The clinical profiles, recovery, and rehabilitation of memory disorders

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Abstract

This article reviews the clinical profiles of memory disorders that are commonly encountered on neurorehabilitation units. Memory is comprised of several dissociable processes and is subserved by a distributed network of brain regions. The cognitive and neuroanatomical bases of memory provide the foundation for clinicians to evaluate and treat patients with memory disorders. Memory disorders occur with disparate etiologies including stroke, aneurysms, head injury, encephalitis and anoxia. Recovery of memory function is dependent on several clinical factors such as etiology and lesion location. There is no direct treatment of amnesia, but memory rehabilitation with pharmacotherapy or cognitive remediation is often attempted. The relative strengths and weaknesses of each therapy strategy must be known.

Keywords: Memory; Amnesia; Anatomy; Recovery; Rehabilitation

1. Introduction

Patients with memory disorders are commonly encountered on neurorehabilitation units as a result of brain injury from a variety of etiologies. Such disorders may present as a pure amnestic syndrome, or memory impairment can be present in the setting of other cognitive deficits. Effective treatment of memory impairments requires understanding of the cognitive, neuroanatomical and neurochemical bases for memory processes. Cognitive neuropsychological investigation of memory function has demonstrated that memory is not a unitary function but a system of dissociable processes. Anatomical studies in humans and other primates have begun to map these dissociable processes onto distributed neural networks. Pharmacological studies have revealed some of the roles of neurotransmitters in memory opera-
tions. Information from these three domains must be used to construct appropriate and specific diagnoses, to understand the natural course of recovery, to predict prognosis, and to develop and evaluate rehabilitation strategies of treatment of memory disorders. This review moves from the theoretical bases of memory processes and anatomical networks to the clinical profiles of memory disorders commonly seen in neurorehabilitation practice and to the rehabilitation strategies that have been attempted for the treatment of memory impairments.

2. Theoretical models of memory

Several subdivisions of long-term memory are proposed (Fig. 1). One of the most widely accepted is a dichotomous classification of ‘declarative’ versus ‘procedural’ memory [1]. Declarative memory represents memories of episodes and facts that can be consciously accessed, and procedural memory represents memory for skills. Unlike declarative memory, procedural memory is not available to our consciousness. Procedural memories can be motor skills, or mental procedures such as performing complex arithmetic. Declarative memory may be further subdivided into ‘episodic’ and ‘semantic’ memory [2]. Episodic memory represents memories for specific personally experienced episodes. In contrast, semantic memory represents memories of facts, principles and rules which make up our general knowledge of the world. It is proposed that semantic memories have evolved from specific episodes when such information was first encountered but with the passage of time these episodes lose their temporal context [3]. An illustration of these distinctions [4] is that you may recall when you last rode your bicycle (episodic memory), know what a bicycle is (semantic memory) or know how to ride a bicycle (procedural memory).

Another proposed classification of memory is a division between ‘explicit’ and ‘implicit’ memory [5]. Explicit memory includes conscious recollection of any type of memory encompassing both episodic and semantic memories. Implicit memory does not require conscious recollection and would include procedural memory, but the implicit memory domain would also account for the phenomenon of priming and classical conditioning. Priming is the phenomenon that previously encountered information has an increased probability of being recalled later even if there is no explicit recall of the earlier (‘priming’) experience [6]. For example, in a prototypical priming experiment, the subject is first presented with a list of words to read (i.e. motel, abstain, house, etc.). Subsequently, the subject is given three letter stems (i.e. mot-), and is asked to produce the first word that comes to mind. The probability of generating a previously encountered word (i.e. motel) is increased as compared to words not on the original list. In summary, these distinctions between different memory operations have great utility in diagnosis and in guiding treatment of impaired memory after brain injury.

In clinical practice, the usage of the terms to describe memory processes has become imprecise and has not always followed these theoretical constructs. Many clinicians use the terms short-term memory to refer to learning new episodic information and long-term memory to refer to remote memories. This clinically sensible distinction does not, however, conform to experimental models of memory structure and only creates confusion when used in clinical reports. Short-term memory is properly defined as a system that temporarily (for seconds) stores information prior to becoming consolidated into long-term memory. Short-term memory can be tested with a span task such as digit span or pointing span and long-term memory is tested by asking the subject to learn items that must be retrieved after a
interval with distraction. The term ‘amnesic syndrome’ properly refers to the loss of long-term memory only. Remote memory is information that has been consolidated in the past and may now be considered episodic, semantic or procedural depending upon its structure. It is tested by asking the subject to remember past public or personal events. Each of these systems (short-term memory, long-term memory and remote memory) consists of dissociable subsystems that must be individually assessed to define the cognitive and neural bases of amnesic syndromes.

