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Deconstructing Human Memory: Insights from Amnesia

Mieke Verfaellie¹, Ph.D. and Margaret M. Keane, Ph.D.^{1,2}

¹Memory Disorders Research Center, VA Boston Healthcare System and
Boston University School of Medicine

²Department of Psychology, Wellesley College

Correspondence address:

Mieke Verfaellie, Ph.D.
Memory Disorders Research Center
VA Boston Healthcare System (151A)
150 S Huntington Avenue
Boston MA 02130
verf@bu.edu

The Amnesic Syndrome

The central feature of amnesia is an impairment in new learning (anterograde amnesia) that is evident regardless of the nature of the information (i.e., verbal or visuospatial) or modality of study presentation (i.e., auditory or visual); it is typically accompanied by difficulty in the ability to retrieve memories acquired prior to the onset of illness (retrograde amnesia), but the severity of this impairment is more variable. Amnesia occurs in the context of otherwise relatively preserved intellectual functioning and cognitive abilities. Most strikingly, amnesic patients have intact immediate or short-term memory, as evidenced by the ability to follow an ongoing conversation, or to immediately repeat back a sequence of words or numbers. Following any interference or delay, however, memory for the information is lost.

Amnesia can arise from a number of different etiologies, including anoxia, herpes simplex encephalitis (HSE), stroke, Wernicke-Korsakoff syndrome (WKS), and rupture and repair of an anterior communicating artery (ACoA) aneurysm (O'Connor & Verfaellie, 2002). The amnesia is a direct consequence of damage to structures in the medial temporal lobes including the hippocampus and surrounding entorhinal, perirhinal and parahippocampal cortices (e.g., anoxia, HSE), midline diencephalon (e.g., thalamic stroke, WKS), basal forebrain (e.g., ACoA aneurysm) or the fiber tracts that connect these regions, such as the fornix. Despite the etiological heterogeneity of the syndrome, the core characteristics of amnesia are relatively consistent. Efforts to delineate qualitative differences as a function of etiology have focused on both the contribution of lesion site (e.g., diencephalon vs MTL; Parkin, 1993) and lesion extent (e.g., hippocampus proper vs hippocampus and surrounding cortices; Aggleton & Brown, 1999), but such distinctions remain the focus of debate. More clearly established is the impact of disruption of frontally mediated executive functions, which is often superimposed on the core amnesia in patients with diencephalic and basal forebrain lesions. In such cases, the anterograde amnesia may be exacerbated by additional impairments in planning and organizing incoming information, as well as in the initiation and evaluation of memory search and effortful retrieval (Moscovitch & Winocur, 2002). In clinical practice, these additional impairments, when severe, can cloud the distinction between selective amnesia and more pervasive cognitive impairment.

Despite the wide-ranging nature of the long-term memory impairment in patients with amnesia, it is striking that the impairment is not uniform across all forms of long-term memory. The distinction between preserved and impaired aspects of memory has guided much cognitive neuropsychological research and has contributed greatly to our understanding of the cognitive and neural architecture of various components of memory. However, the interest in dissociations in patients' performance led to a strong focus on isolating distinct forms of memory. This effort may have overshadowed the fact that many tasks draw on multiple memory processes, not all of which are equally affected in amnesia. More broadly, distinct forms of memory may commonly interact in the service of task performance. We review below some of the salient experimental findings that have led to these insights.

Amnesia: Experimental Studies

Implicit versus explicit memory

Patients with amnesia show severe impairments in their ability to intentionally retrieve recently acquired information, whether in recall or recognition tasks. This explicit memory impairment stands in striking contrast to their intact performance in a number of other memory tasks in which learning is expressed implicitly, through performance rather than recollection. Over the last two decades, an extensive body of research in amnesia has focused on one particular example of implicit memory, namely repetition priming (for reviews, see Moscovitch, Vriezen, & Gottstein, 1993; Verfaellie & Keane, 2001). Repetition priming is typically assessed in tasks in which subjects identify briefly presented words, complete word stems or fragments with the first word that comes to mind, freely generate words in response to cues, or make decisions about characteristics of presented words or pictures. Priming manifests as improved performance (i.e., detection, generation, or faster decision) for those stimuli to which an individual was previously exposed relative to comparable not previously exposed stimuli. Dissociations in amnesia between intact performance on implicit memory tasks and impaired performance on explicit memory tasks have laid the ground work for the view that memory is not a unitary function, but rather, that there are distinct forms of memory that may have functionally and neurally different bases.

