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Cross-Cortical Consolidation as the Core Defect in Amnesia

Prospects for Hypothesis Testing with Neuropsychology and Neuroimaging

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Contemporary methods for monitoring human brain activity during cognition seem poised to power the next stages of advancement in the neuropsychology of memory. An ongoing goal is to map specific cognitive functions to particular brain regions. Beyond mere mapping, however, we must also envision how these functions are coordinated in intricate networks of neural circuits. Many details remain to be elucidated concerning how these networks enable us to accomplish ordinary and extraordinary feats of memory—such as assembling an immense storehouse of knowledge, recalling to mind specific events from many years ago, and maintaining some memories for a lifetime.

Noteworthy neuroscientific insights have been provided by studying many simpler forms of memory. This approach is beneficial, for example, because basic substrates for neural plasticity (e.g., as identified in *Aplysia*) may constitute the building blocks for *all* forms of memory. On the other hand, the neural events supporting *some* forms of memory are fundamentally distinct. Continued investigation of these distinctions may sharpen our abilities to categorize different types of memory. These efforts may simultaneously lead to a more comprehensive understanding of memory and to improvements in our memory classification schemes, which at present tend to rely heavily on behavioral criteria.

DECLARATIVE MEMORY

Observations of preserved and impaired memory in patients with amnesia indicate that the recall and recognition of facts and episodes, or "declarative memory," is dependent on a particular subset of brain regions and can be disrupted selectively. How can we develop a better understanding of this selectivity? Indeed, one might pose this question:

> Why is declarative memory different from all other forms of memory?

Here are four answers to this question:

1. Because declarative memory has distinct behavioral characteristics.
2. Because declarative memory has distinct subjective characteristics.
3. Because declarative memory has a distinct cognitive structure.
4. Because declarative memory has distinct neural substrates.

Memory theorists tend to give one or another of these answers greater emphasis, as discussed further below. In any event, determining precisely how each of these criteria map onto the others is an important goal for future research. Toward this end, a useful strategy may be to favor some defining criteria over others. To be more specific about these four sorts of criteria, here are four possible descriptions of the characteristics of declarative memory corresponding to these four answers:

1. Memory performance produced during recall and recognition tests for facts and episodes.
2. Memory that is accompanied by the experience of conscious recollection.
3. Memory that depends on retrieving a conjunction of distinct informational fragments.
4. Memory that requires cross-cortical consolidation (which is mediated by cortico-hippocampal and corticothalamic networks, and which leads to the gradual formation of new coherence ensembles).

Despite widespread agreement about the selectivity of memory deficits in amnesia, a pervasive problem for research in this area is how to arrive at a generally agreed-upon definition for the type of memory that is impaired in amnesia. Although terms such as "explicit memory," "conscious memory," and "aware memory" have been used in this context, sometimes synonymously, here I will rely on the term "declarative memory." One reasonable tactic is to acknowledge that definitions of declarative memory can be allowed to evolve gradually, so that as its unique characteristics become substantiated, they are folded into the definition. The definition can then freely include behavioral, subjective, cognitive, and neural characteristics. On the other hand, there are advantages to the approach of holding to a behavioral definition of declarative memory. The research agenda can then be described as mapping neural, cognitive, and subjective facets of declarative memory onto each other and onto a static behavioral definition.

Figure 6.1 shows a scheme for relating descriptions of declarative memory at different levels. A complete understanding of disorders of declarative memory should describe the three-way connections among the neural dysfunction, the cognitive dysfunction, and the resultant behavioral shortcomings. In the same manner, the neural, cognitive, and behavioral realms must be bridged by a neurocognitive conceptualization of normal declarative memory.

In the coming years, advances in the neuropsychology of memory can be expected from both studies of patients with memory deficits (traditional neuropsychology) and studies of neural events that accompany normal memory phenomena (neuroimaging). Moreover, attempts to combine neuropsychology and neuroimaging should be situated within the context of contemporary theories of memory informed from both psychological and neuroscientific perspectives. In this chapter, I articulate several hypotheses about declarative memory and amnesia, and then consider prospects for future applications of neuroimaging methods to build on the insights from neuropsychology.

