hippocampal function: the role of synaptic plasticity, synaptic tagging and schemas

R. G. M. Morris

Laboratory for Cognitive Neuroscience, Centre for Cognitive and Neural Systems, The University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, Scotland

Keywords: episodic memory, episodic-like memory, LTP, memory consolidation, paired-associate learning

Abstract

The 2004 EJN Lecture was an attempt to lay out further aspects of a developing neurobiological theory of hippocampal function [Morris, R.G.M., Moser, E.I., Riedel, G., Martin, S.J., Sandin, J., Day, M. & O'Carroll, C. (2003) *Phil. Trans. R. Soc. Lond. B Biol. Sci.*, **358**, 773–786.] These are that (i) activity-dependent synaptic plasticity plays a key role in the automatic encoding and initial storage of attended experience; (ii) the persistence of hippocampal synaptic potentiation over time can be influenced by other independent neural events happening closely in time, an idea with behavioural implications for memory; and (iii) that systems-level consolidation of memory traces within neocortex is guided both by hippocampal traces that have been subject to cellular consolidation and by the presence of organized schema in neocortex into which relevant newly encoded information might be stored. Hippocampal memory is associative and, to study it more effectively than with previous paradigms, a new learning task is described which is unusual in requiring the incidental encoding of flavour–place paired associates, with the readout of successful storage being successful recall of a place given the flavour with which it was paired. NMDA receptor-dependent synaptic plasticity is shown to be critical for the encoding and intermediate storage of memory traces in this task, while AMPA receptor-mediated fast synaptic transmission is necessary for memory retrieval. Typically, these rapidly encoded traces decay quite rapidly over time. Synaptic potentiation also decays rapidly, but can be rendered more persistent by a process of cellular consolidation in which synaptic tagging and capture play a key part in determining whether or not it will be persistent. Synaptic tags set at the time of an event, even many trivial events, can capture the products of the synthesis of plasticity proteins set in train by events before, during or even after an event to be remembered. Tag–protein interactions stabilize synaptic potentiation and, by implication, memory. The behavioural implications of tagging are explored. Finally, using a different protocol for flavour–place paired associate learning, it is shown that rats can develop a spatial schema which represents the relative locations of several different flavours of food hidden at places within a familiar space. This schema is learned gradually but, once acquired, enables new paired associates to be encoded and stored in one trial. Their incorporation into the schema prevents rapid forgetting and suggests that schema play a key and hitherto unappreciated role in systems-level memory consolidation. The elements of what may eventually mature into a more formal neurobiological theory of hippocampal memory are laid out as specific propositions with detailed conceptual discussion and reference to recent data.

Memory and the hippocampal formation

The term 'memory' is used scientifically in a number of different ways: to refer to the capacity to encode, store and retrieve information, to a hypothetical store in the brain, to the contents of that store, and even to a person's phenomenological experience of remembering. Neuropsychologists now generally prefer the first of these definitions, emphasizing the sense that memory is a brain process (Tulving, 2000) rather than being a store, or items of information in such a store, or any particular form of mental experience. They also recognize that there are variety of different 'types' of memory. These are often distinguished in a binary manner with respect to whether information is being retained for a short or a long time (Baddeley, 2001), is

propositional or nonpropositional (Tulving, 1983), and whether its expression is consciously explicit or implicitly expressed as a behavioural disposition (Graf & Schacter, 1985). Given the central role that these different facets of memory plays in human life (in many respects defining a person's individuality) a grand challenge in neuroscience is to understand the neural mechanisms of the capacity to encode, store and retrieve, and to transform unstable memory 'traces' into more lasting biochemical and structural changes in the nervous system (Squire, 1986). Improving our understanding of memory is not only a worthy scientific goal but also one which might impact on translational issues such as the development of novel therapeutics or improved types of artificial cognitive systems (Morris *et al.*, 2005).

This grand challenge of understanding the brain mechanisms of memory can be approached in a 'top-down' or a 'bottom-up' manner but, whatever research strategy is pursued, the scientific goal is to understand the 'mechanism' at many different levels of analysis. For

Correspondence: Professor R. G. M. Morris, as above.

E-mail: r.g.m.morris@ed.ac.uk

Received 28 February 2006, revised 29 March 2006, accepted 30 March 2006

some, the term mechanism is synonymous with 'molecular mechanism'. In contrast, the integrative view taken here is that, for any given type of memory, we need to know what brain regions are implicated, what patterns of neural activity (spiking and local synaptic potentials) are involved, and what signal-transduction pathways, transcriptional or translational processes are activated in distinct memory processes (such as encoding, consolidation or retrieval). Identifying the molecular players is certainly very important, but is only one strand of this analysis. There are many others, including a deeper understanding of local circuits and the information-processing algorithms whose computations they enable, the specification of representational codes in which information is neurally encoded, and the relative roles of fast and modulatory neurotransmission in determining the persistence of memory traces, to mention but a few of the several tasks before us. A 'brain systems' analysis of memory is one which must make contact with observations at many different levels of analysis in an integrative manner (Churchland & Sejnowski, 1992; Kandel & Squire, 2000). At present, there is no type of memory for which we have both an adequate neuropsychological framework and a mapping of this analysis onto underlying brain systems, not least because the task is both conceptually and technically demanding, particularly the linking of different levels of analysis. However, considerable progress has been made, particularly in realizing a neuropsychological understanding the role of the hippocampal formation in memory and, in capitalizing on that understanding, there may be a real prospect of achieving a neurobiological theory of memory.

The mammalian hippocampal formation is a set of brain structures which, in both humans and animals, is widely held to serve an important function in certain types of memory. Neurological patients with damage to the hippocampal formation show memory deficits. From these clinical origins, a diverse field of memory research has flowed. The specific functional contributions of the hippocampus and those of related structures (the entorhinal cortex, the dentate gyrus, the individual CA fields and the subicular complex) remain a matter of dispute. Rival neuropsychological theories include proposals for a role in cognitive mapping and scene memory (O'Keefe & Nadel, 1978; Gaffan, 2001), declarative and relational memory (Squire, 1992; Eichenbaum & Cohen, 2001), the rapid acquisition of configural or conjunctive associations (Sutherland & Rudy, 1989; O'Reilly & Rudy, 2001), context-specific encoding and retrieval of specific events (Hirsh, 1974; Good & Honey, 1991) and the proposal that the hippocampal formation is critical for certain aspects of episodic and/or episodic-like memory (Tulving, 1983; Mishkin *et al.*, 1997; Morris & Frey, 1997; Vargha-Khadem *et al.*, 1997; Aggleton & Brown, 1999). To complement this complexity, neural network modelling studies indicate that its intrinsic anatomy and synaptic physiology could mediate the rapid encoding and distributed storage of a large number of arbitrary associations (Marr, 1971; McNaughton & Morris, 1987; McClelland *et al.*, 1995; Rolls & Treves, 1998). Both approaches suggest that in all mammals, be they man, monkey or mouse, the hippocampus is a particular kind of associative memory network. It does not operate in isolation as several excitatory inputs and outputs reflect important functional interactions with the neocortex (Amaral & Witter, 1989; Witter *et al.*, 2000) and inputs from midbrain and other forebrain nuclei modulate its activity in critical ways for memory formation (Matthies *et al.*, 1990). Comprehensive reviews of these neuropsychological theories and computational models have revealed strengths and weaknesses of each approach (Burgess, 2006; Morris, 2006).

This article outlines elements of an emerging neurobiological theory of hippocampal function that builds upon these foundations. As a

neurobiological theory, it endeavours to make reference to a number of ideas at other levels of analysis: anatomy, physiology and plasticity. More specifically, it builds upon Tulving's 'serial, parallel, independent' (SPI) framework (Schachter & Tulving, 1994) and, with it, the idea that hippocampal memory includes the ability to remember events and episodes. One key supporting observation is that early damage to the hippocampus can affect this type of memory selectively (Vargha-Khadem *et al.*, 1997; Duzel *et al.*, 2001; Maguire *et al.*, 2001). Other structures, notably the frontal lobe, certainly contribute to episodic memory as well through its role in executive function and working memory. The emphasis upon 'automaticity' of some aspects of episodic encoding builds upon earlier frameworks outlined by the author (Morris & Frey, 1997; Morris *et al.*, 2003) and upon ideas developed by Miyashita concerning the differential role of anterior and temporal structures in deliberate vs. more automatic control of memory (Miyashita, 2004). The specific 'elements' of the theory to be outlined below are that (i) the hippocampus and associated structures are involved in the rapid, automatic aspects of context-specific event encoding and retrieval, and that synaptic plasticity is critically involved in the mediation of this process; (ii) such a system needs two separate but temporally interdigitating mechanisms of memory consolidation; and (iii) the creation of lasting event-context memories involves the integration of new information with existing mental frameworks or schemas.

Elements of a neurobiological theory of the hippocampus

Events happen in particular places at particular times, and their later recall generally includes the memory of where an event happened (Gaffan, 1994). Thus, event encoding is necessarily associative in character. Many events cannot be anticipated, occur only once, and may contain distinct features which, in sequence, form short episodes. It is vital that traces representing information about such episodes are encoded and stored in real time, as they happen, a process I and my research colleagues have characterized as the 'automatic recording of attended experience' (Morris & Frey, 1997; Morris, 2001; Morris *et al.*, 2003). Automaticity has a number of implications which lead to predictions and thence to the design of novel behavioural experiments with animals. The reference to encoding and storage also raises the question of what is stored. Although much harder to examine experimentally, it is far from clear that the hippocampus need receive via its extrinsic afferents, neural representations of the detailed sensory and/or perceptual information pertaining to individual objects or events. Rather, all it needs in order to remember events and the sequence in which they happen are 'cartoons' or 'indices' of the locations in the neocortex where this detail is processed and, at least temporarily, is encoded, an idea first proposed by Teyler & DiScenna (1986). Unfortunately, the task of distinguishing between index and detailed representational memory using ensemble unit recording data or other approaches is, presently, unsolved. This feature of the theory will therefore be asserted but otherwise not addressed.