3. The anatomy of memory

The report of the patient HM in 1957 demonstrated conclusively that the hippocampus was critical for long-term memory [7]. HM had intractable epilepsy and underwent bilateral surgical excision of the hippocampus and amygdala. Following surgery, HM was left with a dense and isolated amnesia that has not changed in severity to this day [8]. Anatomical studies in nonhuman primates with experimental lesions of the medial temporal lobe support the importance of this region in declarative memory [9,10]. These studies and correlative lesion studies in humans, have shown that the hippocampus and amygdala are part of a critical neural network that exists to subserve memory functioning (Fig. 2) [11]. This memory network has two anatomical loops or circuits [12,13]. The first circuit includes the hippocampus which projects via the fornices to the mammillary bodies. Via the mammillothalamic tract the mammillary bodies project to the anterior nuclei of the thalamus which in turn send projections to the posterior cingulate cortex. The circuit is completed by projections from the cingulate back to the hippocampus. Within this circuit there are also important reciprocal connections between the hippocampus and basal forebrain via the fornix. The second circuit includes the amygdala which projects to the dorsomedial nucleus of the thalamus via amygdala-fugal pathways. The dorsomedial nucleus sends projections to the prefrontal cortex which has direct reciprocal connections with the amygdala completing the loop. In nonhuman primates, damage to either

pathway alone does not result in amnesia but damage to both of these two ‘memory’ circuits will produce profound amnesia [13]. Memory deficits may be caused by a lesion anywhere within this neural network, including pathways that connect critical structures (i.e., the fornix) [14].

Thus, three main regions with critical pathways that interconnect them form a network for memory functioning. These are the medial temporal lobes, the diencephalon and the basal forebrain. Human studies have consistently supported this anatomical model. For example, HM is the classic example of damage to medial temporal lobes. Another case report of an amnesic patient, RB, had a lesion restricted to the CA1 region of the hippocampus on autopsy. Evidence for the minimal lesion within the medial temporal lobe that is sufficient to cause amnesia is derived from nonhuman primate studies since selective lesions to the medial temporal lobe in humans are quite uncommon. In nonhuman primates, damage to adjacent cortical areas that are anatomically related to the hippocampus, including the entorhinal, perihippocampal and parahippocampal cortices are as likely to cause amnesia as lesions in the hippocampus itself [10,11]. Also, interruption of the pathways that interconnect the hippocampus and medial mammillary nuclei, such as isolated le-
sions of the fornix, which originate in the hippocampus, cause persistent amnesia in humans [15,16]. The best studied example of amnesia due to damage of the diencephalon is Korsakoff’s syndrome which causes damage to both the mammillary bodies and dorsomedial nucleus of the thalamus [17]. Although these two structures are commonly implicated in causing amnesia, the specific lesion within the diencephalon that is sufficient to cause amnesia is still unclear. Two comprehensive clinicopathological studies of four cases of Korsakoff’s syndrome demonstrated the site of damage in the mammillary bodies and in an area of the medial thalamus adjacent to the dorsomedial nucleus of the thalamus [18,19].

Patients with Korsakoff’s syndrome are usually severe chronic alcoholics and may have quite unpredictable cortical atrophy complicating clinico-pathological correlations [20,21]. The pathological lesion is also undefinable in life so other etiologies provide clearer understanding of the role of different diencephalic lesions in causing amnesia. Careful study of amnesia following small thalamic infarcts have defined critical structures [22,23]. Damage to the mammillothalamic tract (origins of the mammillary bodies) and the ventral portion of the internal medullary lamina which includes amygdala-thalamic connections (at the ventrolateral boundary of the dorsomedial nucleus of the thalamus), are the critical structures necessary to cause amnesia. This finding is consistent with studies in nonhuman primates that damage to both memory circuits cause the greatest amnesia [13] and also consistent with the proposal that pathway lesions can be as important as nuclear lesions [24].