Most tasks involve a range of processes from stimulus identification to responding, and accordingly, facilitation as a result of prior experience can occur at several processing stages, including perceptual, phonological/lexical, semantic, and response stages. One particularly influential distinction has been that between perceptual and conceptual priming (Roediger & McDermott, 1993): perceptual priming is sensitive to the reinstatement of physical features of previously presented stimuli at test, whereas conceptual priming is sensitive to the reinstatement of semantic features. The preservation of both of these forms of priming in amnesia establishes that these effects are independent of MTL structures. Behavioral evidence from patients with lesions outside of the MTL implicates posterior visual areas in visuoperceptual priming effects (Gabrieli, Fleischman, Keane, Reminger, & Morrell, 1995; Keane, Gabrieli, Mapstone, Johnson, & Corkin, 1995; Kroll et al., 2003) and higher-order multimodal association areas in conceptually based priming effects (Fleischman & Gabrieli, 1998; Keane, Gabrieli, Fennema, Growdon, & Corkin, 1991). Subsequent imaging research has confirmed and refined these neuroanatomical distinctions, pointing to posterior neocortical regions that represent the perceptual form and structure of items as the neural basis of perceptual priming, and areas in inferior temporal and frontal regions that underlie the conceptual features of items as the neural basis of conceptual priming (for review, see Schacter, Wigg, & Stevens, 2007). Further, these imaging studies have generally shown reductions in cortical activity associated with priming: such activity reductions reflect the increased efficiency of processing of primed stimuli, possibly due to increased “tuning” of neocortical representations (Wiggs & Martin, 1998).

At a cognitive level, increased processing efficiency has been conceptualized as enhanced fluency or ease of processing of stimuli that were previously encountered (Jacoby, 1983). Manipulations of processing fluency influence judgments about a variety of non-

memorial attributes, such as duration, perceptual clarity, and liking, but they also can impact memorial judgments. Indeed, one influential view of recognition memory suggests that recognition judgments can be based on one of two processes: recollection (i.e., retrieval of contextual detail) or familiarity (i.e., an undifferentiated sense of oldness) (Mandler, 1980). Judgments of familiarity are thought to be based on fluency of processing (Jacoby & Dallas, 1981): since prior experience enhances processing fluency, such fluency can be used as a heuristic to make decisions about prior occurrence. Consistent with this notion, a large number of cognitive studies have documented that fluency can be used as a basis for familiarity-based recognition (for review, see Yonelinas, 2002). Importantly, several patient studies similarly have shown that amnesic patients (Verfaellie & Cermak, 1999) and patients with Alzheimer's disease (Wolk et al., 2005) can use fluency as a cue for recognition. Nonetheless, the link between fluency and familiarity has remained a matter of intense debate in the neuropsychological literature, as findings of chance recognition (i.e., familiarity) in the face of intact priming (i.e., fluency) have been taken as powerful evidence for the notion that implicit and explicit memory tasks do not share underlying processes or memorial signals (Hamann & Squire, 1997; Levy, Stark, & Squire, 2004).

In our own work, we have taken a different approach to attempt to reconcile these seemingly contradictory findings. In line with the cognitive literature, we assume that fluency signals support both implicit memory and familiarity-based explicit memory, but we argue that whereas priming is a direct (unmediated) consequence of fluent processing, familiarity-based recognition requires an additional step whereby fluency is attributed to a memorial source. The need for an additional attributional process (and the potential reluctance of amnesic patients to use that process) may provide an explanation for the apparent paradox that despite the fact that priming is largely intact in amnesia, the fluency that supports implicit memory does not more fully support familiarity-based recognition in these same patients.