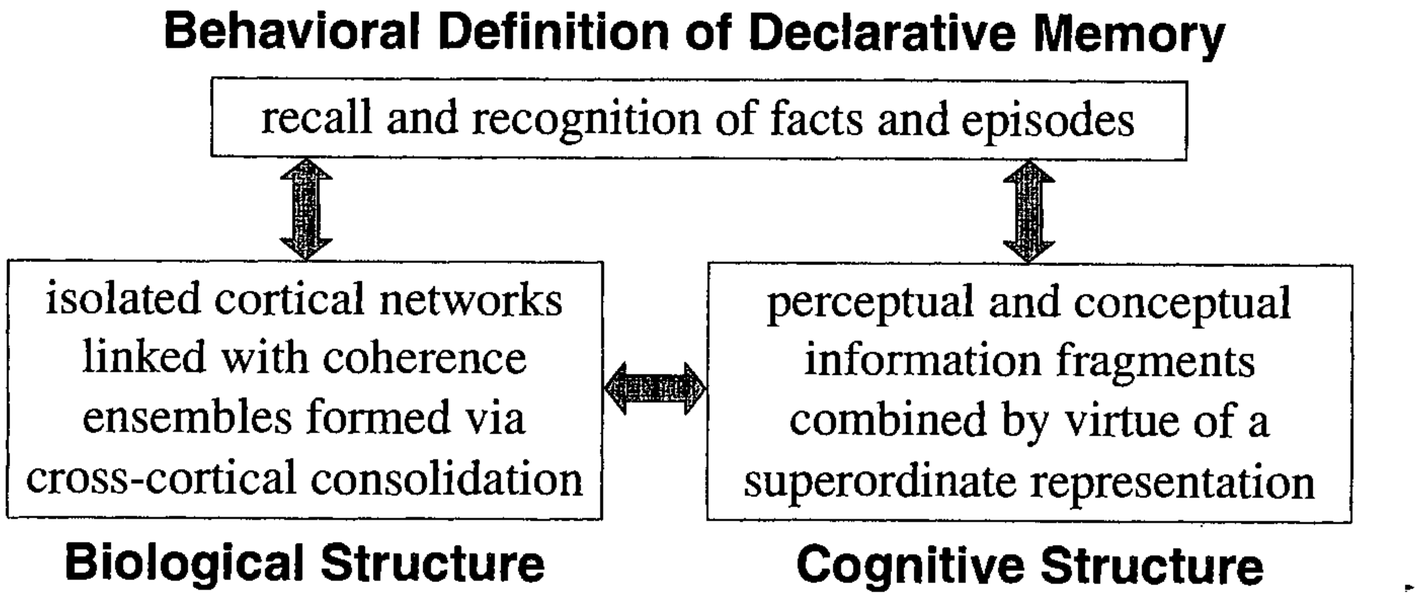

FIGURE 6.1. The three-way theoretical connections among behavior, biology, and cognition that are necessary for a comprehensive understanding of declarative memory. Declarative memory is defined behaviorally, and a neurocognitive theory of declarative memory is depicted in terms of both biological and cognitive structure.

A NEURAL FEATURE OF DECLARATIVE MEMORY: CROSS-CORTICAL CONSOLIDATION

The central hypothesis to be explored here is that *declarative memories characteristically require cross-cortical consolidation*—a process mediated by the confluence of corticothalamic and corticohippocampal networks. The information inherent in personally experienced events and complex facts is stored within a set of distinct zones of the cerebral cortex, each of which is dedicated for processing a specific type of information. Although gaps remain in our ability to describe how information is coded by neuronal connections within and between neocortical zones, it is clear that these zones are specialized for distinct functions. Autobiographical memories are distant reflections of episodes that were originally experienced and understood via information processing in many different neocortical regions. Episodes generally entail a set of attributes (Underwood, 1969), such as a spatial layout of environmental features, sights, sounds, smells, motion, other people, goals, actions, emotional coloring, timing with respect to other events, and so on. Given that major aspects of an episode are represented at distant brain loci, storage of that episode must include new cross-cortical connections. Episodic memory storage depends on a memory trace corresponding to each of these attributes, as well as connections between them. The cortical fragments must be linked together in order for the representation of the episode to survive as a unit to be remembered later.

In short, a memory for an episode inherently has a strong dependence on cross-cortical storage. Whether this applies to memory for facts may depend on how "fact" is defined. When complex information is learned (e.g., factual knowledge about the world expressed as a statement; Shimamura & Squire, 1987), cross-cortical storage may be responsible. On the other hand, when minimal factual knowledge is acquired (e.g., a simple three-word combination; Tulving, Hayman, & Macdonald, 1991), information minimally sufficient to support that learning may be stored within a single neocortical zone responsible for one domain of specialized semantic information. Explicitly stating that this consolidation process is cross-cortical is also important, given that other sorts of consolidation may occur

for other sorts of memory and in other brain regions (see, e.g., Brashers-Krug, Shadmehr, & Bizzi, 1996; Gais, Plihal, Wagner, & Born, 2000). Although linking together separate representations in different cortical regions is considered an essential step in the creation of an enduring declarative memory, additional processing at the time of retrieval is also critical. Prefrontal contributions to declarative memory, in particular, come into play here (see, e.g., Knight & Grabowecky, 1995; Shimamura, 1995; Wheeler, Stuss, & Tulving, 1997). Retrieval requirements include conducting a systematic search for stored information, evaluating the products of retrieval and assessing relevance to the task at hand, escaping from the present moment to bring a prior experience to mind, maintaining information in working memory, inhibiting the intrusion of irrelevant information, constructing a scenario within which retrieved information is put together, evaluating the likelihood of different scenarios, and so on.