Elements of neurobiological theory of the hippocampal formation

The first step of the present neurobiological framework (Table 1, Proposition 1, Encoding and storage) states that, if events are to be encoded, there must exist physiological mechanisms for capturing events on-line as they happen and rapidly encoding relevant memory traces which could later enable the retrieval of event-associated

TABLE 1. Elements of neurobiological theory of the hippocampal formation

1. Encoding and storage
Activity-dependent hippocampal synaptic potentiation is critical for the 'automatic recording of attended events' (a sub-component of episodic-like memory). The memory traces in hippocampus are indices of locations in neocortex where more detailed sensory and/or perceptual features of information are stored.
2. Cellular consolidation
The 'flip-side' of automaticity is the rapid decay of hippocampal memory traces to avoid saturation of the distributed associative storage in hippocampus. However, if encoding happens around the time of the synthesis, distribution and synaptic capture of 'plasticity-factors' at tagged synapses, index traces in hippocampus persist longer.
3. Systems consolidation
These hippocampal traces enable, through indirect association, a 'systems consolidation' process which builds connections between relevant cortical modules. This can sometimes be very rapid when consolidation involves the interaction with activated associative 'schemas' stored in neocortex.
4. Novelty detection
Intrinsic hippocampal circuitry automatically detects mis-match between stored and current information which then re-engages the encoding process. This enables stored information to be updated by new events. Shutting down GABAergic inhibition may contribute to the process of re-engaging memory encoding.

information. This recording process may occur at several points, including the level of area CA1 of the hippocampus which, importantly, receives (i) excitatory inputs from both the lateral and medial entorhinal cortex, and (ii) a separate excitatory input via the intrinsic Schaffer collaterals (Fig. 1). The former inputs, projected via the perforant path input from layer III of the entorhinal cortex (EC), could represent information pertaining to spatial location, such as about a familiar context in which new events are occurring. This would be derived from a re-activation of stored memory representations in neocortex upon re-exposure to the familiar environment. The second input, processed via the classical tri-synaptic circuit of the hippocampus, which courses from layer II of the EC to the dentate gyrus (DG), from the DG to area CA3 of the hippocampus, and then from CA3 to CA1, could involve representations of events including information about the sequence in which they occurred (i.e. episodes). The association of these two inputs (spatial, a; events, b) would then be realized by hippocampal NMDA receptor-dependent synaptic plasticity at CA1 synapses. Assessed via the experimental phenomenon of long-term potentiation (LTP), this plasticity exhibits many physiological properties that are suitable for a role in memory formation (Bliss & Collingridge, 1993) and is embedded into the appropriate anatomical circuitry (McNaughton & Morris, 1987). A growing body of evidence offers support for this view (Martin

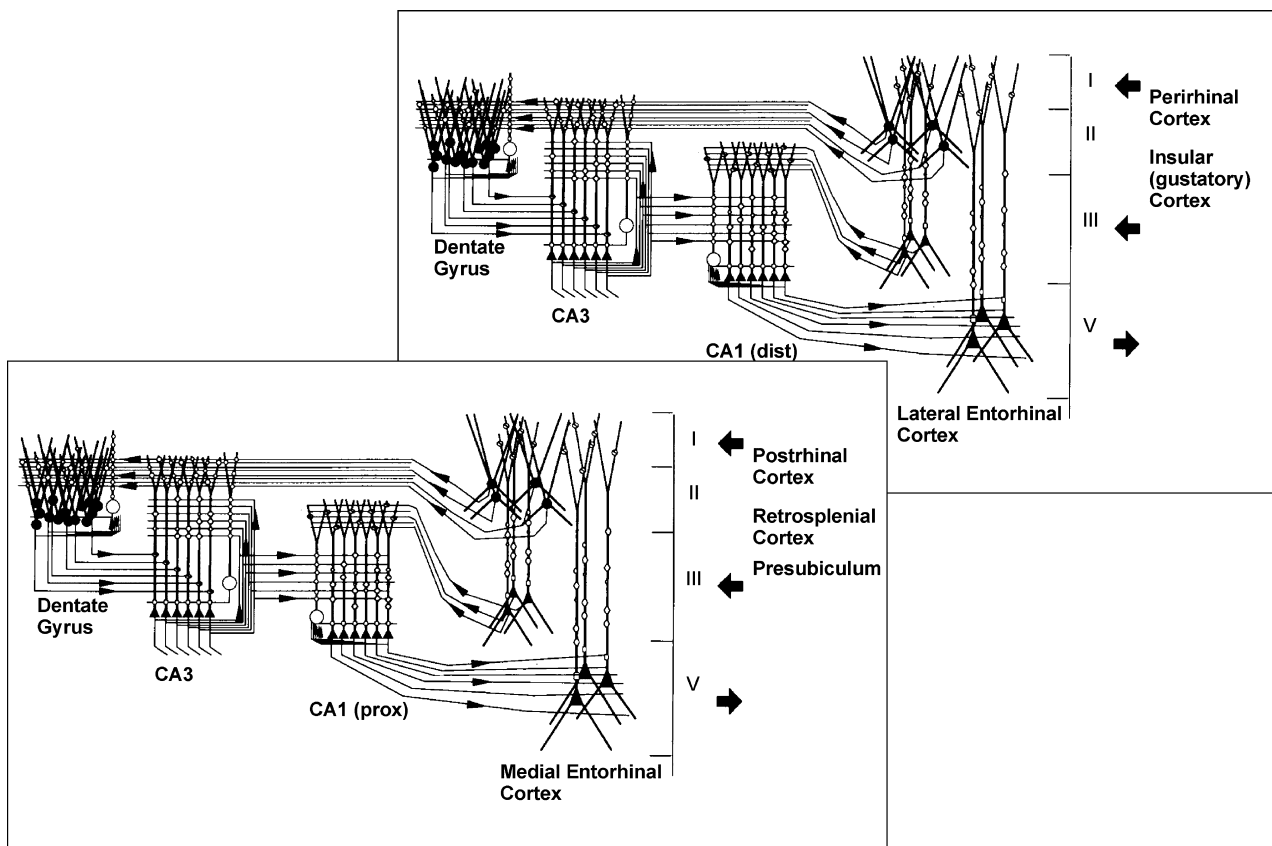


FIG. 1. Neuroanatomical organization of the hippocampal formation. A simplified framework showing sets of principal neurons [filled large circles and triangles, in CA1, CA3 and dentate gyrus (DG)] which have modifiable synapses at either external or internal inputs (nonpotentiated synapses, small open circles; potentiated synapses, small filled circles). The simplification excludes important structures within the subicular complex and assumes only one type of feedforward and feedback inhibition. Theoretical calculations suggest that the hippocampal formation should be able to store many different patterns within such a matrix, and retrieve complete patterns when presented with unique subpatterns (Treves & Rolls, 1994). Two parallel functionally different networks are indicated, one involving the medial entorhinal cortex, the other the lateral entorhinal cortex. Note the different input-output relations, in particular with other parts of the parahippocampal region, of the two subdivisions of the entorhinal cortex (Witter *et al.*, 2000). Diagram courtesy of Menno Witter and the Centre for the Biology of Memory (NTNO, Trondheim).

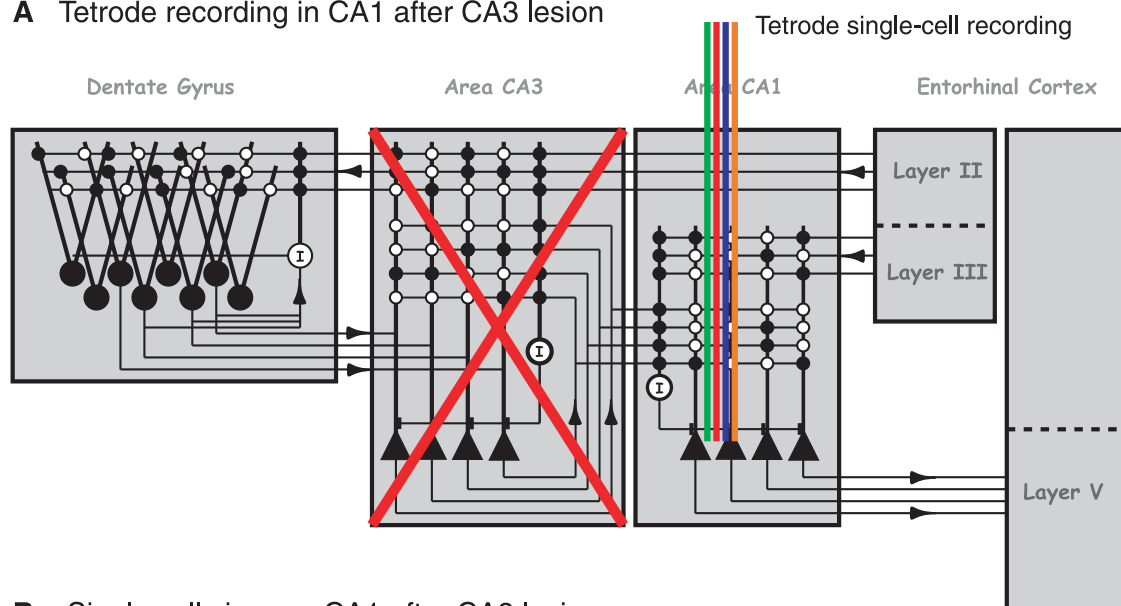
A Tetraode recording in CA1 after CA3 lesion**B** Single cells in area CA1 after CA3 lesion

FIG. 2. Intact place fields in rats with CA3 dysfunction. (A) An equally simplified and stylised version of the network in Fig. 1, now also showing the location of a tetraode multiple single-cell electrode in a freely moving rat to record action potentials from CA1 pyramidal cells (same terminology for cells and synapses as in Fig. 1). The large cross indicates a CA3 lesion or a re-section of the pathway interconnecting CA3 with CA1. (B) Colour-coded place-cell firing (red being the highest firing rate) for several CA1 pyramidal cells in CA3-lesioned rats. Note intact place fields. After Brun *et al.* (2002). Place-cell data courtesy of the Centre for the Biology of Memory (NTNO, Trondheim).



FIG. 3. The event arena. The 1.6-m square arena made of perspex consists of 49 sand-wells, the two intramaze landmarks and the four start-boxes. The arena is typically covered in ~2 cm of sawdust masking the locations of the sand-wells. One sand-well is chosen, and the position of two start-boxes at the side of the arena is clearly visible. On a sample trial, the rat runs from the start-box to find this single sand-well, digs in the sand, and retrieves food which it typically eats back in the start-box. Despite no other contingent requirement on the trial, the rats typically encode the location in the arena where that particular food was found on that day.

et al., 2000; Martin & Morris, 2002; Bliss *et al.*, 2006). The first line of experimentation to be described below relates to this first proposition.

Several findings suggest that spatial information can be generated and stored upstream of the hippocampus. First, location-specific firing is already expressed in the superficial layers of the entorhinal cortex

(Quirk *et al.*, 1992; Frank *et al.*, 2000; Fyhn *et al.*, 2004; Hafting *et al.*, 2005). It is possible that spatial firing in superficial entorhinal neurons depends on spatial input from cells in deep layers, which in turn relies on associative computations in afferent hippocampal structures. However, place fields can be observed in CA1 both after selective lesions of the dentate gyrus (McNaughton *et al.*, 1989) and after disconnection of CA1 from CA3 (Brun *et al.*, 2002). In CA3-lesioned animals, CA1 pyramidal neurons receive cortical input only via the direct connections from the entorhinal cortex. The presence of place fields in these preparations (Fig. 2), recorded using optimal tetrode technology, suggests that direct entorhinal–hippocampal circuitry has significant capacity for transforming weak location-modulated signals from layer III of the entorhinal cortex into accurate spatial firing in CA1. Several simple filter mechanisms could accomplish such a transformation. For example, firing rates of perforant path fibres to CA1 could be thresholded by feedforward inhibition, such that only the highest afferent firing rates, i.e. those in the centre of the entorhinal place field, are able to drive postsynaptic neurons in the hippocampus. Alternatively, single EPSPs in distal pyramidal cell dendrites of CA1 may often not be sufficient to trigger somatic action potentials in these cells; reliable discharge may require summation of EPSPs, i.e. high afferent firing rates (Golding & Spruston, 1998; Golding *et al.*, 2002).