In several studies, we have demonstrated that amnesics' use of a fluency-heuristic in recognition can be experimentally enhanced. In one study (Verfaellie, Giovanello, & Keane, 2001), we encouraged fluency attributions through task instructions that provided participants information about the alleged proportion of old items on a recognition test (30% vs 70%). The actual proportion of old items on the test was constant across conditions, but we hypothesized that providing participants instructions that a majority of items were old would lead them to relax their response criterion and rely to a greater extent on processing fluency. Consistent with this hypothesis, amnesic patients had higher recognition accuracy in the 70% than in the 30% condition. In another study (Keane, Orlando, & Verfaellie, 2006), we manipulated the salience of fluency cues by drawing targets and distractors from the same pool of letters (yielding high perceptual overlap between targets and distractors) or different pools of letters (yielding low perceptual overlap between targets and distractors). Amnesic patients had higher accuracy in the low- compared to the high-overlap condition, presumably because of the increased salience of the fluency "contrast" between targets and distractors in the low-overlap condition. These findings suggest that the increased salience of fluency cues promotes the use of a fluency heuristic that is ordinarily not fully engaged in amnesia. Findings such as these highlight the importance of understanding factors that influence

the use of a fluency heuristic in amnesia, as a means of gaining a fuller understanding of the relationship between priming and recognition memory (see also Voss & Paller, 2009; Willems, Salmon, & Van der Linden, 2008).

So far we have focused on priming and fluency effects for single items; another area of interest concerns amnesics' performance on tasks that assess priming of associations newly established at study. The interest in new-associative priming in amnesia stems from its relevance to theories that postulate that the hippocampus is critical for computing arbitrary links between unrelated stimuli, and to theories that characterize the core deficit in amnesia as one of binding arbitrary pieces of information (J. D. Ryan, Althoff, Whitlow, & Cohen, 2000). Here, we focus specifically on implicit memory for novel perceptual associations, because at present, most research has focused on the establishment of novel associations in the context of visual perceptual tasks. Even within this restricted domain of study, different outcomes have been obtained. On the one hand, several studies have assessed priming for the association between two words by comparing performance when a target stimulus at test is presented with the same context word as at study rather than with a different (albeit also studied) context word. Using both perceptual identification and lexical decision tasks, associative priming has been found to be intact in amnesia (Gabrieli, Keane, Zarella, & Poldrack, 1997; Goshen-Gottstein, Moscovitch, & Melo, 2000; but see Yang et al., 2003). On the other hand, several studies have examined the formation of associations between visual contextual information and target items in the context of a visual search task. Whereas normal individuals show facilitation in visual search for a target embedded in repeated arrays, amnesic patients (Chun & Phelps, 1999), and specifically those with extensive MTL lesions (Manns & Squire, 2001), have not shown such contextual facilitation. In a somewhat different paradigm examining preferential looking, normal participants show enhanced eye movements to regions of a previously viewed scene that have been altered, but again, amnesic patients have failed to show this pattern (J. D. Ryan et al., 2000). Importantly, the priming effects in these tasks, reflecting the establishment of relationships between different elements of complex visual displays, occur in control subjects even in the absence of explicit memory for repeated contexts or changes in scenes, and thus appear to reflect an unaware memory mechanism (but see, Smith, Hopkins, & Squire, 2006).

How can we understand the presence of intact new associative priming for perceptual associations between two words, but impaired new associative priming for more complex visuospatial contexts? One possibility relates to the nature of the binding operations that are required in these respective tasks. Mayes and colleagues (Mayes, Montaldi, & Migo, 2007) make a useful distinction between within-domain associations (formed between the same or very similar kinds of items) and cross-domain associations (formed between items from distinct modalities or linking information spatially), and suggest that whereas the former may be mediated by activation in closely adjacent neocortical regions, the latter may be mediated by activation in distant neocortical regions that requires integration through the MTL. Although this formulation was proposed to account for findings in explicit memory, it may also provide an explanatory framework for the divergent findings concerning implicit associative memory: associations between two words may be established directly within visual word processing areas, through co-

activation of the representation of individual word forms. In contrast, associations between objects and a spatial context or scene may require MTL mediation. Supporting this notion, neuroimaging studies of implicit memory point to the importance of MTL cortical regions (Goh et al., 2004; Preston & Gabrieli, 2008) and hippocampus proper (Goh et al., 2004) in the establishment of spatial and contextual representations that integrate multiple elements.

