Interleaving brain systems for episodic and recognition memory

John P. Aggleton¹ and Malcolm W. Brown²

¹School of Psychology, Cardiff University, Cardiff, CF10 3AT, UK
²MRC Centre for Synaptic Plasticity, Department of Anatomy, University of Bristol, Medical School, Bristol, BS8 1TD, UK

Conflicting models persist over the nature of long-term memory. Crucial issues are whether episodic memory and recognition memory reflect the same underlying processes, and the extent to which various brain structures work as a single unit to support these processes. New findings that have resulted from improved resolution of functional brain imaging, together with recent studies of amnesia and developments in animal testing, reinforce the view that recognition memory comprises at least two independent processes: one recollective and the other using familiarity detection. Only recollective recognition appears to depend on episodic memory. Attempts to map brain areas supporting these two putative components of recognition memory indicate that they depend on separate, but interlinked, structures.

Introduction

There are two related debates about long-term memory. The first concerns the relationship between episodic memory and recognition memory. Some researchers see these components of long-term memory as part of the same continuum [1–3]. Others argue that recognition memory involves two or more qualitatively different processes [4–6], one of which shares features with episodic memory. The second debate concerns the degree to which structures supporting long-term memory in the medial temporal lobe make qualitatively different contributions [3,6–10]. Advances in the resolution of functional magnetic brain imaging (fMRI), allied to key developments in the behavioural testing of memory in animals, have helped the debate to reach a consensus on some issues, with unresolved issues becoming more precisely formulated.

First, it is necessary to be clear about terminology. Episodic memory refers to our conscious memory for personal events and experiences occurring at a specific time in a specific place [11]. Recognition memory signals whether an event has previously been experienced. An immediate problem for animal studies is that it is unlikely that episodic memory could ever be demonstrated in animals. Key features of such tests for animals include the simultaneous learning of the ‘what’, ‘where’ and ‘when’ of an event. Such tests were first created for birds [12] but recent tests of episodic-like memory have been devised for rodents [13,14]. The findings from these studies not only increase the likelihood that there are primitive forms of episodic memory in animals, but also provide a platform for future studies into the neural basis of episodic-like memory.

In contrast to episodic memory, testing recognition memory in animals should be straightforward, providing direct comparisons with human data. In fact, the situation is again complex: if human recognition memory comprises two different processes (recollection and familiarity discrimination), do animals only use one of them?

Here, we explore these possible divisions within long-term memory and, on the balance of evidence, support two-process models of recognition that allocate the different processes to separate, but interconnected, brain structures. The starting point is a consideration of anterograde amnesia because this condition should not only reveal those structures necessary for episodic memory, but also whether dissociations between episodic and recognition memory can exist.

Anterograde amnesias: a network for episodic memory?

Anterograde amnesia disrupts memory for new autobiographical information, and so always impairs episodic memory. Damage in one of two key regions, the medial temporal lobe or the medial diencephalon, is most frequently associated with amnesia. (The diencephalon comprises the thalamus and hypothalamus.) In addition, damage in the basal forebrain, the retrosplenial cortex and the prefrontal cortex can result in amnesia or elements of the condition.