It is important to note that the computation and storage of positional information outside the hippocampus does not preclude the processing, storage and use of spatial information (or indices of such information) within the hippocampus. Indeed, the internal recurrent connectivity of hippocampal area CA3 makes the region highly suitable for storage of just this type of patterned information, at least for an intermediate period of time and possibly for longer (Abraham *et al.*, 2002). Recent results also suggest that plasticity in associative synapses of CA3 is necessary for the successful encoding of spatial information in a manner that later allows recall with partial cues (Nakazawa *et al.*, 2002). Mice with targeted deletions of NMDA receptors in CA3 were trained in a reference memory task in the watermaze. These mice were unable to locate the hidden platform on a recall trial with only a limited set of the landmarks used during training. However, when the full set of cues was available, retention was better and statistically indistinguishable from that of control animals. Place fields in CA1 were more dispersed than in control mice in the limited-cue condition, but not in the full-cue test. These findings suggest that the CA3 may support the CA1 under circumstances in which information about a familiar environment is incomplete; the CA3 circuitry will perform ‘pattern completion’ during the automatic recall of spatial information. Longitudinal axon collaterals in CA3 may also be important for the successful retrieval of such information, as memory retention may be impaired by a single transversely orientated cut through the dorsal CA3 region of each hippocampus (Steffenach *et al.*, 2002).

Propositions 2 (Cellular consolidation) and 3 (Systems consolidation) in Table 1 relate to the persistence of encoded memories and the need for two separate consolidation mechanisms: cellular and systems. Not all events are remembered for any length of time. A key supposition of the theory is that, notwithstanding the large storage capacity of the human brain, there is no need to store everything permanently and the system is not designed to do so. Most automatically encoded traces will fade and be lost. Only a few will persist. In fact, it is vital that this happens, the ‘flip-side’ of automaticity being the need to guard against saturation of the distributed associative memory systems in which trace storage occurs. If most automatically encoded event memories are temporary, there must be psychological processes and neural mechanisms for selecting

the subset of traces that are to be rendered longer lasting or even permanent. The determinants of these processes include the content of the information itself and the emotional significance of the event to be remembered or, more accurately, of it and other events happening close together in time. Persistence of memory will also be determined by the relevance of ongoing events to the existing knowledge structures and interests of the person witnessing them (Bartlett, 1932; Bransford, 1979), an idea long known in educational circles but which has had curiously little impact on neuroscience (Maguire *et al.*, 1999). Addressing this latter issue leads to certain novel experiments which are also discussed below, albeit at an early stage of the research programme.

Mediating these psychological processes of persistence are two separate mechanisms of memory consolidation: (i) cellular consolidation mechanisms which include the synthesis and synaptic capture of plasticity proteins that stabilize memory traces within neurons at the level of the individual synapse (Goelet *et al.*, 1986; Frey & Morris, 1998b); and (ii) systems-level consolidation mechanisms which reflect a dynamic interaction between populations of interconnected neurons within hippocampus and neocortex (Dudai & Morris, 2001). Understanding the mechanisms of cellular consolidation is presently a very active area of cellular and molecular research with considerable effort being devoted to identifying the key signal transduction pathways and relevant gene activation (Sweatt, 2003). Cellular and systems consolidation are distinct but also interdependent because the products of cellular consolidation are stable memory indices in the hippocampus that can last long enough for the slower systems-level consolidation process to work. Accordingly, the time courses of these processes dovetail, with cellular consolidation providing an initial ‘filter’ on what might be retained. The synaptic tagging and capture hypothesis of cellular consolidation makes a number of ostensibly counterintuitive predictions at both the synaptic and behavioural levels of analysis, one of which is considered below.

In contrast to cellular consolidation, the underlying neural mechanisms of systems-level consolidation are less well understood. Its role is to ensure that initially labile memory traces in the neocortex become persistent. One theory holds that this requires a dynamic interaction between the hippocampus and neocortex which gradually enables the cortex to act as a stable associative memory, linking arbitrary items of information which have been connected in experience (Squire, 1992). Another asserts that long-lasting traces may exist for certain kinds of memory, e.g. spatial memory, but in hippocampus rather than neocortex (Nadel & Moscovitch, 1997), and there are now grounds for suspecting that, at least in rodents, the evidence is consistent with this view (Clark *et al.*, 2004; Martin *et al.*, 2005). A third perspective, introduced here, is that a neocortical site is more likely for long-lasting information but that gradual learning in the cortex is not inevitable. Distinct from the standard model, this alternative holds that cortex has the potential to be just as fast a learning system as the hippocampus but that it rapidly loses new transient connectivity unless new hippocampally processed information is interleaved within existing, activated neural frameworks or schema. This idea is a neurobiological version of the ideas originally developed by Bransford (1979). In the absence of these preconditions, consolidation must take place more slowly as the ‘standard theory’ has long supposed, but still by intersection with the hippocampus.

There is an important strand of anatomical thinking behind the standard theory but it is also compatible with the ‘schema’ alternative. The defining functional characteristics of associative networks such as the hippocampus are held by several theorists to include distributed representations, interleaved storage across multiple synapses and associative retrieval. These characteristics enable stored patterns of

activity to be 'completed' from partial fragments of the original input (Marr, 1971; McNaughton & Morris, 1987; Paulsen & Moser, 1998; Nakazawa *et al.*, 2002). Several factors determine the operating characteristics and storage capacity of such networks. One of these, emphasized by McNaughton *et al.* (2003), is connectivity density (i.e. the number of connections per cell) as it provides an anatomical basis for understanding an important feature of the relationship between hippocampus and neocortex. Specifically, the average connectivity within the cortex is too low to support the encoding of arbitrary associations (Rolls & Treves, 1998). The cortical mantle contains on the order of 10^{10} neurons, but each cortical principal neuron receives only $\sim 10^4$ connections. Thus, the average connection probability in cortex is only $1 : 10^6$. To overcome this apparent biological limitation, mammals seem to have evolved an arrangement whereby distributed associative memory between items represented in different sensory modalities can be accomplished through indirect associations mediated by a hierarchical organization (McNaughton *et al.*, 2003). In such a scheme, neocortical modules at the base of the hierarchy are reciprocally connected via modifiable synapses with one or more hippocampal 'modules' at the hierarchy's apex. These hippocampal modules include networks of cells in CA3 as well as the dentate hilus, both characterized by high internal connectivity as well as modifiable synapses. In CA3, each pyramidal cell is contacted by $\sim 4\%$ of the pyramidal cells of the same subfield (Amaral, 1990), implying that most CA3 pyramidal cells are connected via two or three synaptic steps (Rolls & Treves, 1998). This high degree of internal recurrent connectivity is probably sufficient to allow autoassociation, or association among individual elements of a patterned input (Marr, 1971). Activity patterns reflecting sensory detail in neocortical modules may generate a unique identifying pattern in such a network: the 'index' traces referred to earlier (Teyler & DiScenna, 1987). This higher-level index is no longer 'sensory' in any strict sense, but is stored associatively with other indices and the output may be fed back to lower-level neocortical modules via modifiable synapses. Activation of a cortical pattern (e.g. a specific flavour of food) could then result in activation of its index in the hippocampus. In turn, this could enable the retrieval of associated indices and thence the complementary pattern in the other cortical modules (e.g. where the food is to be found). Indirect associations would therefore enable memory retrieval between cortical modules which are initially too sparsely connected to do this directly.

This principle of 'indirect association' in memory (via hippocampal indices) places high demands on the synaptic storage capacity of the hippocampus, bringing the danger of saturation. Once saturated, learning can no longer proceed effectively (McNaughton & Barnes, 1986; Moser *et al.*, 1998). There are several ways in which this burden may be limited. One, as already noted, is via the rapid decay of a high proportion of the traces that are automatically encoded on-line. Heterosynaptic depression may also serve a normalizing function and so increase effective storage capacity (Willshaw & Dayan, 1990). A second way to relieve the burden, a key feature of the present neurobiological ideas, would be to ensure that what is stored in the hippocampus is merely an index of the neocortical sites of trace storage where the full sensory and/or perceptual details are encoded and stored. The third way of protecting against overload, the process of systems-level memory consolidation, would be to enable hippocampal associations that are repeatedly recalled (generally representing environmental regularities) to trigger the gradual development of low-level intermodular connections within neocortex. It is these connections that will later enable cortical retrieval in the absence of neural activity in the hippocampus. Identified originally through experiments on retrograde amnesia (Squire &

Zola-Morgan, 1991; Kapur, 1999), it is unlikely that insensitivity to brain damage is the adaptive pressure that led to the evolution of a systems-level consolidation process. The standard model of consolidation implies that, in part, its real function is to avoid the distracting 'recovery to consciousness' of irrelevant associations which could otherwise interfere with ongoing mental activities (Moscovitch, 1995). To work, it is vital that the intermodular connections which develop are appropriate to the associations represented. This requires the gradual interleaving of appropriate connections (McClelland *et al.*, 1995), perhaps during sleep (McNaughton *et al.*, 2003) and involving neocortical activity and gene activation (Bontempi *et al.*, 1999; Maviel *et al.*, 2004). The rate of consolidation may not be strictly time-dependent as it will be determined by the frequency with which hippocampal indices are reactivated.

There is, however, another way in which many of the key ideas of this framework can be incorporated into the alternative 'schema' model in which cortical learning could sometimes take place very rapidly. This would be if the slow process of developing intermodular connections within neocortex occurs as we develop the 'frameworks' or 'schema' into which we could, at the time and later, assimilate information. On this view, hippocampal index traces may still guide the process by which new information is subject to consolidation, but it would not do it by building new intermodular connections for each and every new item of information. Instead, new information might sometimes be rapidly incorporated into activated schema whose very existence is predicated by such intermodular connectivity, possibly by altering the synaptic weights of new, initially silent, connections. On this view, a schema may take a long time to build to start off with (as long as the period of time ascribed to memory consolidation in the standard model) but, once built, new information that pertains directly to a particular schema may be stored very rapidly in cortex. A prediction of Proposition 3 is therefore that damage to the hippocampus very soon after learning may not always result in retrograde amnesia. The interleaving of information into schema may sometimes occur very rapidly.

The last idea of the framework outlined above (Proposition 4, Novelty detection) relates to the detection of novelty and acting upon it. If the hippocampus is critical for building spatial representations and encoding events in relation to them, it is likely that neural activity there will reflect changes to the environment and be necessary for detecting them. This is not a new idea, the possible 'comparator' functions of the hippocampus having been extensively discussed before (Gray, 1982; Vinogradova, 1995; Gray, 2000). Evidence in favour of this proposition has come from many experiments on different forms of novelty detection, including studies of exploratory behaviour in which rats examine objects and landmarks in simple arenas. After exploring these for a period, the location of one of the objects is changed. This triggers renewed exploration but this is not just a sensitization effect, for the renewed exploration is directed towards the moved object (Save *et al.*, 1992). The misplace cells of O'Keefe (1976) and the more recent observations of neural firing in response to the movement of a hidden escape platform in a watermaze (Fyhn *et al.*, 2002) also suggest that the hippocampus, perhaps acting in concert with neuromodulatory systems, detects and represents change. This is Gray's 'comparator' function. What should and does then seem to happen is that inhibition is temporarily decreased and neural activity that promotes the encoding of new information related to the change is engaged (Paulsen & Moser, 1998). This feature of the theory is not discussed further as novelty detection seems to be a property of a number of different neural systems. There is still no principled understanding of why novelty detection should be so

diverse, but it is clearly a puzzle to which it will be necessary to return in due course.