An additional consideration relates to the fact that neocortically- and hippocampally-mediated associations are qualitatively different (Eichenbaum & Cohen, 2001): whereas neocortical binding leads to the establishment of unitized representations that are inflexible and can only be accessed as a whole, hippocampal binding allows for the establishment of relational representations that can be accessed flexibly through their separate parts. Consistent with the notion that amnesic patients can only form inflexible unitized representations, studies examining implicit memory for words pairs in which the study and/or test stimuli were presented sequentially rather than simultaneously, have yielded impaired associative priming in patients with amnesia (Carlesimo, Perri, Costa, Serra, & Caltagirone, 2005; Paller & Mayes, 1994).

Semantic versus episodic memory

The cardinal impairment in amnesia is an inability to form and retrieve memories of personally experienced events (i.e., episodic memory). Seen in contrast to patients' generally preserved intelligence and good fund of general knowledge, this led to early conceptualizations of amnesia as a selective impairment in episodic memory, with sparing of semantic memory (Cermak, 1984; Wood, Ebert, & Kinsbourne, 1982). Further research, however, has made clear that such a view is inaccurate: whereas premorbid semantic memory is largely intact in amnesia, new semantic learning is substantially impaired. Here we briefly describe findings both in the retrograde and anterograde domain, with the aim of demonstrating that although functionally and neurally separable, episodic memory and semantic memory do not operate in isolation.

Within the domain of remote semantic memory, with the exception of information acquired within the years immediately preceding the onset of amnesia, MTL patients show sparing of general semantic and factual knowledge (Manns, Hopkins, & Squire, 2003; Verfaellie, Reiss, & Roth, 1995). This sparing stands in stark contrast to their impairment in retrieving detailed, episodic memories, an impairment that is temporally extensive and in cases of severe amnesia can cover the entire lifespan (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Rosenbaum et al., 2008; Steinvorth, Levine, & Corkin, 2005) although this has not always been observed (Bayley, Gold, Hopkins, & Squire, 2005; Kirwan, Bayley, Galvan, & Squire, 2008). The differential impairment in amnesia in remote episodic compared to semantic memory reinforces the distinction between these two forms of memory. Further, it suggests that the permanent storage and retrieval of detailed episodic information is mediated by MTL structures, whereas the storage and retrieval of semantic memories, once consolidated, occurs neocortically, without MTL mediation.

Whether the acquisition of new semantic memories can occur independent of the MTL structures that mediate episodic learning is more controversial. The impairment of new

semantic learning in amnesia is now firmly established, and it is clear that the severity of the semantic learning impairment is linked to the extent of MTL pathology (Verfaellie, 2000). However, it is equally clear that some new semantic information can be acquired even in patients with dense episodic impairment (Kitchener, Hodges, & McCarthy, 1998; Vargha-Khadem et al., 1997). These findings can be reconciled if it is assumed that the acquisition of semantic memory can occur independent of episodic memory/MTL structures, but that nonetheless, semantic learning is typically enhanced by MTL mediation. Newly acquired information is always embedded in an episodic context, and as such, episodic learning helps support semantic acquisition. Only with time and/or repeated presentation will the gist information become dissociated from its spatiotemporal context, reflecting a process of gradual neocortical transfer with the establishment and consolidation of context-free semantic representations. In patients with extensive MTL lesions, however, gradual neocortical learning may occur of necessity in isolation. Thus, whereas the acquisition of semantic and episodic memory may be tightly coupled in normal cognition, in patients with MTL lesions this coupling is disrupted, exposing the operation of neocortical learning by itself.

The contribution of episodic memory, however, is not limited to new semantic learning. Recent evidence suggests that even in tasks measuring retrieval of long-established semantic information, episodic memory may play a role. Ryan and colleagues (L. R. Ryan, Cox, Hayes, & Nadel) observed hippocampal activation during a prototypical semantic memory task – retrieval of category exemplars. This finding suggests that the hippocampus is involved in the retrieval of semantic information, but leaves unanswered whether it is needed to do so, and if so what role it plays. To address these questions, we (Greenberg, Keane, & Verfaellie, 2009) asked patients with MTL lesions to generate category exemplars for three types of categories that tended to elicit different retrieval strategies in control participants: categories that elicited autobiographical spatial retrieval strategies, categories that elicited autobiographical but nonspatial strategies, and categories that elicited neither autobiographical nor spatial strategies. Patients with MTL lesions were more impaired for the former two types than for the latter, and once phonemic fluency was taken into account, the impairment was selective to categories that elicited autobiographical strategies. These findings suggest that the hippocampus may contribute to semantic retrieval through the retrieval of autobiographical detail; hippocampal damage prevents this contribution of autobiographical memory to semantic retrieval in amnesia. In a similar vein, it has been shown that having a personal autobiographical experience associated with famous names (as evidenced by judgments of recollective experience) facilitates fame judgments, but amnesic patients with MTL lesions fail to show this facilitation (Westmacott, Black, Freedman, & Moscovitch, 2004). The inverse also holds: in patients with semantic dementia, relatively unimpaired autobiographical memory can help preserve or re-establish degenerating semantic knowledge (Snowden, Griffiths, & Neary, 1994; Westmacott et al., 2004). Such findings reinforce the notion that episodic memory and semantic memory do not operate in isolation.