Within the temporal lobe, bilateral hippocampal damage is sufficient to cause anterograde amnesia [15]. Although pathology in no other single structure in the temporal lobe appears to be sufficient to induce anterograde amnesia, disruption of other temporal areas can increase the scale of the amnesia [3]. The sources of diencephalic amnesia are less certain, owing to the lack of cases with focal brain damage and, hence, are more speculative. One exceptional case (B.J.) occurred when a freak accident with a snooker cue produced selective, bilateral damage to the mammillary bodies that was sufficient to induce anterograde amnesia [16]. This unique case accords with a wide array of less specific
Figure 1. Schematic drawing of the main connections between the brain regions that underlie episodic memory. (a) The principal connections between the prefrontal cortex and the medial temporal lobe is shown in more detail. The dotted lines indicate unidirectional links, whereas the solid lines are bidirectional. Note the convergence of projections to the medial and orbital frontal cortices, and the way in which the return projections pass through the parahippocampal region (the perirhinal, parahippocampal and entorhinal cortices). (b) The parallel components of the extended hippocampal system, which anatomically form medial and lateral subsystems. (c) The main links between the parahippocampal region and the hippocampus. The anterior part of the parahippocampal region, centred on the perirhinal cortex, is the most probable source of familiarity information. Abbreviations: AD, anterior dorsal thalamic nucleus; AM, anterior medial thalamic nucleus; ATN, anterior thalamic nuclei; AV, anterior ventral thalamic nucleus; cingulum, cingulum bundle; HPC, hippocampus; MB, mammillary bodies; MD, medial dorsal thalamic nucleus; PFC, prefrontal cortex.
neuropathological evidence implicating the mammillary bodies in diencephalic amnesia [17]. The mammillary bodies are also noteworthy because they receive dense hippocampal inputs via a tract called the fornix (Figure 1). If this fornical route links temporal lobe and diencephalic amnesia, then fornix lesions must also induce anterograde amnesia. In contradistinction to early reports, more recent patient studies do, indeed, find that bilateral fornix damage is sufficient to induce anterograde amnesia [18]. However, the main projection of the mammillary bodies is not back upon the hippocampus (Figure 1). Rather, they project to the anterior thalamic nuclei via the mammillothalamic tract. Evidence that this tract is also crucial for memory comes from comparing thalamic infarcts that do or do not cause amnesia [19]. Numerous studies have described the pathology in Korsakoff’s syndrome, the most common form of diencephalic amnesia. Arguably the most precise analysis found that anterior thalamic pathology is the best predictor of memory loss [20]. Thus, the nature of the anatomical connections, along with current neuropsychological data, indicate that hippocampal projections to the anterior thalamic nuclei, many of which are relayed via the mammillary bodies, form part of an extended hippocampal system supporting episodic memory. Although additional clinical support is required, this view is reinforced by lesion studies in monkeys showing how the fornix, mammillary bodies and anterior thalamic nuclei are all essential for the normal performance of an ‘object-in-place’ task [21]. This task is thought to tax elements of episodic memory by encouraging animals to associate item and place (what? and where?). Disconnection studies in rats have also shown that the hippocampus and anterior thalamic nuclei require each other for spatial learning [22,23].

The retrosplenial cortex (areas 29 and 30) also fits within this system because this posterior cingulate region has dense reciprocal connections with both the anterior thalamic nuclei and the hippocampus (Figure 1). Pathology centred in the retrosplenial cortex can induce anterograde amnesia [24], whereas fMRI studies increasingly implicate the posterior cingulate in the recall of episodic information [24–27]. Furthermore, disconnection techniques indicate that the retrosplenial cortex is functionally dependent on the anterior thalamic nuclei and the hippocampus [28] in the rat brain. The projections from the anterior thalamic nuclei and retrosplenial cortex to the hippocampus create a means for the diencephalon to regulate medial temporal lobe activity but it will be important to uncover what additional memory functions are provided by these diencephalic links (Box 1). At the same time, brain pathologies are rarely confined to this extended hippocampal system. It is assumed that additional damage to adjacent temporal and diencephalic regions (the typical situation) will increase the severity of the amnesia, principally by disrupting other cognitive processes [8,9] (Box 1 and 2).

Having established a core of interlinked regions potentially important for episodic memory, it is time to consider evidence of dissociations between recognition memory and the recall of episodic information. To do this, the nature of recognition memory must first be discussed.

Box 1. How might the diencephalon contribute to memory mechanisms?
Relatively little is known about why or how diencephalic structures support memory, although important clues are provided by their anatomical connections (Figure 1). The extended hippocampal system naturally divides into two subsystems, the ‘medial’ and the ‘lateral’ [17,76,77]. The ‘medial system’ comprises the subiculum, medial mammillary nucleus, the anterior medial and anterior ventral thalamic nuclei, along with the ventral tegmental nucleus (Figure 1c). A characteristic feature of the medial system is the presence of neurones that fire at a theta rhythm. There is growing agreement that the medial system acting back upon the hippocampus could optimise conditions for effective encoding [77]. Not only can synaptic plastic change (long-term potentiation) in the hippocampus be produced by stimulation at theta frequency [77], but this oscillation might also provide a temporal signature to help to link episodes [78]. Recordings indicate that theta oscillations might also be important in signalling precise positional information [79]. One specific proposal is that the medial component of the extended hippocampal system reduces interference between competing signals by separating encoding and retrieval [80]. This medial system also has links with the prefrontal cortex (via the thalamus), thought to have a strategic role in encoding and retrieval.