Predictions and experimental observations

Proposition 1: automatic encoding of associative information via NMDA receptor-dependent synaptic plasticity

There have been a number of claims that vertebrates possess an episodic-like memory system analogous to at least components of human episodic memory. One-trial spatial working-memory tasks, such as delayed matching-to-place in a watermaze and T-maze alternation, are of this character (Steele & Morris, 1999; Aggleton & Pearce, 2001; Brown & Aggleton, 2001), but the argument is not watertight as these tasks might be solved using only stimulus familiarity (Griffiths *et al.*, 1999). A valuable breakthrough was the food-caching paradigm developed by Clayton & Dickinson (1998). They observed that scrub jays can recall 'what, where and when' using a paradigm in which, under laboratory conditions, the birds are required to cache both a favoured foodstuff (mealworms) and a less favoured foodstuff (peanuts) at various times in specific locations in sand-filled ice-cube trays that are surrounded by prominent and unique visual cues. This caching experience gives the animals an opportunity to encode which foodstuff is located where. When cache retrieval is allowed a short time later (a few hours at most) the birds preferentially seek out the mealworms. However, when caching is delayed for several days, a period over which the mealworms degrade, the birds preferentially search for peanuts. As the birds have a chance during training to learn that mealworms become distasteful to eat with the passage of time, the switchover with respect to which item to go for at retrieval indicates that the birds had some sense of the duration of time since the 'what–where' encoding had taken place. Their behaviour is, in effect, guided by a representation of what, where and when.

Inspired by this experiment, Day *et al.* (2003) developed a one-trial paired-associate task in an 'event arena' in which rats recall (rather than merely recognize) in which of two locations a particular flavour of rat chow is to be found within a large (1.6×1.6 m) arena (Fig. 3). There are various different ways in which such experiments can be conducted, but one example is as follows. In each of two sample trials given on each successive day of training, rats leave the start-box to run around, find and then dig in a single open sand-well where they find flavoured food (Fig. 4A). There is no choice to be made on these sample trials between a rewarded and a nonrewarded sand-well and no requirement for the animals to attend to or learn anything. They have only to retrieve some flavoured food. However, on the view presented here, the act of running into the arena and then finding food at a particular place is an 'event' which the animals would automatically encode into memory. The two sample trials, separated by an interval of 5 min, use two different locations and two different foods. Thus, if the animals do attend and incidentally encode information on each trial, they would have the opportunity of learning that one flavour of chow is at one location and another flavour at a separate location. On the daily choice trial, scheduled 20 min or more later, the rat is now given one of the two flavours to eat in the start-box (Fig. 4B). This constitutes its recall cue. Approximately thirty seconds later, the animal is allowed to run into the arena. It now finds that two sand-wells are available. A win–stay rule is applied in the task whereby going to the location associated with the flavour cue in the startbox is, during training, rewarded by more of that same flavour (nonrewarded 'probe trials' are also run). This reward is no more than the usual procedure in paired-associate learning with humans who are given feedback on how well they have done. Up to 30 different locations and

flavours can be paired in novel combinations at the rate of two pairs per day (enabling $30 \times 29 \times 28, \dots, \times 3, \times 2$, i.e. 30!, novel pairings).

This 'what–where' paradigm lacks the 'when' time element that is necessary to claim this is a true episodic-like memory task (Griffiths *et al.*, 1999). However, using this paradigm, it was observed that performance was reliably above chance after a single trial of encoding. The rapid, automatic 'what–where' association seemed to fade quite quickly, in keeping with the notion that such automatically encoded memories are not ordinarily retained for any length of time (Fig. 4C). Within the window of time that is feasible, Day *et al.* (2003) then examined the effects of intrahippocampal infusion of (i) an NMDA receptor antagonist, D-AP5, at a concentration that has no effect on baseline field potentials but does block LTP (Fig. 4D), and (ii) an AMPA receptor antagonist, CNQX, which switches off the hippocampus for a period of about an hour (Fig. 4F). The impact of these drugs upon memory encoding and memory retrieval was as expected. Encoding was sensitive to the acute intrahippocampal infusion of D-AP5 without any effect on retrieval, while retrieval was sensitive to the AMPA receptor antagonist CNQX (Fig. 4E and G). These observations were made by timing the infusions either 15 min before, or 5 min after, encoding trials across a series of days, using a full 3×2 experimental protocol (three drugs, including aCSF; and two conditions). It seems reasonable to suppose that an NMDA receptor-dependent mechanism similar to that responsible for the induction of LTP in the hippocampus is involved in encoding the paired associate into memory.

These findings complement earlier work (Steele & Morris, 1999) using the repeated one-trial learning paradigm in the watermaze called delayed matching-to-place (DMP). However, whereas DMP examines only spatial memory, the event arena training procedure looks at 'what–where' associations. It reveals that one-trial learning of event–place associations is possible and that they can decay quite quickly (within a day). From a neuropharmacological perspective, it points to a partial dissociation between the role of NMDA and AMPA receptors in the hippocampus with respect to memory encoding and memory retrieval, respectively.

However, there are several weaknesses of the Day *et al.* (2003) experiment as it stands. First, the levels of performance achieved after just one encoding trial for each flavour–place pair are not very good. Choice performance during training is above chance, and the distribution of dig times in nonrewarded probe trials is significant, but first-choice performance does not approach the levels usually regarded as necessary for claiming that effective learning has occurred in a discrimination task ($> 85\%$). One reason for this is that the animals may quickly learn that there is no permanence to any flavour–place association which they form. What is found and where it is found changes from day to day, and the information is hardly of great emotional significance (unlike the watermaze where the memory of a one-trial event seems to be more long-lasting). A second weakness of the study is that the deficit in recall observed when the AMPA receptor antagonist was infused prior to recall could be a strictly spatial deficit, rather than a deficit in the ability to recall the association of a place and its flavour cue. This ambiguity was addressed experimentally in two ways. The first way was to look at the impact of overtraining of flavour–place associations and then ask whether the animals could choose effectively under CNQX. When two pairs of flavours and locations were extensively trained for 8 weeks, with these pairings contingently 'hidden' amongst other new one-trial problems (to prevent the animals from falling into a purely spatial strategy), bilateral intrahippocampal infusion of CNQX was observed to have no effect on cued-recall performance (Experiment 2 of Day *et al.*, 2003). This finding implies that fast synaptic transmission in the hippocam-

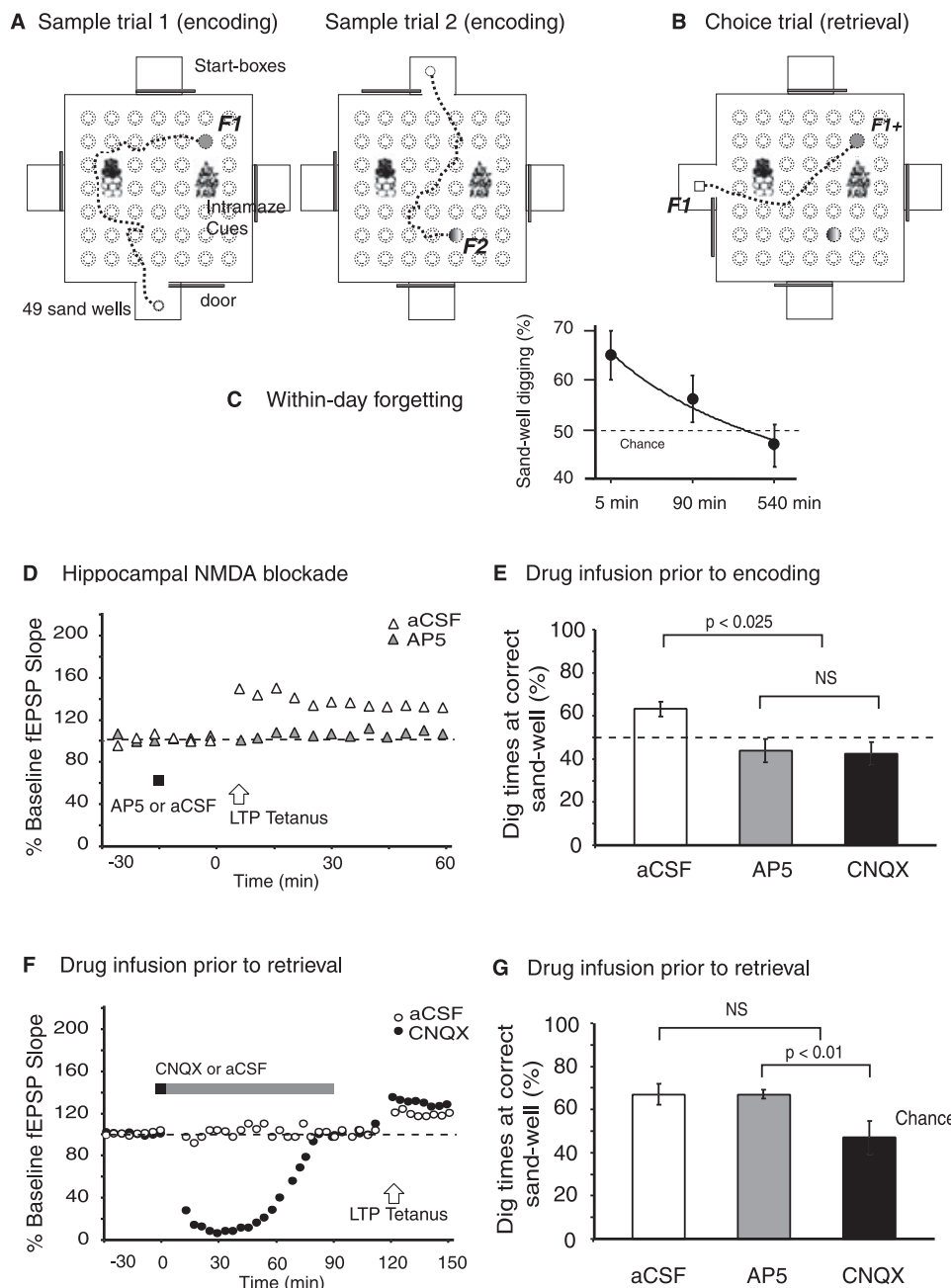


FIG. 4. Cued recall of paired associates in the event arena. (A) On sample trials 1 and 2, the door to a start-box is drawn back and the rat runs out into the arena (dotted line) where it displays occasional lateral head movements to find food F1 at the single open well. Sample trial 2 is to a different food (F2) at a different location. (B) The cued-recall choice trial begins with presentation of either of the two sample trial foods (food F1 is shown) followed by the rat being rewarded selectively for digging at the sand-well containing this same food. (C) Within-day forgetting of spatial information cued by its associated flavour. (D) Electrophysiological data showing impact of local infusion of D-AP5 on the induction of LTP in the hippocampus of an anaesthetized rat. The drug has no effect on field excitatory postsynaptic potentials (fEPSPs). (E) Proportion of choice trials in which the first chosen sand-well had been cued in the start-box in the presence of aCSF, D-AP5 or CNQX given 15 min prior to sample trials. Both drugs block the encoding of paired associates. (F) Electrophysiological data showing the impact of local infusion of CNQX on fEPSPs in the hippocampus of an anaesthetized rat. Note 'switch-off' of hippocampus for ~1 h. Upon resumption of the baseline, it is again possible to induce LTP showing that normal function has returned. (G) Proportion of choice trials in which the first chosen sand-well had been cued in the start-box in the presence of aCSF, D-AP5 or CNQX given 5 min after sample trials and 15 min prior to retrieval (choice) trials. While CNQX continues to impair performance, D-AP5 has no effect on the retrieval of paired associates.

pus is not an absolute requirement for making accurate choices in the event arena; the animals can navigate effectively to a correct place if that cued association has been overtrained. The second way was to ask whether similar effects of CNQX would be observed in a strictly spatial task in the arena. For this, the single base flavour was used

across days, with the location of the place where the food was to be obtained varied each day. When this was done, Bast *et al.* (2005) observed that D-AP5 impaired encoding and CNQX impaired recall performance as effectively as in the flavour-place task. This implies, in contrast to the overtraining study, that the encoding and retrieval of

a 'one-shot' strictly spatial memory engages NMDA- and AMPA-mediated mechanisms in the hippocampus in the same manner as a 'what-where' memory.