While so far, we have considered the contribution of episodic memory to semantic learning and retrieval, there is also evidence for the contribution of semantic memory to episodic learning. The “levels of processing” framework established many years ago that

new information is remembered better when it is processed semantically, presumably because semantic encoding allows new information to be linked with prior knowledge (Craik & Lockhart, 1972). In keeping with this framework, patients with semantic dementia and aphasic patients with semantic impairments perform poorly on verbal learning tasks (Graham, Simons, Pratt, Patterson, & Hodges, 2000; Ween, Verfaellie, & Alexander, 1996). However, the contribution of semantic memory extends beyond the simple analysis of incoming formation. Evidence in normal individuals suggests that information is remembered better when it can be anchored to pre-existing schematic knowledge (e.g., Anderson & Pichert, 1978; Brewer & Treyens, 1981). To evaluate whether schematic activation can support episodic learning in amnesic patients, we asked patients to remember prices of everyday grocery items (Kan, Alexander, & Verfaellie, 2009). In one condition the to-be-remembered prices were consistent with prior knowledge about the items, whereas in another condition they were not. Control subjects had higher recognition memory for prices of items in the congruent than in the incongruent condition. A similar congruency benefit was seen in patients with restricted MTL lesions, who had intact semantic systems, but patients with lesions extending into the lateral temporal lobes, who had compromised semantic systems, failed to show a congruency benefit. These findings suggest that when prior knowledge structures are intact, they can support the acquisition of new information by facilitating the integration of new information into existing knowledge structures. The contribution of pre-existing semantic memory to episodic learning illustrated by these findings provides a potential explanation for the surprising clinical observation that some amnesic patients are able to acquire a considerable amount of new information relevant to long-standing personal interests.

Lessons Learned

In the eighties and nineties, cognitive neuropsychological studies of amnesia, with their focus on demonstrating dissociations between different aspects of memory, played a critical role in laying bare distinct forms of long-term memory. The emphasis on fractionation of memory was useful in that it allowed broad distinctions, such as those between implicit and explicit memory and between semantic and episodic memory, and allowed researchers to fully characterize these distinct forms of memory. More recent patient studies have led the way to a more refined understanding of the processes that are impaired and preserved in amnesia, revealing that process-impairments associated with amnesia do not necessarily respect taxonomic boundaries. Rather, these component processes contribute to putatively different forms of memory. Moreover, selective impairments in amnesia provide a window onto functional interactions between different forms of memory in normal cognition.

This gradual shift in emphasis reflects the accumulation of critical evidence. Early studies of implicit memory in patients with amnesia, under conditions where explicit contamination was carefully avoided, were essential to elucidating the nature of the processes that underlie priming in different tasks. Similarly, systematic study of amnesics' performance on recall and recognition tasks was necessary to recognize the existence of distinct explicit memory processes that may be differentially affected in amnesia. The emphasis on processes underlying performance within each type of

memory task was prerequisite to the examination of their potential overlap, leading to the recognition that a fluency process is not unique to implicit memory, but is also a critical building block for familiarity-based (explicit) recognition memory.