Establishing long-lasting links between cortical fragments must, of course, be distinguished from establishing analogous but temporary bindings in the present moment, as occurs when an event is experienced. Amnesic patients apparently experience events normally and are able to maintain that information while it stays at the focus of attention (see, e.g., Cave & Squire, 1992). It is in this sense that we claim that encoding can be normal in amnesia. Amnesic patients can form cross-cortical associations temporarily, such that factual or episodic information can be represented and effectively support immediate memory or working memory. The difficulty is in storing that information in an enduring way.

Cross-cortical consolidation proceeds when a set of neuronal ensembles in the neocortex is repeatedly activated, as has been assumed in computational models of consolidation (e.g., McClelland, McNaughton, & O'Reilly, 1995; Murre, 1997; Squire & Alvarez, 1995). A distributed cortical network ultimately represents the remembered information, but it starts out in an unstable form at the time of encoding. The memory generally includes representations of discrete components of an event at multiple levels of relevant perceptual processing streams. Consolidation produces a stable network of distributed cortical representations, but it is not conceptualized here as a passive or automatic process that inevitably runs its course. Rather, consolidation proceeds as the memory is actively used. Components of the network are loosely connected via interposed limbic connections, in such a way that partial information can cue the retrieval of the whole memory (as in "pattern completion"; McClelland et al., 1995; Squire, 1992; Treves & Rolls, 1994). These limbic connections are formed swiftly at encoding so as to unify the distinct cortical components, but the connections are not long-lasting and gradually become less effective with disuse. Importantly, when these connections are used to reactivate the distributed cortical representation for a declarative memory, I have speculated that the process of cross-cortical consolidation is moved forward in a particular way that involves the gradual formation of new neuronal ensembles in the cortex, termed "coherence ensembles" (Paller, 1997).

ANOTHER NEURAL FEATURE OF DECLARATIVE MEMORY: COHERENCE ENSEMBLES

Whenever the network of neocortical neuronal ensembles is activated, one commonly proposed outcome is a strengthening of the corticocortical connections between parts of the network. In contrast, cross-cortical consolidation is here conceptualized as depending on additional neural changes. The network reactivation coincides not only with memory re-

trieval, but also with associations between that memory and other memories, and with changes to the declarative memory representation in question. The memory may lose some detail, and also gain new meaning in the context of the associations. It may be categorized with other memories. It may also come to be interpreted in a new way in the light of subsequent events. Consolidation proceeds whether or not the individual is intending to memorize or rehearse the memory; it proceeds in conjunction with any associative processing that involves that memory. As the memory takes on additional meaning by taking its place in the context of other stored knowledge, other neurons come to represent this higher-order meaning or thematic information. These other neurons may be located in adjacent portions of the temporal lobe (such as entorhinal cortex or the temporal pole) and perhaps in other areas (such as orbitofrontal cortex, retrosplenial cortex, or posterior cingulate). I refer to these hypothetical neuronal ensembles as "coherence ensembles" (Paller, 1997) because they function to provide coherence to the neocortical fragments that constitute a declarative memory. At the same time, they take over the function of representing the central, superordinate meaning of the memory, including its relationship to other memories and its place within autobiographical and/or general semantic frameworks (akin to "thematic retrieval frameworks"; Hodges & McCarthy, 1995). When coherence ensembles are activated and the gist of the memory is retrieved, their connections enable specifics of the memory to be retrieved. Hippocampal neurons initially participate in this reactivation of a memory, whereas later the newly formed coherence ensembles are sufficient to accomplish this.

Many of the present speculations regarding cross-cortical consolidation and coherence ensembles present prime opportunities to use neuroimaging to seek novel sorts of empirical evidence relevant to these issues. At the same time, this conceptualization of consolidation has much in common with views from many other memory theorists. The memory-indexing theory of Teyler and DiScenna (1986), for example, also suggests that the hippocampus is involved in connecting sets of neocortical ensembles while a cortically based memory is established incrementally. Squire, Cohen, and Nadel (1984) described a consolidation process in which neocortical activity is modified by input from the hippocampal region, leading to neocortical reorganization (see also Damasio, 1989; Eichenbaum, 2000; Halgren, 1984; Marr, 1971; Mesulam, 1998; Milner, 1989; O'Keefe & Nadel, 1978; O'Reilly & Rudy, 2001; Wickelgren, 1979). Nonetheless, one distinctive aspect of the current conceptualization is that new representations, instantiated by neuronal coherence ensembles, are proposed to take over the function of reactivating the array of neocortical loci.

RETROGRADE AMNESIA, ONGOING HIPPOCAMPAL CONTRIBUTIONS, AND SLEEP

What would happen if coherence ensembles were damaged while other medial temporal circuitry was left intact? This condition may constitute a description of damage to critical storage zones leading to focal retrograde amnesia (Kapur, 1993; Markowitsch, 1995; but see Kopelman, 2000). Retrograde impairments could present along with a relatively preserved (though not entirely unaffected) ability to form new declarative memories. This impairment could make old memories inaccessible, because the fragments would be present in the cortex but not connected, so that the episode could no longer be reassembled. Likewise, circumscribed damage to lateral temporal regions may lead to semantic dementia, with remote memories disrupted more than recent memories (Hodges & Graham, 1998). Differential loss of autobiographical versus general semantic information could also be

explained if different sorts of coherence ensembles were not randomly scattered about, but functionally clustered in different regions.