Notwithstanding the ambiguity that the Bast *et al.* (2005) data create for the appropriate interpretation of the Day *et al.* (2003) study, they do not affect the interpretation of the experiments conducted using D-AP5. Blocking hippocampal NMDA receptors after the daily flavour-place association trials but prior to a choice trial had no effect on choice accuracy relative to aCSF infusions. It follows that NMDA receptor activity is not critical for the recall of place-flavour associations. In turn, this implies that the deficit in choice trials seen when D-AP5 is infused prior to sample trials also cannot be due to impaired spatial recall. Thus, the memory deficit seen following presample D-AP5 infusions must result from a failure of encoding and storage. As the representation of the environment has already been well learned at the time of the drug infusions, this must be a deficit in associating new information about flavours with information retrieved from the neocortex about locations within the familiar testing environment. These data are consistent with Proposition 1 but they fall short of a definitive test. They imply that the network of the hippocampus, and possibly area CA1 itself, has the circuitry and the synaptic plasticity to rapidly encode and at least temporarily store associations between locations and events. Further experiments are required to establish the flow of different streams of information, to address the issue of automaticity more thoroughly and to investigate the subtle but important distinction between the encoding and storage of indices vs. detailed representations.

Proposition 2: cellular consolidation, determined by the process of synaptic tagging and capture, alters the persistence of hippocampal memory traces

The idea that hippocampal memory indices are encoded as distributed patterns of synaptic weights requires that synaptic changes last long enough for the slower systems-level hippocampal-neocortical consolidation process to take place. Early LTP (E-LTP) lasts at most 3–4 h. This is not long enough for a hippocampal memory trace to guide systems-level consolidation. Protein synthesis-dependent late-LTP (L-LTP) lasts longer, but perhaps not indefinitely (cf. Abraham *et al.*, 2002). An interesting possibility is therefore that persistence entails an interaction of two processes. One process creates the potential for a lasting memory to be formed without any commitment to do so. This is the function of cellular consolidation in hippocampus. The second process enables persistent hippocampal memory traces to

guide the process by which detailed information in cortex becomes stabilized through systems-level consolidation.

A new perspective on cellular consolidation is the 'synaptic tagging and capture' hypothesis of memory trace formation (Frey & Morris, 1997, 1998b; Frey & Morris, 1998a; Dudai & Morris, 2001; Kelleher *et al.*, 2004; see Fig. 5). A similar framework has been outlined by Lisman & Grace (2005). This hypothesis accepts that plasticity proteins are critical for the persistence of synaptic potentiation within neurons, but argues against obligatory *de novo* synthesis of these proteins in response to the events that are to be remembered as originally proposed by Goelet *et al.* (1986). The idea is that cellular consolidation involves (i) the potential for persistent LTP being established at excitatory synapses in the form of rapidly decaying early LTP accompanied by the setting of a local synaptic tag; and then (ii) a series of biochemical interactions, including protein-protein interactions, which convert this synaptic 'potentiality' (E-LTP) into a longer lasting trace at those synapses at which tags have been set (i.e. L-LTP). The somatic or, possibly, the dendritic protein synthesis which is necessary for these interactions can be set in motion shortly before the event to be remembered, or at the same time (as in most behavioural and *in vitro* brain slice experiments to date), or after the event. Critically, the persistence of memory does not have to be determined at the time of initial memory trace formation, but depends on the 'history' of neuronal activation in the population of neurons in which the synaptic change occurs. Frey & Morris (1998b) proposed that conjunctive patterns of afferent glutamatergic activation and post-synaptic spiking induce short-lasting changes in synaptic weights (E-LTP) and, simultaneously, set synaptic tags by a post-translational mechanism. One logical but apparently counterintuitive prediction was that L-LTP could occur in response to weak tetanization which ordinarily induces rapidly decaying E-LTP, provided that the weak tetanization is given shortly before or shortly after strong tetanization to separate, independent, afferents. This prediction was first confirmed by Frey & Morris (1998a) and has been recently reconfirmed, as shown in Fig. 6, by O'Carroll & Morris (2004). Heterosynaptic activation, proposed in Frey & Morris (1998b) to occur via neuromodulatory inputs (particularly dopamine afferents from the ventral tegmentum to areas CA1 and CA3 of the hippocampus, and noradrenergic inputs to the dentate gyrus), is responsible for helping to trigger *de novo* protein synthesis. These proteins travel diffusely in dendritic compartments until sequestered locally by the synaptic tags whereupon they help induce synaptic stabilization.

A further twist on these ideas about cellular consolidation has come in intriguing new experiments from the Frey lab indicating that

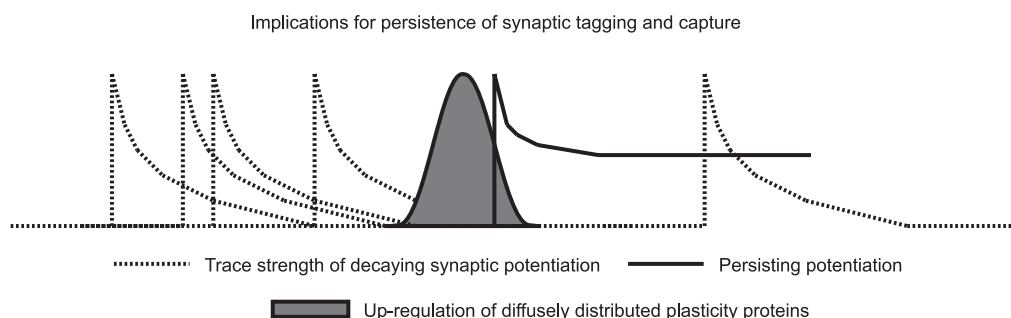


FIG. 5. The synaptic tagging and capture (STC) theory of cellular consolidation. The induction of LTP by a weak tetanus results in potentiation that follows a decaying time-course back to baseline. It is supposed that most memory traces are of this form, particularly those which are automatically encoded within hippocampus corresponding to the inconsequential events of the day. However, if there is a temporary up-regulation of plasticity proteins in the same neuron, synaptic potentiation occurring around the same time will result in a more persistent change. The same should happen to memory. Collectively, across many neurons of a distributed network, the result will be cellular consolidation of a memory trace.

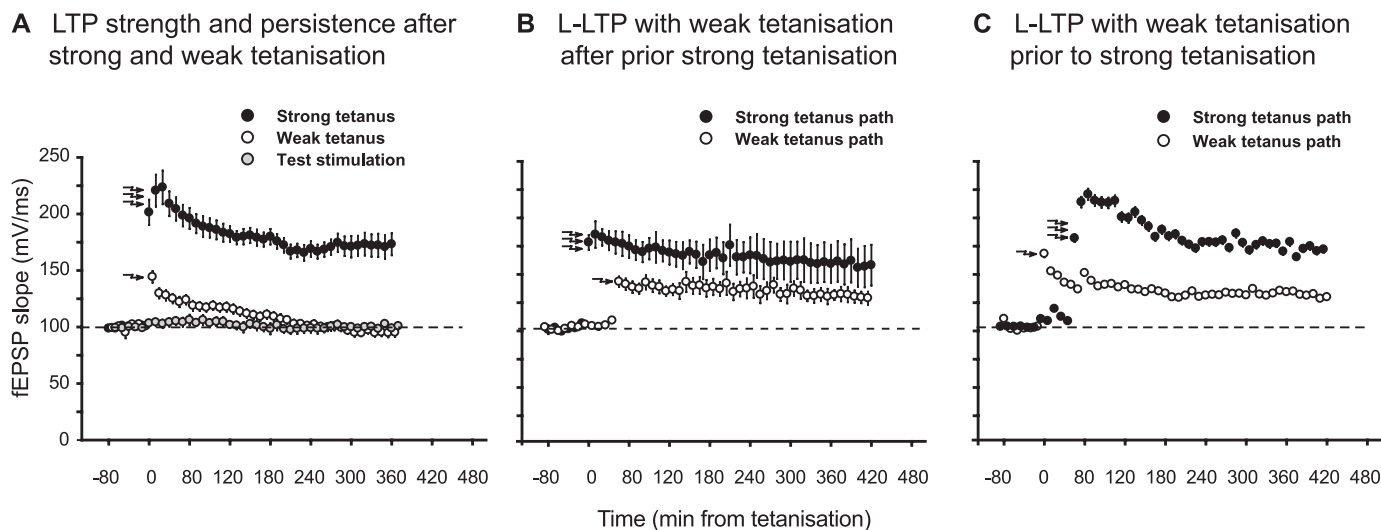


FIG. 6. Synaptic tagging and capture of plasticity proteins at a weakly potentiated input in CA1 hippocampal slices. (A) Strong tetanization of one input pathway produces strong, lasting LTP which endures for 8 h. Weak tetanization of a pathway in separate brain slices produces weak LTP which rapidly decays to baseline. (B) When strong tetanization of one pathway preceded weak tetanization of an independent pathway in the same brain slice and to a common population of neurons, the weakly tetanized input showed modest LTP immediately after induction but, critically, this LTP persisted for 8 h (i.e. L-LTP). (C) The same outcome as (B) prevailed when the weak tetanization preceded strong tetanization.

interactions can occur between LTP and long-term depression (LTD) in the domain of persistence. Sajikumar & Frey (2004b) have shown that if L-LTP is induced on one pathway prior to a low-frequency tetanus which normally induces E-LTD (a short-lasting form of long-term depression), then a more persistent L-LTD is induced. Symmetrically, the induction of L-LTD by multiple trains of low-frequency stimulation prior to a weak tetanus which ordinarily induces only E-LTP results in the potentiation being observed to last a long time (i.e. L-LTP). This 'cross-capture' phenomenon shows pharmacological sensitivity to both anisomycin and the D1/D5 receptor antagonist SCH23390. One interpretation of this finding is that a common set of plasticity proteins mediate both L-LTP and L-LTD, with differential tags set at each synapse (Kelleher *et al.*, 2004). Conceptually, this is also an attractively counterintuitive suggestion for it implies that the activity-dependent up-regulation of a single set of genes and their resulting protein products could be equally responsible for helping to mediate a persistent increase in synaptic efficacy (L-LTP) and a persistent decrease in efficacy (L-LTD).