The recognition that there is not a one-to-one mapping between cognitive processes and categories of memory is similarly illustrated by more recent findings indicating that amnesia does not yield a uniform dissociation between binding processes in the service of implicit and explicit memory task performance. First, the finding that amnesic patients show intact performance on associative priming tasks that require the establishment of a novel association among similar items, but impaired performance on associative priming tasks that require the establishment of associations among heterogeneous items, suggests that – even within the domain of implicit memory – not all implicit binding processes are alike. Rather, they differ depending on the nature of the representations that are created, with within-domain associations being instantiated directly in neocortex and cross-domain associations requiring hippocampal mediation. Second, the finding that hippocampal damage interferes not only with the formation of episodic memories, which inherently places high demands on associative processes, but also with some forms of implicit associative memory, challenges the notion that the hippocampus plays a selective role in binding processes that support explicit or aware memory performance. Rather, it suggests that memory representations made up of disparate, non-local elements require hippocampal mediation, regardless of whether they are accessed in the context of implicit or explicit memory tasks. Taken together, these insights have shifted the focus of memory research from an emphasis on long-term memory systems that can be differentiated according to conscious awareness, to an emphasis on the nature of the representations and processes that support performance on any particular task (see e.g., Reder, Park, & Kieffaber, 2009).

A similar emphasis on the nature of memory representations enhances our understanding of the operation of and interactions among episodic and semantic memory. While episodic representations bind together the different aspects that make up an experienced event in its contextual richness, semantic representations are a-contextual abstractions formed across time and repeated experience. In many tasks, however, these representations operate in concert. As discussed above, episodic contextual information may routinely support the acquisition of new semantic knowledge, making it difficult to disentangle the two forms of learning. In this respect, the study of patients with extensive MTL lesions offers a unique opportunity to elucidate neocortical semantic learning in isolation. Such learning occurs very gradually and lacks the flexibility associated with episodic memory (Bayley, Frascino, & Squire, 2005), but its boundaries are still not fully established (Stark, Stark, & Gordon, 2005).

Perhaps even more compelling are interactions between episodic memory and already well-established semantic memory, in that they suggest continued MTL-neocortical interactions once neocortical representations are fully established. Such interactions reflect the fact that retrieval from semantic memory may be enhanced through the use of autobiographical retrieval strategies – a process that is impaired in patients with amnesia. This process may be particularly beneficial when relatively preserved autobiographical memory can help buttress degraded semantic memory, as in patients with semantic

dementia. A question that remains to be addressed more fully concerns the nature of the “episodic” representations that support semantic retrieval. In some cases semantic retrieval may be supported by autobiographical retrieval strategies that lead to recovery of information pertaining to a unique past event. In other cases semantic retrieval is more likely supported by autobiographical memory for repeated events or contexts (e.g., retrieval of a variety of past tea-making experiences when asked to identify a teapot). Such summarized events, which are highly detailed and contextualized despite the fact that they are not time-specific, may fit Neisser’s (1981) concept of “reepisodic memory” or Conway’s (2001) “general events” level of autobiographical knowledge. Interestingly, neuroimaging work suggests that such repeated events also activate the autobiographical memory network, and that such activation is modulated by the richness of retrieved memory (Addis, Moscovitch, Crawley, & McAndrews, 2004). Such memories share with unique episodic events the quality of recollective experience (Moscovitch, 2008), and it is this recollection of details that facilitates retrieval of information from the semantic knowledge base.

Finally, there is also support for the converse interaction – semantic memory affecting episodic memory – as evidenced by the fact that the integrity of semantic memory in general, and the availability of premorbid semantic information in particular, influence new episodic learning. As illustrated in the study by Kan et al. (2009), new learning can be facilitated by the existence of an established schematic structure into which new information can be incorporated. However, the impact of pre-existing knowledge need not always be beneficial. For instance, in patients who confabulate, the content of their confabulation is often based on true personal history (Schnider, 2003). In this case, established knowledge structures may interfere with the retrieval of episodic information, leading to the production of context-inappropriate information. Nonetheless, it appears likely that such interactions can be usefully exploited in the context of memory rehabilitation. Future studies are needed to delineate the boundary conditions of such effects.

In closing, key insights about the functional and neural organization of memory have emerged from the study of patients with amnesia. These studies in turn have influenced the direction of both cognitive and neuroimaging studies of memory in normal cognition. The studies reviewed herein have highlighted the fact that complex interactions among distinct forms of memory can be elucidated by careful attention to the nature of processes and representations that mediate task performance. Systematic study of patients with well-characterized lesions will remain central in further advancing this effort.

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