Heterogeneity of symptoms in amnesic patients, and dissociations between anterograde and retrograde impairments, may then be explained as follows. A core amnesia with retrograde and anterograde deficits results from brain damage to either corticothalamic or corticohippocampal networks. In severe cases, damage to major portions of the medial temporal region disrupts cross-cortical consolidation entirely and also destroys previously established coherence ensembles. The extent of retrograde impairment depends on the extent to which coherence ensembles are also destroyed. Retrograde memory loss for long time periods results from extensive damage to cortical coherence ensembles. Retrograde deficits are observed in a relatively pure fashion when a subset of established coherence ensembles is damaged, leaving the major machinery for cross-cortical consolidation intact. Other retrieval problems with respect to search, organization, and evaluation emerge and contribute to the memory disorder with additional prefrontal damage.

Whether hippocampal neurons continue to participate after cross-cortical consolidation produces a durable memory remains a question currently under active debate (Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). According to the present view, if an episode continues to be recalled periodically (as is the case for most significant life episodes), new associations will be formed with other events. If a memory is not totally isolated from the rest of an individual's ongoing experiences, it may continue to change rather than remain in a static state. In this sense, cross-cortical consolidation may continue indefinitely. Continued dependence on the hippocampus is determined by the extent to which the fact or episode in question continues to be associatively processed with new information and to evolve accordingly. There may thus be two distinct means for long periods of retrograde amnesia to be produced. One cause would be significant damage to cortical storage zones, and, in particular, to coherence ensembles essential for retrieving declarative memories. The other cause would be prolonged disruption of the hippocampus and related circuitry, so as to disrupt continuing cross-cortical consolidation of remote memories that would otherwise be strengthened through recurring associations with other information (including subsequent episodes of retelling the story to others). As mentioned earlier, deficits in intentional retrieval, such as those produced by frontal damage, could also contribute to failures to consolidate and to retrieve declarative memories. Even in the absence of neurological dysfunction, memories of the contextual details of an episode tend to be difficult to maintain, because they are so heavily based on the singular initial experience of the episode. As time goes by, contextual details of an episode are postulated either to be forgotten or to be represented in the neocortex and linked together with other recallable aspects of the episode by virtue of coherence ensembles. An episodic memory can become thoroughly integrated with other stored information and largely devoid of distinctive contextual detail, and can eventually come to constitute a semantic memory (Cermak, 1984).

Finally, it should be noted that the repeated activation of the neocortical network that is critical for cross-cortical consolidation occurs not only when the memory is retrieved intentionally, but also when it is retrieved unintentionally, and perhaps particularly when retrieval occurs during sleep. Indeed, a high proportion of dreams incorporate recent events of the day or the past several days, such that the consolidation of an episodic memory may progress significantly during the first few nights after the event occurs. Moreover, if dreams provide an opportunity for evaluating possible solutions to ongoing life issues, recent events can be related to long-term goals accordingly. Consolidation will continue to occur to the extent that related events occur on subsequent days. Empirical support for these ideas con-

cerning consolidation during sleep is relatively sparse, although there are several lines of supportive evidence (e.g., Stickgold, 1998; Sutherland & McNaughton, 2000; Winson, 1985).

BEYOND DECLARATIVE MEMORY: QUESTIONS OF DEFINITION

The memory dysfunction in amnesia is not strictly limited to declarative memory. Damage to medial temporal or medial diencephalic brain regions can produce both a deficit in storing declarative memories *and* deficits in certain other types of memory that fall near definitional borders, such as some variations on simple classical conditioning (see, e.g., Gluck, Ermita, Oliver, & Myers, 1997) and some types of new-association priming (see, e.g., Cermak, Bleich, & Blackford, 1988; Paller & Mayes, 1994; Schacter & Graf, 1986; Shimamura & Squire, 1989; but see Gabrieli, Keane, Zarella, & Poldrack, 1997). Some memory phenomena that would normally fall within the category of nondeclarative memory, but that are not preserved in amnesia, should perhaps be reclassified within a new subcategory of nondeclarative memory. The category could be called "nondeclarative memory that depends on neocortical associations."

Would it be a good idea to choose to define new types of memory based on neurobiological criteria instead of behavioral criteria? If so, another possible category would be "cross-cortical consolidation memory," which depends on neocortical associations that require cross-cortical consolidation, and which includes both declarative and nondeclarative varieties. This neural distinction might be the best way to carve nature at the joints. And yet it also risks the danger of circular definitions, given that we don't have an objective marker for cross-cortical consolidation. Future research should pursue this goal. In the meantime, should we continue using current definitions of declarative memory (or explicit memory, conscious memory, or aware memory), or should we define new memory categories in order to cover all the memory abilities impaired in amnesia?