Other studies have suggested that the synaptic tagging process is subject to both activity-dependent 'setting' and 'resetting'. Sajikumar & Frey (2004a) began by confirming earlier observations that the application of low-frequency stimulation (LFS) very shortly after the induction of E-LTP reset the potentiation back to baseline (Staubli & Lynch, 1990; Staubli & Chun, 1996). As the interval between LTP induction and LFS was lengthened from 5 min to longer periods, there were indications that the re-setting was incomplete. Noting this, they used the heterosynaptic two-pathway protocol of tagging experiments in an innovative way to explore whether the partial re-setting of E-LTP with delayed LFS also entailed a partial re-setting of an activity-dependent tag. To do this, they first induced E-LTP on one pathway and then gave LFS 15 min later. This should have resulted in only partial tag re-setting. They then applied strong tetanization to the second independent pathway 30 min after the initial E-LTP induction. Not only did this result in persistent L-LTP on the second pathway, it also limited the decay normally seen in the E-LTP pathway after partial tag resetting. Persistent L-LTP was observed on that pathway also. Young & Nguyen (2005) have extended this intriguing finding by

establishing that LFS given prior to tetanization can limit tag setting and so cause strong tetanization to result only in E-LTP, an effect which they show through rescue of L-LTP on a separate pathway not to be due to any impact on the synthesis of plasticity proteins. Thus, the induction of E-LTP, tag setting and the up-regulation of genes responsible for plasticity proteins are all regulated in an activity-dependent manner.

At present, we still do not know whether synaptic tagging occurs *in vivo* and whether the principle also extends to behavioural memory as implied by Proposition 2. Is it possible to induce a long-lasting memory as a consequence of an experience which ordinarily gives rise only to a short-lasting memory if the triggering event occurs around the time there is a separate up-regulation of the synthesis and distribution of relevant plasticity proteins? Some intriguing approaches to this question are under way, some involving taste memory (K. Rosenblum, personal communication) and others context-fear conditioning (J. W. Rudy, personal communication). Our approach, in its early stages, involves studies of memory in both the watermaze and the event arena, with novelty exploration or other experiences being explored as ways of up-regulating plasticity proteins in a strictly behavioural way.

In one pilot study using the event arena, rats were trained in the 'one-shot' spatial memory task to remember the varied daily location where food could be obtained in one of the 49 sand-wells. The first trial of the day was the opportunity to run into the arena to find a single open sand-well. Then, 20 min later, the animals were allowed back into the arena with now five sand-wells available. Only the sample trial sand-well contained food. Once performance on this spatial recall task was optimal, which took a few weeks, two nonrewarded probe tests were given on separate days, separated by further training, at memory delays of either 20 min or 6 h after the daily sample trial. There were again five sand-wells, but this time none of them contained food (a nonrewarded probe trial). The data from this probe test shows that memory after 20 min is very good, with animals showing a strong preference to dig preferentially at the sample sand-well (Fig. 7). However, after 6 h this memory has dissipated.

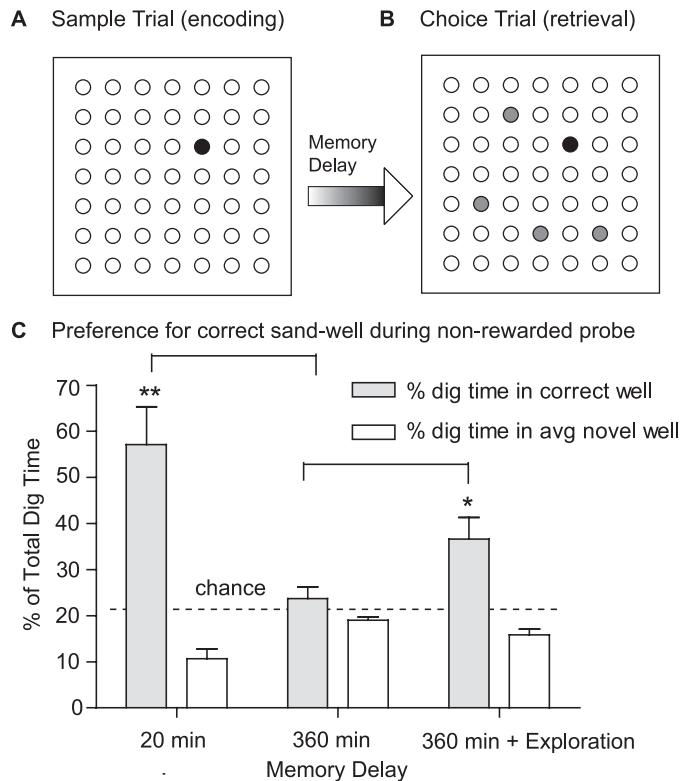


FIG. 7. Extending the persistence of memory. (A and B) Behavioural protocol involved a sample trial with one sand-well (solid circle), located in a different position each day, followed by a choice trial consisting of five sand-wells of which only the sample location was rewarded (solid, rewarded; shaded, empty). In probe tests, all choice trial sand-wells were nonrewarded and the measure was the proportion of time digging at the remembered location. (C) Proportion of time spent digging at the correct or incorrect locations after memory delays of 20 or 360 min. Novelty exploration, up-regulating plasticity proteins, extended the persistence of a memory ordinarily forgotten over 6 h. R. Redondo, K. Berry, H. Koëver & Z. Richmond, unpublished data. * $P < 0.05$, ** $P < 0.01$.

The point of the study was to explore whether manipulations which have been shown to up-regulate relevant gene activation and protein synthesis could extend the persistence of this short-lasting memory. Importantly, these manipulations should have no overlap, in informational terms, with the location of the correct sand-well. Novelty exploration is one procedure which has been shown by Guzowski and colleagues to cause an up-regulation of the immediate early gene *Arc* (Guzowski *et al.*, 1999; Vazdarjanova & Guzowski, 2004). Antisense oligonucleotides to *Arc* are known to inhibit long-term memory (Guzowski *et al.*, 2000). Novelty is also implicated by Lisman & Grace (2005) as likely to drive ventral tegmental neurons to release dopamine onto D1/D5 receptors in the hippocampus. This would then drive relevant intracellular signal transduction pathways. Thus, if novel context exploration up-regulates mRNAs that are involved in the synthesis of plasticity proteins, allowing a period of such exploration an appropriate interval before the daily sand-well sample trial may enable any short-lasting synaptic potentiation associated with a memory of its location in space to be transformed into a persistent potentiation through tag-protein interactions. This should result in a more persistent behavioural memory. As shown in Fig. 7, this prediction was upheld. To achieve this result, the same rats were given 5 min of novelty exploration in a large square Perspex box placed inside the event arena 30 min prior to the daily

sample trial. Memory encoding during the ensuing sample trial in the event arena which ordinarily gave rise to a memory that fades to baseline over 6 h now resulted in a more persistent memory. These pilot data are suggestive, but several issues are outstanding. First, is the interaction between novelty exploration and persistent spatial memory actually due to the synthesis of plasticity proteins? Studies with local *in vivo* administration of anisomycin need to be completed. Second, for this interaction to occur, is it necessary to ensure that the behaviourally driven up-regulation of protein synthesis occurs in a common population of neurons to those used by the animal later during learning? The original framework due to Frey & Morris (1998b) implies that it is necessary, whereas that due to Lisman & Grace (2005) indicates that novelty may drive a more diffuse up-regulation of neuromodulatory afferents. The two possibilities are not mutually exclusive.

These studies are part of a systematic series of experiments testing certain features of the synaptic tagging and capture hypothesis of cellular consolidation in behaving animals. As the critical predictions of the hypothesis require protein synthesis to be triggered at one point in the sequence of events but not at another shortly thereafter (or shortly before), it is unclear how gene-targeting techniques can be deployed most usefully. They will, as in the work of Barco *et al.* (2002), help us identify many of the mechanisms of persistence of LTP and LTD at a genetic level and establish more definitive evidence for tag-protein interactions. They may also help to identify the relevant molecular players. However, addressing the heterosynaptic issue will be more difficult as even inducible constructs require several days to work, and the study is also at the mercy of the rate of protein turnover (which may not be known). In contrast, using physiological and pharmacological techniques it may be possible to activate dopaminergic or other neuromodulatory afferents to the hippocampus prior to a learning experience and then train in the presence of an antagonist. This and other related tests of the synaptic tagging and capture hypothesis are under way with the priorities being to establish (i) whether tagging occurs during *in vivo* physiologically and (ii) whether such a phenomenon could be the basis of 'flashbulb' memory.

Proposition 3: the puzzle of the location of spatial memory traces and an activated schema model of systems-level consolidation

Proposition 3 relates to the neurobiology of systems-level memory consolidation and the probable sites of more permanent memory trace storage for episodic-like information. Our theoretical framework identifies the hippocampus as critical for the initial encoding of associative indices linking disparate neocortical modules whose connectivity is too sparse to support the encoding of arbitrary associations, but the neocortex as the site of long-term storage. The usual view is that systems consolidation is a gradual process which takes place over days or weeks. On this view, lesions at various times after initial learning should reveal a temporal gradient of retrograde amnesia. A new idea, distinct from the standard and multiple-trace models of consolidation, is that neocortical schema may enable rapid interleaving of new information with stability of trace memory over time. A major puzzle in considering either idea is that, to date, evidence from studies of retrograde amnesia is equally consistent with the notion that long-term spatial memory traces are in hippocampus. While the indirect association principle makes this unlikely, the published data remain equivocal.

The 'standard model' of memory consolidation asserts that systems-level consolidation takes place after learning which, by enabling an interaction of hippocampal and neocortical ensembles, secures the

stabilization of memory traces outside the hippocampus (Squire & Alvarez, 1995; Manns *et al.*, 2003). There is a large body of evidence in humans and animals which is consistent with this view (Squire *et al.*, 2004; Bayley *et al.*, 2005). This type of memory consolidation is thought to have at least two functions. First, it provides a mechanism to 'gate' whether memory traces are to be retained. Second, once consolidation is complete, a lasting neocortical memory site exists which would enable much faster retrieval of information than would be possible if neural throughput of the hippocampus were always necessary at the point of retrieval. The alternative 'multiple trace' model of memory persistence (Nadel & Moscovitch, 1997; Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1998) holds that a subset of memories, specifically spatial memories, are permanently mediated by corticohippocampal circuitry because trace storage is within the hippocampus. The central idea of this hypothesis is that reactivation of spatial memory leads to, or at least can lead to, the formation of additional traces in the hippocampus. There would then be multiple traces at different locations within the hippocampus. According to a later version of this model (Nadel & Bohbot, 2001; Rosenbaum *et al.*, 2001), this multiple-trace theory applies particularly to 'contextually rich' memories but not to those that are context-free or more semantic in character.

The 'declarative memory' and the 'multiple trace' theories make contrasting predictions about retrograde amnesia for spatial memory in the particular case of partial lesions. The declarative theory predicts that partial lesions may only partially disrupt consolidation and that there should therefore be higher overall levels of performance in hippocampal-lesioned animals. The multiple trace theory predicts that complete lesions will result in no memory, but partial lesions may reveal a temporal gradient. However, studies using the watermaze have consistently shown a flat gradient of retrograde amnesia when it is first tested postoperatively in both partial- and complete-lesioned rats. Typically, rats have first been trained on a reference memory version of the task (i.e. to find a single hidden platform) and then, at periods ranging from a few days to up to 3 months later, been given large excitotoxic or radiofrequency lesions of the hippocampal formation (Bolhuis *et al.*, 1994; Mumby *et al.*, 1999; Sutherland *et al.*, 2001; Clark *et al.*, 2004, 2005; Martin *et al.*, 2005). Subsequent to surgery, the animals are retested in the watermaze using probe tests (platform absent). Whether given complete or even partial

hippocampal lesions, there is no evidence for retention of either recent or remote spatial memory in the first probe test given after surgery, a finding that, on the face of it, argues against both models of memory consolidation. However, the performance of sham-lesioned rats in the watermaze tends to be poor after surgery, possibly reflecting a 'floor' effect which masks any consolidation process. Several techniques have been used to address this problem: retraining after surgery (Bolhuis *et al.*, 1994; Mumby *et al.*, 1999; Sutherland *et al.*, 2001), presurgery training for as much as 80 trials (Clark *et al.*, 2004), training from very early in life (Clark *et al.*, 2005), and the use of the annular watermaze which obviates the need for navigation (Clark *et al.*, 2004). In none of these cases was there any evidence for a temporal gradient of consolidation of spatial memory. A different approach was used by Martin *et al.* (2005), who conducted a series of rewarded probe trials, each serving as a 'reminder' of what was required in the task rather than an opportunity for re-learning (de Hoz *et al.*, 2004). This did successfully reveal above-chance spatial memory in partial-lesioned animals but, contrary to both the standard and multiple-trace models, better memory was observed when the lesion was made early after training than at a longer interval (Fig. 8).