The ‘lateral system’ comprises the presubiculum, the postsubiculum, the lateral mammillary nucleus, the anterior dorsal thalamic nucleus, along with the dorsal tegmental nucleus. A common feature of lateral system structures is the presence of head-direction cells, which show increased firing when an animal is facing in a particular direction [76]. The lateral (head-direction) system contributes to navigation (e.g. to path integration [76,79]) but might also help to create discrete contextual snapshots (such as the view on entering a room), thereby supporting episodic memory.

In addition, pathology in diencephalic sites outside the extended hippocampal system probably exacerbates amnesia. Neuropsychological studies indicate that damage to the nonspecific thalamic nuclei or the medial dorsal thalamic nucleus has qualitatively different effects on cognition to those seen after disruption of the extended hippocampal system (e.g. causing executive deficits); these effects are probably not sufficient to induce anterograde amnesia [19,81]. This might be because damage to these additional thalamic sites brings about cortical dysfunction, primarily in the prefrontal and cingulate cortices, therefore affecting recall and recognition via these mechanisms.

Assumptions about the nature of recognition memory
Introspection tells us that when we recognize a name or a person, two different subjective experiences can occur. Recognition might solely reflect a feeling of familiarity (‘knowing’) or recognition might be verified by recollecting something about the episode when that name or person was last encountered (‘remembering’). This distinction is captured in two-process models of recognition that regard ‘knowing’ and ‘remembering’ as separate processes that both support recognition memory [5]. A variety of techniques [4,5] is currently used to distinguish recollective recognition from familiarity detection. These techniques include: ‘remember/know’ – asking subjects to make introspective judgements about recognized stimuli [i.e. if it familiar (‘know’) or if the event can be recollected (‘remember’)]; the ‘process-dissociation’ procedure – where the ability to remember when or where each test stimulus was first presented provides a measure of recollective-recognition; the ‘receiver operating characteristic’ (ROC) procedure – where the subjects’ ratings of their confidence of individual recognition judgements is used to plot an ROC curve, in which the relationship between
It has proved possible to develop economical, fast, high-capacity computational models of familiarity discrimination based on response changes when stimuli are repeated [10,82]. These models provide fast and reliable signalling of novelty (or familiarity) for the cost of relatively very few neurons. Indeed, such models using the number of neurons available in the human perirhinal cortex have the capacity to store the prior occurrence, and hence judge familiarity with high accuracy, for new pictures appearing every few seconds throughout the whole of a human life. Such modelling has revealed that a network where the primary change is one of synaptic weakening rather than synaptic strengthening (Figure 3) is very much more efficient [82]. Essentially, this efficiency gain is because synaptic strengthening drives the network in the direction of feature detection (stimulus classification and identification) — that is, registering and signalling what is common across stimuli. Synaptic weakening has the opposite effect — that is, emphasizing what is not shared and hence novel across stimuli. An important further implication is that neurons responsible for novelty-familiarity discrimination should not be the same as those responsible for feature extraction (stimulus classification). Even so, a familiarity discrimination network requires highly processed sensory information as its input. Together, these ideas suggest that there should be both a dependency upon and a separation between semantic memory and the familiarity discrimination component of recognition memory. The observed close proximity of neurons that do (putative familiarity discriminators) and those that do not (putative classifiers) change their response on stimulus repetition within perirhinal and adjacent cortices is consistent with this model, as is also the additional role of the perirhinal cortex in perceptual functions [8,9,83]. It is important to note that lesions of perirhinal cortex that involve both types of neuron would be expected to impair both familiarity and perceptual processes.

Box 2. Neurophysiological models of familiarity discrimination

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Confidence and accuracy is used to signal recollective recognition.

Dual-process models readily permit dissociations between recognition memory and episodic memory. One way is if it is assumed that only recollective recognition relies on episodic memory (a parsimonious account). As a consequence, dissociations could occur between familiarity-based recognition and episodic memory. However, two-process models of recognition are not universally accepted because single-process models can be derived that are even more parsimonious [1,2]. For example, feelings of familiarity (‘know’) could reflect low confidence, whereas ‘remember’ reflects high confidence [2], so leading to single dissociations of spared ‘familiarity’. Thus, the key test is whether these recognition components can be doubly dissociated. Furthermore, because each of the techniques used to distinguish putative components of recognition relies on assumptions that have been challenged [4,29], it is necessary to consider evidence from various sources.