Some researchers have advocated using cognitive criteria to define the type of memory impaired in amnesia. Qualities such as "flexible," "configural," "relational," or "dependent on complex associations" can be emphasized (see, e.g., Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Ryan, Althoff, Whitlow, & Cohen, 2000). But should these attributes be central to the definition of declarative memory? This approach might meet with the same circularity problems as would making the neural criteria central to the definition. Definitions of such terms as "relational" or "flexible" are themselves rather flexible in practice, though operational definitions are possible. Moreover, it is likely that attributes such as "relational" can apply to some memories that are not stored in the cortex and that should be considered nondeclarative, such as some complex motor memories and habits. When a new memory phenomenon is demonstrated via some novel behavioral paradigm, objectively determining whether it depends either on cross-cortical consolidation or on complex associations of some sort may present a challenge.

Until ways to surmount these challenges are well established, it may be best to maintain the behavioral definition of declarative memory as referring to the recall and recognition of facts and episodes, while at the same time hypothesizing neurocognitive reasons for why declarative memory is different from all other types of memory. Cross-cortical consolidation is presumably necessary for normal declarative memory, and it is here hypothesized to be the core defect in amnesia. Importantly, cross-cortical consolidation is also necessary for certain types of associative nondeclarative memory that likewise depend on dispersed neocortical representations.

DECLARATIVE MEMORY AND CONSCIOUS RECOLLECTION

The approach outlined above provides a natural segregation between declarative memory and conscious recollection as follows. "Conscious recollection," the subjective experience of remembering, appears to be contingent on declarative memory, and it tends to happen in concert with the recall and recognition of facts and episodes. Although recollection is central to definitions of aware memory, conscious memory, and explicit memory, it is not formally part of the definition of declarative memory advocated here. Rather, recollection is an additional phenomenon that depends on some of the same neurocognitive substrates as declarative memory. Cross-cortical consolidation is a necessary but not sufficient condition for the conscious recollection of a declarative memory. Cross-cortical consolidation allows a set of isolated cortical networks to become linked together, and once linked in this manner, the composite set of networks corresponds to a declarative memory. This memory can then become accessible to conscious awareness when the distributed cortical representation is reactivated.

Indeed, a central function of corticothalamic connections in declarative memory may be in the temporary activation of the distributed declarative memory. As such, this role may constitute a key difference between the functions of corticothalamic and corticohippocampal networks. Speculatively, the thalamic neurons that are particularly relevant here may be the same neurons characterized neurochemically as calbindin cells that form a so-called "thalamic matrix" (Jones, 1998), given that they are found in all thalamic nuclei and project widely to superficial cortical locations. Medial thalamic connections to multiple cortical regions may be able to support the conscious experience of a remembered event, together with prefrontal networks that support working memory. Medial thalamic damage could thus indirectly disrupt cortical function (Paller et al., 1997). The medial diencephalic contribution to conscious recollection may also entail inhibiting other potential conscious contents, so as to facilitate the conscious retrieval of the memory. Although further evidence is needed on this point, it is conceivable that thalamic control networks are critical for consolidation because they can support both the retrieval and activation of a distributed declarative memory, which thus sets the stage for consolidation to proceed through the action of corticohippocampal networks, as coherence ensembles are formed and strengthened.

NEUROIMAGING AND DECLARATIVE MEMORY

Empirical tests of hypotheses such as those developed above can be expected not only from studies of amnesic patients, but also from monitoring neural activity while memories are normally formed and expressed. In fact, neuroimaging in humans may present fruitful avenues for advancing theories couched at this level. The term "neuroimaging" is used here in the wider sense to refer to techniques that make it possible to observe neural activity or correlated hemodynamic changes, either in specific brain regions or with sufficient temporal resolution to monitor changes in neural activity as cognitive events unfold in time, or both. I place particular emphasis on neurophysiological methods for recording event-related potentials (ERPs), which may be useful for charting the time course of relevant memory processing and ultimately, in conjunction with other neuroimaging measures, for deciphering the dynamics of brain network interactions. Issues that arise in taking this approach apply to multiple methods for monitoring brain activity (e.g., MEG, fMRI, PET, EEG responses in the frequency domain, optical imaging, etc.).

So how can we observe the neural events responsible for forming and remembering declarative memories? One useful step is to make comparisons between declarative memory and other types of memory, in order to search for specific ways in which the neurocognitive structure of declarative memory is distinctive. This approach may not be effective, however, if presumed associations between neural measures and cognitive operations are not valid. Given that our working hypotheses strongly influence how we conceive of the cognitive functions in question, the inaccuracy of our current theories about the component processes of memory may corrupt our observations, and so hamper our ability to test our hypotheses. Fortunately, our understanding of memory can move forward on many fronts simultaneously. For example, better conceptualizations of how information is represented in the cortex may affect how we think about the storage of declarative memories in the cortex (e.g., Mesulam, 1998), which may then lead to corresponding refinements of our views on the component processes of memory.