Spatial probe tests in the watermaze can be characterized as being analogous to a 'free recall' test for humans. This is known to be very demanding and may always require, in circumstances where instructions cannot be given (as they cannot with animals), a 'recovery of consciousness' which Moscovitch (1995) argued would always require a neural loop through the hippocampus. The event arena offers an opportunity of looking at spatial memory using cued recall in which a specific location in space is associated with a particular flavour of food. Instead of using the apparatus to test memory acquired in a single trial, it can instead be used in 'reference memory' mode in which each of several flavours are associated with different locations in the arena, with these associations remaining stable over an extended period of training. Hippocampal lesions could then be given at varying times after training to examine, in cued-recall rather than free-recall mode, whether there is a temporal gradient reflecting a consolidation process. Cued recall may not always entail a 'recovery of consciousness' (or its equivalent in animals).

In the process of conducting pilot work for such a study, it became apparent that normal rats develop a mental framework or 'schema' that represents the relative locations of each of the flavour-place pairs

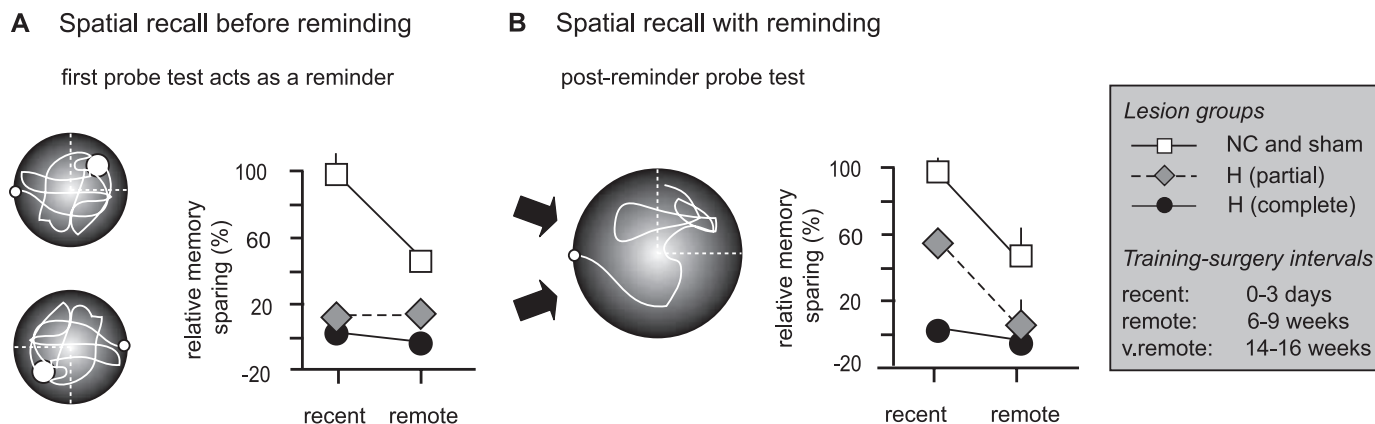


FIG. 8. Retrograde amnesia for spatial memory. (A) Spatial memory in a watermaze on the first probe trial after surgery consisting of sham, partial or complete hippocampal lesions. Only the sham-lesioned groups showed memory and this declined as a function of the interval between the end of training and surgery (forgetting). Paths taken in the watermaze are representational for each of two counterbalanced locations. (B) Impact of reminding. The first probe trial ended with an Atlantis Platform becoming available after 60 s in either the correct or a diagonally opposite location (de Hoz *et al.*, 2004). In both cases, performance in a second probe test 1 h later was changed. Rats given partial hippocampal lesions now showed memory for the correct spatial location if testing took place after a short memory retention interval. After Martin *et al.* (2005).

being trained. Unlike human paired-associate learning where the successive pairs of words are generally arbitrary and not semantically or otherwise connected with one another, the training of several flavour–place associations in a single arena creates the opportunity to learn a schema that represents the cryptic locations where food is to be found (Fig. 9A). Before this spatial schema is acquired, the animals are not likely to remember the location where a food item is to be found for any length of time. In the one-trial paradigm, for example, forgetting consistently occurs over ~ 90 min (Fig. 4C). However, if six different flavour–place pairs are trained concurrently, the animals are observed to gradually improve their choice performance over a period of about a month (with six trials per day, one trial to each flavour, and training every 2 days). The procedure involves giving different cue flavours in the start-box on each of six successive trials within a day, with more of that flavour of food available at the sand-well with which it is consistently associated. Unlike the one-trial paradigm in which only one sand-well is available on each of the two sample trials (Fig. 4A), this reference memory protocol has all six sand-wells available on each of the six daily trials. That is, all trials are

discrimination trials (with six choices) and there are no trials corresponding to sample (encoding) or choice (retrieval) trials. All trials serve as both encoding and retrieval trials.

As shown in Fig. 9B, with normal rats trained every 2 days, choice performance averaged across the six daily trials gradually increased until, after 18 sessions of training, the animals were averaging 80% correct with minimal variability. Precautions were taken to ensure that the animals could not smell the correct food available at any one sand-well by adulterating the sand with 6% of ground food (1% for each flavour). In addition, when a single day was scheduled in which no cue flavours were provided in the start-box (after day 18) but the protocol was otherwise unchanged, performance fell to chance (Fig. 9C). In keeping with the results of this control procedure, if given a cue flavour in the start-box in a nonrewarded probe test, the animals spent much more time digging at the correct sand-well than at the other five sand-wells (Fig. 9D). No food was available in the arena to guide choices; the only way that the animals could do this was by cued recall. This combination of choice data, noncued control and probe-test data suggests that the animals were able, in the start-box, to use a

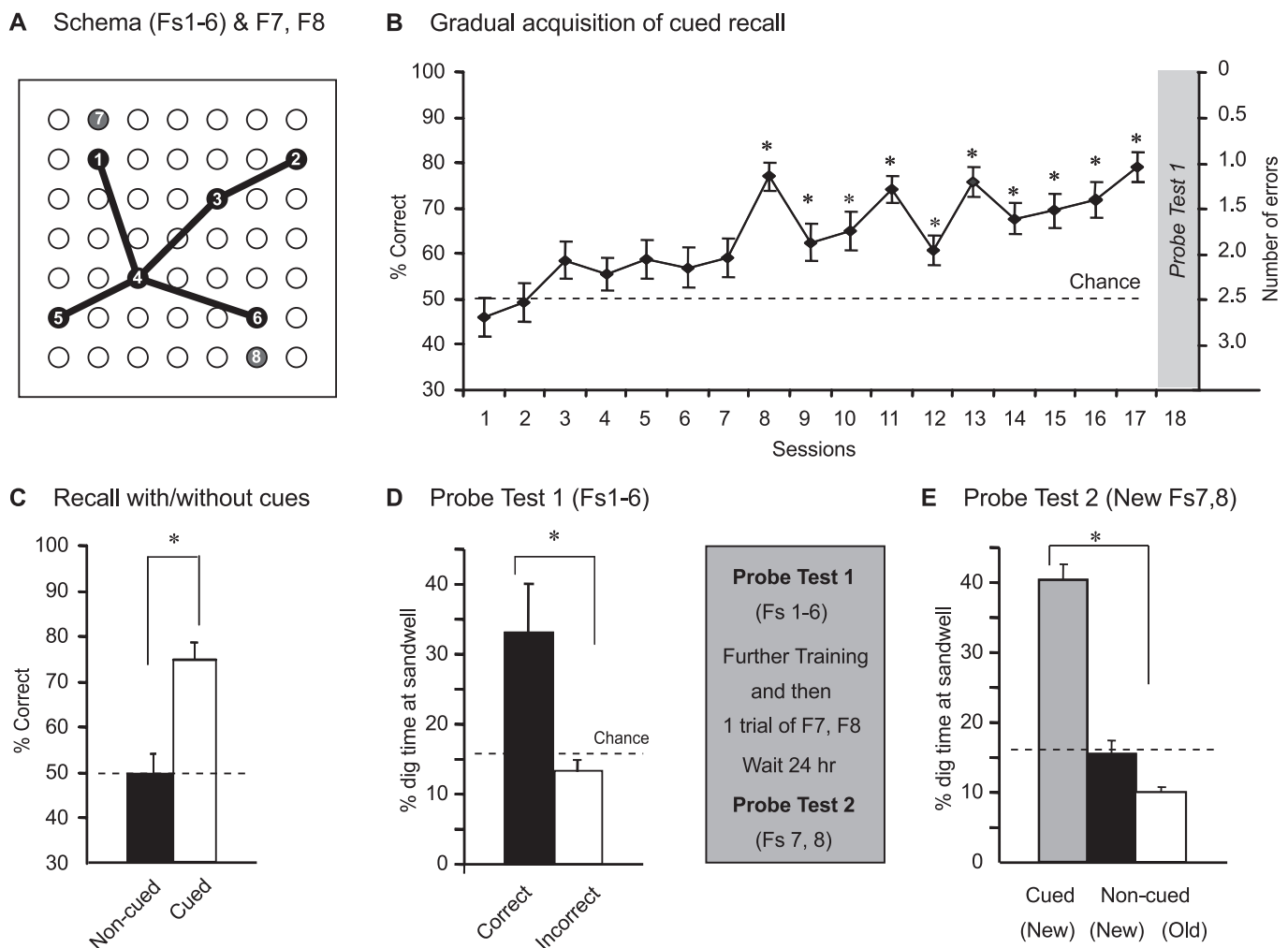


FIG. 9. Schemas and paired-associate learning. (A) Rats were trained to find six different flavours of food in six different locations, cued by a different one of the flavours for each of six trials per day. The six flavour–place pairs formed an associative schema whose spatial connectivity is displayed. (B) Gradual learning of the six paired associates over 18 sessions of training. Performance is calculated as the number of errors (digging at an inappropriate sand-well) during a trial. Chance performance = 2.5 errors per trial. (C) Choice performance falls to chance when the flavour cue given in the start-box is omitted, implying that there are no cryptic cues contributing to performance. (D) Performance during Probe Test 1 (nonrewarded). The animals dig preferentially at the cued location. (E) After a single trial of training to novel flavours (F7 and F8, at two of the six locations shown in Panel A), performance in a second probe test conducted one day after training shows preferential search at the cued location. This is not a novelty effect, as there is successful discrimination between the cue and noncued novel flavours. $*P < 0.01$.

flavour of food reliably associated with a specific location in the arena to retrieve a memory of that location, go there and then dig preferentially at that location for more food.