Evidence for dissociations between episodic and recognition memory

One source of evidence comes from event-related potentials. Two different anatomical populations have been identified that are functionally and temporally dissociable [4]. The first population is indexed by activity over the frontal scalp from 300–500 ms poststimulus, and the attributes of this scalp activity (e.g. insensitivity to levels of processing) make it a likely neural correlate of familiarity [4]. The second population is evident over the parietal scalp from 500–800 ms and might index recollection [4].

A second source is the growing number of fMRI studies that support dual-process accounts of recognition memory because dissociable patterns of activity are found for measures of familiarity and recollection [26,27,30–35]. Some of these dissociations reflect the nature of the response — for example, activation for recollection and deactivation for familiarity [30,33,34]. Other dissociations are structural. Using the remember/know procedure [27,32], increased hippocampal activity has been correlated with reports of recollection of the learning episode but not with familiarity. Variants on the process-dissociation procedure have linked hippocampal activity with recollection but anterior parahippocampal cortex activity with familiarity [26,31,34–36]. Finally, use of confidence judgements has revealed a double dissociation between hippocampal and anterior parahippocampal cortex activity — the former associated with recollection, the latter with familiarity [26].

The third source is from studies of amnesia. Most amnesics are densely impaired for both episodic recall and recognition. Nevertheless, occasional amnesics show a seemingly normal performance on some tests of recognition [16,36–40] (Figure 2). Other amnesics show relative sparing of recognition over recall [18,41,42] (Figure 2). Although care must be taken in equating the level of difficulty (recognition tests are often easier), there seems to be little doubt that this single dissociation can be found in some patients. Very occasionally, patients show the reverse pattern: impaired recognition but preserved episodic memory [43].

Is there a feature that links amnesic cases with apparent sparing of recognition? Two logical candidates are severity of amnesia and site of brain pathology. Direct comparisons of the severity of amnesia depend on standard psychometric measures that exclude tests of recollection. The Delayed Recall Index from the Wechsler Memory Scale Revised is sensitive to amnesia, although is prone to floor effects. The mean index score for Korsakoff’s amnesia [44], which invariably impairs recognition, is 57.3 (100 is...
normal, 50 is the lowest score). Cases or cohorts with spared recognition (Figure 2) are variable but many show similar poor index scores – 50 (case K.N. [37]); 72 (case Y.R. [36]); 54 (case B.J. [16]); 57 [38]; 59 [39]; and a mean of 56.3 [18] (Fornix) – so that mildness of amnesia does not predict spared recognition.

The site of pathology looks more promising because a high proportion of cases with spared recognition show bilateral pathology (based on MRI) that appears to be largely confined to one of a core group of structures. Thus, the key pathology in these cases is thought to be located in the hippocampus [36–40,42], the fornix [18] or the mammillary bodies [16]. The implication is that damage within the extended hippocampal system impairs recall but partially spares recognition – suggesting that damage outside this system selectively contributes to the recognition deficit. This view is challenged by some cases with hypoxia (lack of oxygen to the brain), in whom there appears to be selective hippocampal shrinkage [45,46]. These particular patients have consistently revealed clear, often equivalent, deficits in recall and recognition [45,46], yet the extent of hippocampal shrinkage is no greater than that in cases with spared recognition. The cause of this inconsistency is much debated, especially because other hypoxic cohorts do show a relative sparing of recognition [41,47]. Because there is much individual variability with this aetiology, combined with the likelihood of more diffuse damage that contributes to memory loss [48], the effects of precise hippocampal lesions in animals should help to clarify this debate (see later).

The study of amnesia, with its loss of episodic recall, would provide even stronger support for two-process models if cases with spared recognition reflect the selective preservation of familiarity based recognition. Using a variety of techniques (‘remember/know’, ‘process dissociation’, the ROC procedure, structural equation modelling), this key prediction has recently been tested. Amnesics with recognition sparing do, indeed, typically show a selective sparing of familiarity [36–39,41,42,47]. In all of these cases, the pathology was focused in the hippocampus, supporting the view that this structure is necessary for recollective, but not familiarity-based, recognition. However, there is some counter evidence because hypoxic amnesics with hippocampal atrophy can show a loss of both recognition components [41,45–47].