Observations of neural activity associated with encoding and retrieval are clearly needed to support continuing theoretical progress. Whether these observations can be connected to current theories, and to future theories, may depend on the extent to which valid and specific associations are made between the neural measures and discrete cognitive events. Memory functions, however, can be difficult to isolate. Encoding and retrieval, in particular, do not occur *only* when an experimenter instructs a subject to store or recall information, respectively. So how can neural measures extracted from the EEG be tightly associated with the neurocognitive events responsible for declarative memory?

To start to answer this question, we may first note that differential EEG responses to remembered items in recognition tests, as compared to responses to new items, constitute a robust electrophysiological phenomenon tied to declarative memory (see reviews by Friedman & Johnson, 2000; Mecklinger, 2000; Paller, 2000; Rugg & Wilding, 2000). ERPs recorded at the time of retrieval differ systematically between old and new items in both explicit and implicit memory tests. Presumably, these "ERP repetition effects" reflect several cognitive events potentially related to memory retrieval. Given the foregoing discussion, it is clearly appropriate to determine the extent to which observed neural activity specifically reflects component processes of declarative memory.

In my laboratory, we have used several methods for gaining this specificity. Contrasts between responses to test items associated with different levels of memory performance have been particularly informative. In several experiments, two types of studied words gave rise to perceptual priming effects of the same magnitude, but provoked very different levels of recognition accuracy. We inferred that the contrast could be recast in terms of high and low recollection, such that corresponding ERP differences could be interpreted as electrophysiological correlates of recollecting declarative memories, devoid of any confounding influence related to perceptual priming (Gonsalves & Paller, 2000a; Paller & Kutas, 1992; Paller, Kutas, & McIsaac, 1995; see also Paller, Bozic, Ranganath, Grabowecky, & Yamada, 1999, for similar effects with faces).

A variation on the same basic strategy was used in other experiments, such that conditions were set up to provide a contrast between words associated with similar levels of recognition but systematically different levels of perceptual priming. As a result, brain potentials were linked to neural events underlying perceptual priming restricted to the level of visual word form (Paller & Gross, 1998; Paller, Kutas, & McIsaac, 1998). These electrophysiological correlates of visual word-form priming were most prominent at occipital scalp locations and occurred at a latency slightly earlier than that typically found for electrophysiological correlates of visual word recollection (Figure 6.2). Neuroimaging studies using PET and fMRI suggest that perceptual priming may result from decreased neural activity following percep-

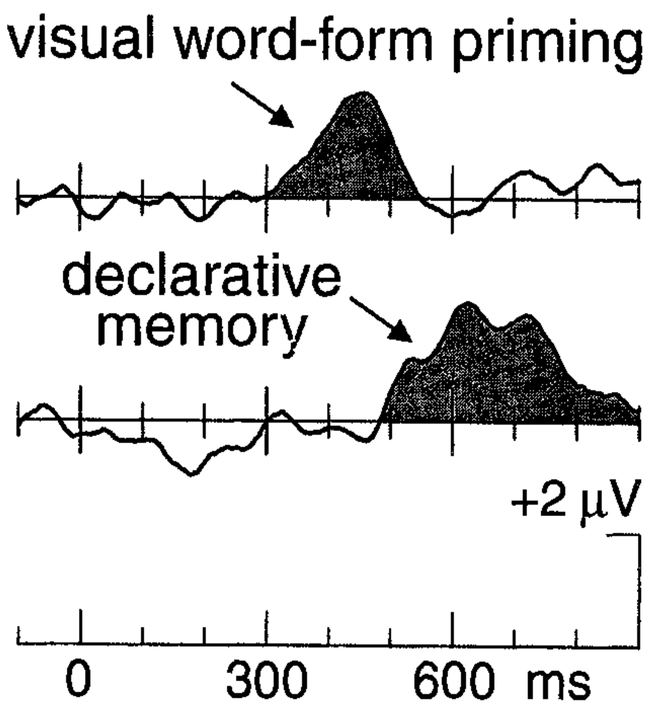

FIGURE 6.2. Brain potentials specifically associated with declarative memory and one type of nondeclarative memory, priming of visual word form. The upper waveform was computed by subtracting brain potentials elicited by words previously viewed forward or backward; priming was greater in the former than in the latter condition. Data from Paller and Gross (1998). The lower waveform was computed by subtracting brain potentials elicited by words previously studied with emphasis on visual imagery versus orthographic processing; recollection was stronger in the former than in the latter condition. Data from Paller and Kutas (1992).

tual learning (Schacter & Buckner, 1998; Wiggs & Martin, 1998). Furthermore, MEG evidence concerning the timing of repetition-related changes implicates top-down influences on earlier cortical regions, rather than effects on initial stages of sensory information processing (Dale et al., 2000). Electrophysiological correlates of perceptual priming can also be revealed in recordings from single neurons in monkey visual cortex. In particular, some neurons in ventral temporal areas tend to show reduced responses during stimulus repetition—a phenomenon termed "repetition suppression" (Desimone, 1996). Combining results from these different methods may lead to a better understanding of priming, as well as a better understanding of how priming is different from declarative memory.