The indication that the animals may have developed a mental 'schema' for the relative locations of the sand-wells came in a further observation. On a single day of training, several days after Probe Test 1, two sand-wells were closed [locations (L)1 and L6, containing flavours (F)1 and F6] and two new sand-wells were opened (L7 and L8). The usual six trials were given, with one trial for each flavour, and thus only one cued trial for F7 and one for F8. With successive trials separated by ~1 h, the training on that single day took ~7 h. A nonrewarded probe test was then conducted on the next day consisting of a single trial in which half the animals were cued with F7 and the other half with F8. Remember that, in the previous one-trial episodic-like protocol, cued recall of a spatial location declined over 90 min. Here, F7 and F8 had also been trained for only one trial. However, the data for Probe Test 2 (Fig. 9E) indicated that memory for their spatial locations in the arena was now as good as that shown for the other six flavours (F1–6) in Probe Test 1. The persistence of memory had been transformed from lasting no more than 90 min to lasting at least 1 day.

There are several different ways to interpret this finding. Mental schemas are one possibility and the acquisition of a learning set is another. Further studies will be required to dissociate these and other alternatives. Preliminary data argue against a learning-set account as experienced animals trained on a new layout of six flavours in a second arena in a different room learn these at the same slow rate (over many days) as they learn the first layout of foods in the first arena. Our preferred view is that, in addition to the hippocampus being involved in encoding the association between indices of the detailed neocortical representations of flavour and place, it may also be involved in building a schematic representation of the relative locations of the different flavours that can then help the animal to find the appropriate sand-well at which to dig when cued with a specific flavour. This representation of six different hidden locations might even be an entity that can be 'mentally rotated' from one day to the next as the start-box used is kept the same within a day but is varied between days. That is, if cued with F6, the path to L6 where more of F6 is to be found may be short or long, to the left or the right, depending on the start-box in which the animal is to be found. The animals must therefore retrieve information about their location in the arena in relation to extramaze cues, and rotate their representation of the schema to make it appropriate for that starting location. However, even if the hippocampus is essential for building a schema, it is very unlikely to be the long-term store for such detailed sensory and/or perceptual information. The schema is more likely to involve a set of new intermodular connections between relevant sensory and associational cortical areas, as discussed above. Once such a schema is built (and this is likely to take a long time as the data in Fig. 8B indicate), it is able to incorporate new paired-associate information which can be readily interleaved into the same framework. On this view, encoding the association between F7 and L7, and between F8 and L8, will each require NMDA receptor-dependent synaptic plasticity in hippocampus but the probable site of relatively immediate long-term storage will be in cortex. It is for this reason that we see no rapid forgetting over 90 min as in the one-trial paradigm. If this is correct, it leads to an astonishing prediction. Specifically, it predicts that hippocampal lesions given very soon (within 1 day) after the training of novel, schema-relevant, flavour–place pairs will have no effect on memory recall even though the encoding of such flavour–place pairs is hippocampal-dependent. Such an experiment is under way (D. Tse and R.F. Langston, unpublished observations).

The data discussed in this section point to a potential contradiction. The experiments in the watermaze strongly suggest that the integrity of the hippocampus is essential for the recall of spatial memory. However, the present neurobiological framework is built on the notion that spatial memory traces are in cortex. Can these data and ideas be reconciled? One possibility, as discussed by Martin *et al.* (2005), relates to the role of the hippocampus in the retrieval and expression of consolidated memory traces that reside in the neocortex. On the view that the hippocampus stores indices, it might retrieve a cortical memory in a manner analogous to conducting a keyword search on an electronic document. Partial lesions would compromise the 'indices' rather than the detailed sensory–perceptual memory traces and so limit the ability to retrieve cortical memory traces when a free 'recall' process is necessary. The circumstances surrounding memory retrieval in humans (e.g. the availability of instructions), and the very character of the information retrieved (Nadel & Bohbot, 2001), may determine whether or not the hippocampus plays a necessary role in this process. Retrieval of the right combination of traces might be possible in animals under circumstances in which specific retrieval cues are either particularly apposite or sufficiently rich to disambiguate cortically based traces with overlapping components. However, under circumstances in which the retrieval cues do not permit easy disambiguation, or where they have to be generated indirectly through the process that Moscovitch (1995) identified as 'recovered consciousness', the processing capacity of the hippocampus and its stored indices would remain essential. Disambiguation would generally be critical for context-dependent episodic memory in which a unique combination of traces corresponds to the particular event from the past that needs to be reactivated. The revision by Rosenbaum *et al.* (2001) of the multiple-trace theory is relevant here. It distinguishes between context-dependent and context-free memories, and suggests that only the former remain dependent on the hippocampus for our lifetime. Teng & Squire (1999) have reported data consistent with both this and the 'standard model' in their patient E.P. who is capable of remembering locations in the town in which he grew up. In animal studies, Winocur *et al.* (2005) have reported data consistent with this view in a study on rats that lived in a 'rodent village' for 3 months prior to explicit training on a spatial problem within the village. Post-training hippocampal lesions had no effect on effective navigation to the correct location in the village, which they interpreted as implying the existence of a detailed 'semantic' map stored in neocortex. Rats with less experience of the village were impaired by post-training hippocampal lesions because, presumably, they lacked a context-free memory of the village. Unfortunately, the lesions used in their study were partial (~50%), potentially allowing some use of spared hippocampal tissue in memory retrieval. Winocur *et al.* (2005) argue against this being of significance on the grounds of finding no correlation between lesion size and retrieval, but their argument is not definitive as it is based on only a small number of subjects with different sized lesions.

From a neurobiological perspective, studies of interactions and correlations between single-unit and field-potential recordings in hippocampus and neocortex during and after sleep are highly suggestive of consolidation-like processes (Siapas & Wilson, 1998; Sirota *et al.*, 2003). Targeted molecular studies will also help to resolve some of the ambiguities at the mechanistic level, although not necessarily all of them as a daunting combination of novel behavioural protocols, lesions and molecular interventions will probably prove necessary to unravel the complexities. Frankland *et al.* (2001) made the intriguing observation that heterozygous α CAMKII-mutant mice show normal LTP in hippocampus, decaying LTP in cortex and a failure to consolidate contextual information. They suggest that the

instability of synaptic potentiation in cortex could be the basis of the consolidation failure. This is an interesting idea, but it is equally consistent with the idea that effective retrieval relies upon the synergy of different kinds of information permanently stored in both hippocampus and neocortex. Frankland & Bontempi (2005) summarize these developing new lines of research using transgenic animals and immediate early gene markers to plot the time-course and regional contributions of neocortex and hippocampus to memory consolidation.

Conclusion

This article has afforded an opportunity to update a developing neurobiological theory of hippocampal memory (Morris *et al.*, 2003) with reference to new ideas and new findings. First, the distinction between 'automatic' and more 'deliberate' components of episodic memory led up to the development of a rapid, associative memory task for animals which might depend upon incidental encoding. The one-trial version of the event arena (Day *et al.*, 2003) has this character as there is nothing about the sample trials which requires the animals to encode information about the locations of the retrieved food but the rats seem to do this naturally. Memory encoding of flavour-place pairs in this task, but not their retrieval, appears to be exquisitely sensitive to the local blockade of NMDA receptors in the dorsal hippocampus. Encoding events (such as finding food) in relation to the context in which they occur does not require that all familiar contexts be repeatedly processed in the machinery responsible for rapid memory formation. Instead, context memory can be retrieved from a neocortical store via separate pathways (the layer III input from entorhinal cortex), bypassing much of hippocampal circuitry but still enabling one-trial events to be effectively linked to their context of occurrence. This idea is based on new ideas about hippocampal circuitry developed by Witter *et al.* (2000) and on findings about place cells observed by the Moser group in Trondheim (Brun *et al.*, 2002).

Second, the synaptic tagging and capture idea (Frey & Morris, 1998b) has developed further to enable a more principled understanding of the temporal relationship between cellular and systems-level consolidation and the functional need for both forms of memory. There are several strands to this temporal interdigitation. Systems consolidation typically takes time. It follows that the hippocampal-dependent traces that help guide the neocortical stabilization must last long enough to serve this function. However, if every memory trace encoded by the hippocampus were to last for this intermediate length of time, everything recorded would be subject to systems-level consolidation. The system would soon saturate. It is possible to avoid this by having both cellular and systems-level mechanisms of consolidation. In addition, automatic encoding ensures that no 'decision' has to be made at the time of encoding as to whether a particular item of information is to be retained. Instead, there is first one and then later a second window of time in which some filtering of retained information can be realized. Over and beyond these conceptual ideas, important new data from the Frey group in Magdeburg have established that both the setting and re-setting of synaptic tags is subject to activity-dependent regulation (Sajikumar & Frey, 2004a).

Third, much of the discussion about memory consolidation to date has emphasized biological ideas (about anatomy, neuromodulatory transmission or protein synthesis) but there has perhaps been less thinking about the 'semantic' or other associative mental frameworks into which information is to be placed within cortex. Classical studies in neuropsychology have provided strong evidence that activated schema are a major determinant of memory (Bransford, 1979). Studies of retrograde amnesia to date have typically revealed either flat or long

temporal gradients reflecting a drawn-out consolidation process. These gradients have been thought to reflect a rapid hippocampal learning process and a slower cortical system. An alternative perspective, compatible with McNaughton's principle of indirect association (McNaughton, 1998), is that it takes time to build the cortical connectivity that is necessary as the physical substrate for mental schema. Accordingly, if this process of schema creation occurs and then new information is encoded which is relevant to an activated schema, it is possible that the interleaving of this new information could take place very rapidly and result in a much more persistent memory. Preliminary strictly behavioural data are consistent with this idea.

Acknowledgements

This article is based on the European Journal of Neuroscience Award Lecture (2004) given at the meeting of the Federation of European Neuroscience Societies in Lisbon. I am indebted to FENS for this award and for the opportunity to prepare a written version. The research described reflects the contributions of several collaborators, notably my colleagues in the Centre for the Biology of Memory (CBM) at the Norwegian Technical University in Trondheim (NTNU). I wish to thank its Director, Edvard Moser, and others affiliated with the Centre (Carol Barnes, Bruce McNaughton, May-Britt Moser, Ole Paulsen, Alessandro Treves and Menno Witter) for their scientific friendship and support. I also wish to thank Julietta Frey of the Leibniz Institute in Magdeburg, with whom I developed the ideas about synaptic tagging and capture and who did the original experiments on the phenomenon, and my research colleagues in the Laboratory for Cognitive Neuroscience in Edinburgh who contributed to the experimental work: Tobias Bast, Kat Berry, Mark Day, Masaki Takeyama, Hania Koeber, Ros Langston, Stephen Martin, Colin O'Carroll, Roger Redondo, Zoe Richmond and Dorothy Tse. I am also grateful to Patrick Spooner and Jane Tulloch, mainstays of the lab, to the Medical Research Council of the United Kingdom for their longstanding support of my research (Grant G9200370/2), to the Norwegian Research Council (CBM 145993) and the European Union (QLG3-CT-1999-00192) for their research funding.

Abbreviations

E-LTP, early LTP; F1-F8, flavours 1-8; L1-L8, locations 1-8; LFS, low-frequency stimulation; L-LTP, late LTP; LTD, long-term depression; LTP, long-term potentiation.

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