As already mentioned, aetiologies such as hypoxia pose problems when defining effective pathology. Such problems prompted an ingenious study in rats [49], based on the ROC procedure. Rats were given odour recognition tests with varying amounts of reward and involving greater effort for some choices (i.e. measuring the ‘confidence’ that the animal could solve each recognition trial). Similarly to the human ROC procedure, the rat ROC curves could be broken into two components, indicating separate recollection and familiarity. Furthermore, hippocampal lesions removed the recollective component, while sparing familiarity [49]. The results again support the view that the hippocampus is required for recollective, but not familiarity-based, recognition.

An even stronger case for two-component recognition processes, based on different neuronal populations, would emerge if the opposite dissociation were found – that is, a loss of familiarity but a sparing of recollective recognition. Although cognitive manipulations [5] and fMRI studies [26] support this double dissociation, it has not been found clinically. This might be for anatomical reasons. Selective damage to the anterior parahippocampal cortex would be the most likely cause of this dissociation but the same region also provides sensory information to the hippocampus and is a major route for prefrontal influences upon the hippocampus (Figure 1). Thus, parahippocampal damage might cause a loss of familiarity, but through different neurones (Box 2) disconnect the hippocampus and so alter recollection. Evidence that familiarity-based recognition memory processes rely on the parahippocampal cortex, rather than on the hippocampus, will now be considered.

The role of the parahippocampal cortex and the neural basis of familiarity-based recognition

Recordings in monkeys performing visual recognition tasks indicate that up to 25% of neurones in the anterior parahippocampal region, centred in the perirhinal cortex, respond strongly to pictures or objects that are new but only weakly when items have been seen previously [6,50,51] (Figure 3a). The change is sometimes termed ‘repetition suppression’ but there is no evidence that response reductions rely upon a suppressive or inhibitory process; selective, activity-dependent synaptic weakening is a more plausible hypothesis (Box 2). These neuronal changes are appropriate for making familiarity judgements because they show single-exposure learning, the responses being attenuated on the second appearance of stimuli. Such response reductions are found even after long (>24 h), distraction-filled delays that involve the presentation of many other stimuli. Moreover, there is evidence of a very high potential memory capacity: individual neurones continue to respond strongly to novel stimuli and weakly when shown previously presented stimuli, even after an animal has seen many hundreds of stimuli.

If the perirhinal cortex is vital for familiarity judgements, then removal of this cortex will impair recognition memory. The lack of patients with discrete perirhinal cortex lesions means that this prediction has only been tested directly in animals. It has been shown repeatedly, both in monkeys and rats [3,6,8,52], that perirhinal cortex damage does severely impair object recognition memory. These findings can be contrasted with the effects of discrete hippocampal lesions. Some studies of monkeys and rats have found no effect of hippocampal lesions, whereas others have reported mild impairments [3,53–57]. A vigorous debate has centred on the causes of this inconsistent hippocampal effect because it has considerable bearing on divisions of functions within the temporal lobe – that is, is the hippocampus also required for familiarity?

Simple explanations for the inconsistent effects of hippocampal lesions in animals on tests of recognition, such as the extent of hippocampal damage or length of retention interval, do not explain the data [56–58]. Although the ROC data already mentioned suggest that hippocampal-based recollection could potentially explain mild recognition deficits [49], this explanation is prone to circularity. Furthermore, the presumption remains that
animals rely on familiarity because recollection requires more complex cognitive processes, which remain to be proven. Other potential explanations relate to tests using relative rates of exploration for novel versus familiar stimuli where hippocampal lesions can have more consistent effects. However, the same lesions could affect spatial search strategies and, hence, patterns of exploration [56]. A related issue is whether learning the spatial location of an object might affect its subsequent recognition, given that hippocampal lesions impair object-in-place tasks [21]. Two things are agreed. First, hippocampal lesions in animals often have no apparent effect on tests of recognition. Second, perirhinal damage is far more disruptive than is hippocampal damage [8,52]. Interestingly, a double dissociation is found in rats because hippocampal damage is much more disruptive than perirhinal damage on tests of spatial memory [7,59], highlighting qualitatively different functions within the medial temporal lobe.