In addition, however, we will also need more thorough evaluations of neural correlates of recollection that will allow us to decompose the various steps that lead to recollection. Many neuroimaging studies have tackled these questions—for example, by manipulating the type of information that subjects retrieve during a recognition test (e.g., Johnson, Kounios, & Noble, 1997; Ranganath, Johnson, & D'Esposito, 2000; Ranganath & Paller, 1999, 2000; Wilding, 2000). However, much controversy currently surrounds our ability to empirically separate retrieval success, retrieval effort, and other processes relevant for retrieval (see review by Rugg & Wilding, 2000).

Memory research using ERPs has not only focused on the retrieval phase, but also on neural events that take place at the time of encoding. Many studies have shown that both hemodynamic and electrophysiological measures can be predictive of later declarative memory performance (for review, see Wagner, Koutstaal, & Schacter, 1999). These effects are sometimes termed "Dm" as a shorthand for neural differences based on later memory performance (Paller, Kutas, & Mayes, 1987). In a recent example of this sort of work, ERPs were recorded in response to pictures of common objects and to corresponding words presented during a study phase (Gonsalves & Paller, 2000b). When the words were shown, subjects were instructed to generate a visual image of the object. For half of the words, a picture of that object

was never presented. Nevertheless, subjects later claimed to remember some of the non-presented pictures that were only imagined; these can be considered "false memories" or "source-monitoring errors" (Johnson, Hashtroudi, & Lindsay, 1993; Schacter, Norman, & Koutstaal, 1998). As shown in Figure 6.3, ERPs in response to words differed according to whether the items would later be falsely remembered or not. These ERP differences were interpreted as reflections of visual imagery generated in response to the words, given that similar ERPs in a prior experiment were shown to vary systematically as a function of the extent to which visual imagery was engaged (Gonsalves & Paller, 2000a). Other ERPs in response to pictures also differed systematically in amplitude according to whether the picture would be accurately recognized later. Neural activity observed at encoding thus influenced the outcome of later recognition testing, both for accurate and for false memories. Furthermore, similar ERPs were also recorded during retrieval, and the amplitude of these ERPs was larger for accurate picture memories than for false memories, suggesting that visual imagery was less vivid for false memories.

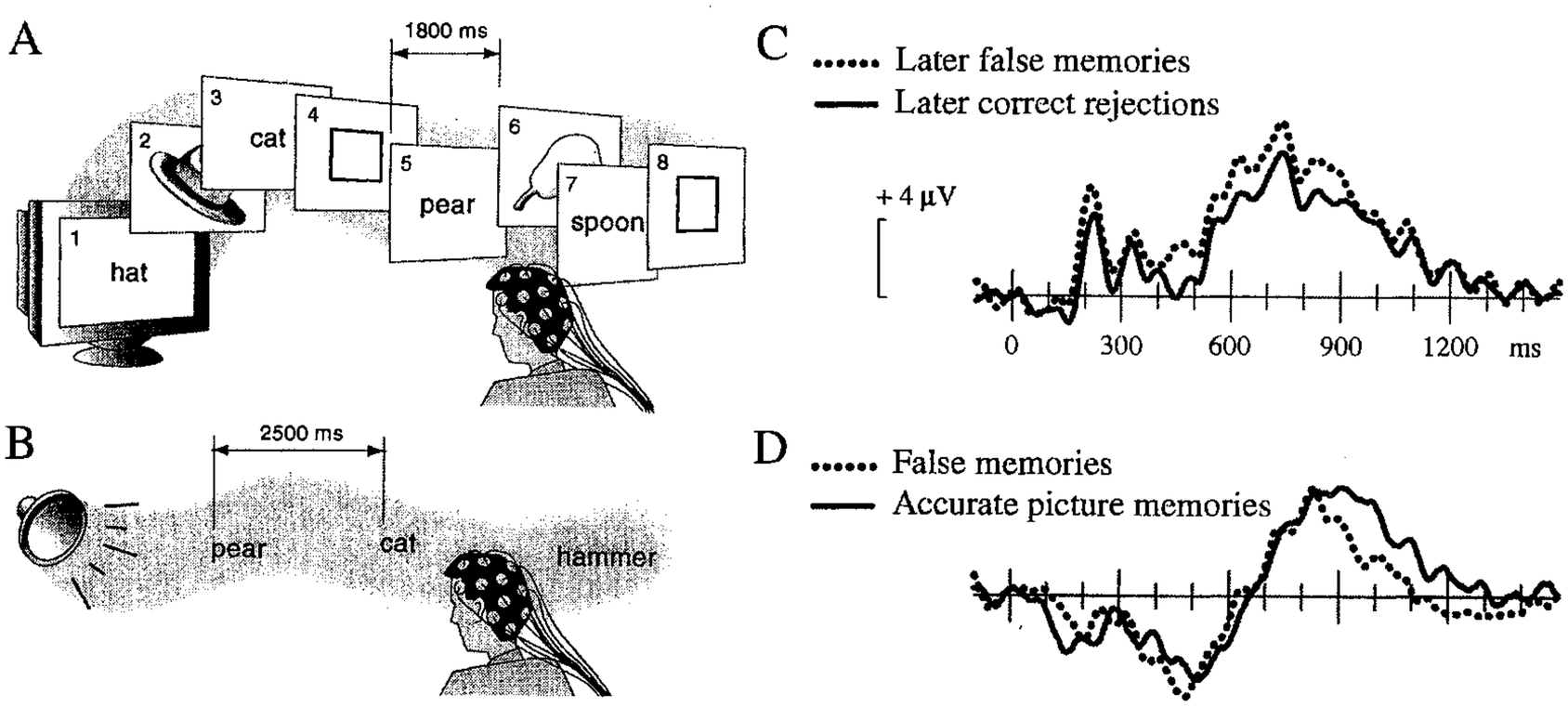

FIGURE 6.3. Behavioral paradigm and electrophysiological results from an investigation of false memories (Gonsalves & Paller, 2000b). (A) In the study phase, subjects viewed a series of words and were required to make a size judgment for each one ("Is the object larger or smaller than the video monitor?"). Half of the words were followed by a color image of the corresponding object, and half were followed by an empty rectangle. (B) In the test phase, subjects listened to a series of words and were required to decide whether the corresponding image had been viewed during the study phase. When a subject claimed to remember seeing a picture that was only imagined, these trials were designated "false memories." (C) ERPs recorded to words in the study phase (from the midline occipital scalp location) differed at 600–900 milliseconds according to whether a false memory occurred in the test phase for that item. (D) Midline occipital ERPs recorded to auditory words in the test phase differed at 900–1,200 milliseconds according to whether that trial constituted an accurate memory or a false memory. These potentials were interpreted as indications of visual imagery that was recapitulated at retrieval for pictures either perceived in the study phase or, to a lesser extent, imagined in the study phase. A and B are from de Schipper, S. (2000, December 2). Sterke verbeelding: Valse herinnering blijkt uit hersengolven [Strong imagination: False memory is evident from brainwaves]. *NRC Handelsblad*, p. 47. Copyright 2000 by *NRC Handelsblad*. Adapted by permission. Data in C and D from Gonsalves and Paller (2000b).

Thus it is possible to monitor relevant neural activity both at encoding and at retrieval using ERPs. Yet, as stated above, the core defect in amnesia is postulated to be at storage rather than at encoding or retrieval. How should future theory-driven research attempt to promote advances in our understanding of consolidation? According to the views expressed above, storage and retrieval are intertwined, because cross-cortical consolidation entails retrieval. Therefore, one way to study consolidation would be to observe neural activity during a retrieval event wherein associations are made and the memory in question is strengthened. It may also be helpful if distinct cortical networks can be monitored as consolidation proceeds. The configuration of cortical networks involved in an episodic memory might be expected to change over time in ways that implicate storage processes. For example, informative differences may emerge if comparisons can be made between declarative memories that are matched in strength but systematically differ in only the number of distinct types of information linked together to form the memory. There are also many open questions regarding the role of the hippocampus and whether this role changes over the lifetime of a memory. If hippocampal contributions decrease over time, one might expect that new activity corresponding to the formation of coherence ensembles might emerge in other brain locations. Although there is not currently an abundance of evidence that can be brought to bear on these and many other related questions about human memory, approaches utilizing scalp and intracranial ERP recordings and fMRI time series analyses do hold promise for clarifying these issues. The further addition of deactivation studies using transcranial magnetic stimulation may also be useful.

Finally, a coming together of neuropsychology and neuroimaging can also be expected in studies with patients suffering from memory disorders (e.g., Eustache, Desgranges, Aupee, Guillery, & Baron, 2000; Olichney et al., 2000). Structural neuroimaging in patients tells only part of the story, in that the pattern of cognitive deficits must be related not only to sites of structural damage but also to distant neural dysfunction that results from the structural damage. Patients with alcoholic Korsakoff's syndrome, for example, have patterns of glucose hypometabolism that suggest cortical dysfunction secondary to thalamic damage (Paller et al., 1997). Future neuroimaging research may thus be able to reveal other indications of impaired cross-cortical consolidation.

In conclusion, theory-driven research into the neurocognitive structure of human memory can receive support from neuropsychological studies of amnesic patients and from neuroimaging studies in healthy and memory-impaired populations. The combination of neuropsychology and neuroimaging will certainly produce new perspectives on neurobiological hypotheses about declarative memory. Previously it may have appeared that some speculations couched at the level of neural networks—as exemplified by groups of temporarily connected neuronal ensembles, unitized representations in discrete cortical zones, a linking process for dispersed neocortical representations based on corticothalamic and corticohippocampal networks, and the concept of coherence ensembles—were hypotheses about human memory that could not easily be addressed in humans. Now, due to methodological advances in cognitive neuroscience, we can more easily envision how hypotheses like these can be put to proper empirical test using a range of techniques for studying the human brain.

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