Thus, animal studies show that response reductions in the perirhinal region could provide the key temporal lobe substrate for familiarity discrimination involving single-trial learning for infrequently presented stimuli [6]. Crucially, recent fMRI studies now support this view because noncontextual recognition (i.e. familiarity) in humans is associated with decreased activation in the anterior parahippocampal region containing the perirhinal cortex [26,33,34,60–62] (Figure 3). Increased feelings of familiarity, for example, are associated with decreased perirhinal activity [26,34]. At present, response reductions are the only discovered change in neuronal responsiveness in perirhinal cortex satisfying the requirements for general, long-term familiarity discrimination involving single-exposure learning for rewarded and unrewarded stimuli [6]. By contrast, a different mechanism underlies learning when stimuli are repeated frequently. Here, familiarity is of limited value. Both recording and animal lesion studies indicate that such learning involves the hippocampus [63,64].

Current evidence suggests that the familiarity discrimination mechanism in the perirhinal and adjacent cortices is related to individual stimuli, so that it does not deal with the novel arrangement of familiar spatial stimuli.
[49,65], nor with associative and contextual aspects of recognition memory. Thus, there needs to be a further component to recognition memory that uses other brain structures (e.g. the hippocampal system) to deal with these more complex stimuli and events [42,66–70].

**Bringing familiarity and recollection together**

In a prescient paper, Warrington and Weiskrantz [71] suggested that inputs to the prefrontal cortex from the mammillary bodies and medial thalamus ensured effective cognitive mediation for optimal encoding (e.g. elaboration, organization, imagery, embellishment), such that their disconnection could contribute to amnesia [71]. To their model, we can add direct prefrontal inputs [72] from the retrosplenial cortex, the anterior and rostral midline thalamic nuclei and the hippocampus (via the fornix) (Figure 1). Many of these projections converge in the medial and orbital prefrontal cortex, regions that also receive parahippocampal projections (Figure 1).

Distinct prefrontal regions have been identified with processes that are important for preparing to retrieve, and for monitoring or manipulating the outcome of retrieval operations [4,73,74]. These encoding and retrieval processes are likely to involve prefrontal projections acting back upon the hippocampus. In fact, these return projections are primarily to the parahippocampal region (Figure 1), which then projects to the hippocampus. Intriguingly, there is evidence from frontal activation patterns that familiarity might form a gateway to recollection attempts, so that low familiarity might disengage recollection attempt [61]. This process might explain the finding that familiarity might form a gateway to recollection that familiarity might form a gateway to recollection attempts, so that low familiarity might disengage recollection attempts [61]. This process might explain the finding that familiarity might form a gateway to recollection attempts, so that low familiarity might disengage recollection attempts [61]. This process might explain the finding that familiarity might form a gateway to recollection attempts, so that low familiarity might disengage recollection attempts [61]. This process might explain the finding that familiarity might form a gateway to recollection attempts, so that low familiarity might disengage recollection attempts [61].

It is evident that understanding the neural basis of long-term memory will not come from analysing just one structure or even one region. This task will require clearly formulated cognitive models set within extensive anatomical frameworks. The notion espoused here is that there are two separate components to recognition memory (familiarity based and recollective based), which have different neural substrates. This issue is addressed with the background assumption that amnesias caused by temporal lobe and diencephalic damage share common core features and, hence, common causes. Further advances will depend on addressing some of the questions outlined in Box 3.

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**Box 3. Future questions**

- Can we find cases of diencephalic amnesia with highly selective pathology? What is the status of their recognition memory?
- What are the limitations on perirhinal familiarity discrimination, and under what circumstances might it contribute to associative recognition?
- When is perirhinal input important for hippocampal functioning, and how and when do the two systems interact?
- Why does diencephalic amnesia typically involve a loss of recognition, given that the anterior parahippocampal region is spared?
- How might the projections from the prefrontal cortex to the medial diencephalon contribute to memory?
- Is it possible to develop independent, valid measures of familiarity-based and recollective-based recognition?
- Can functional brain imaging be used to test the contributions from different diencephalic brain areas to memory?
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