Isolated lesions of the basal forebrain, which includes the septum, diagonal band of Broca, and nucleus basalis, occur most commonly following anterior communicating artery aneurysm rupture and can result in dense amnesia [25]. This region has strong reciprocal connections with the medial temporal lobe. Also, the nucleus basalis projects widely to the cortex and is the primary source of cortical cholinergic input. Patients with Alzheimer’s disease have early and profound memory loss and a marked reduction of neurons in this region [26,27]. The minimal lesion in this region that produces amnesia is unknown. It may be as small as damage to the septal nucleus or isolated damage to the diagonal band of Broca [28,29].

In summary, damage to the medial temporal lobes, diencephalon, basal forebrain, or the pathways that interconnect these regions can cause severe impairments in long-term memory. An important target of the medial temporal lobes and the diencephalon is the prefrontal cortex, which has also emerged as an important region that contributes to long-term memory function. This knowledge of the neuroanatomy of memory is crucial for evaluating patients with brain damage and characterizing patients with memory disorders.

4. Patterns of amnesia

Specification of lesion sites associated with amnesia has led to investigation of possible differences in the pattern of memory loss with different lesion sites. Most investigations have focused on a comparison between damage to bilateral medial temporal versus diencephalic structures. More recent investigations have compared bilateral medial temporal versus frontal damage. Although each of these regions are part of the same functional network subserving memory, it is possible that damage to different regions in the network affect different stages of memory processes leading to different patterns of deficits [30]. The classic example of bilateral medial temporal amnesia is patient HM. HM has a severe long-term memory impairment and a rapid rate of forgetting. Exemplified by patient HM, bilateral medial temporal lesions produce amnesia with the following characteristics. Short-term memory is normal. There is a severe impairment in long-term memory (anterograde amnesia). Once learned, for information in long-term memory there is a very rapid rate of forgetting. It is uncertain if the rate of forgetting is more rapid in patients with temporal lesions than with other profiles. Lhermitte [31] demonstrated more rapid forgetting, but others [32,33] have shown comparable rates with different lesions. Semantic memory is generally
preserved although acquisition of new semantic knowledge is deficient [34] and retrieval of general semantic knowledge may be subtly defective after medial temporal damage [35]. Remote memory of personal events (reversible amnesia) is variably affected, but in cases with damage limited to the hippocampus, the retrograde deficit is usually restricted to a brief period (weeks to a few years) prior to the injury [8,36]. All implicit memory tasks are performed normally [37,38].

The classic contrasting example of diencephalic amnesia has been Korsakoff's syndrome (KS), but for at least two reasons studying KS may have a limited value. First, because the etiology is chronic alcoholism, many patients have diffuse cortical atrophy (but especially prominent in frontal lobes), have had numerous mild head injuries and may have had recurrent seizures. Second, damage to the dorsomedial thalamus may produce impairments in ‘executive functions’ that modify the clinical appearance of the amnesia without directly causing amnesia. Despite these limitations, patients with KS have many similarities to patients with medial temporal damage. They also have normal short-term memory, severe antegrade amnesia, rapid rates of forgetting, normal semantic memory and normal implicit memory [39].

The major differences between KS and medial temporal lesions are in retrograde amnesia and performance on several complex memory measures. Patients with KS have a more severe retrograde amnesia than patients with medial temporal lesions, often showing a temporal gradient with better recall of more remote information [40]. Patients with KS perform poorly on the Brown-Peterson task, a measure of long-term memory in the face of significant interference; exhibit increased sensitivity to proactive interference; and perform poorly on tasks that require memory for context. Performance on these memory measures is related to performance on ‘frontal’ cognitive measures [41,42]. Patients with medial temporal lesions perform much better on all of these memory tasks. Thus, the pattern of memory impairment in KS on these tasks is similar to patients with frontal lesions, further supporting the important role of the dorsomedial thalamus in frontal functions. Data from patients with diencephalic lesions from other causes (usually small infarctions) suggest that the pattern of memory impairment is similar to KS.

Patients with frontal lobe damage have memory impairments. They differ from those with medial temporal damage in obvious ways; they are not amnesic as defined above. Hecaen and Albert [43] summarized an enormous literature on frontal memory deficits and concluded that the impairments in memory were due to inefficiencies caused by poor attention or poor ‘executive’ function. The most consistent finding in patients with frontal lesions is impairment in multiple trial list learning tasks [44]. On this task they fail on recall measures but have generally normal performance on recognition measures. This has been interpreted as defective retrieval — a function that requires strategy and effort — as opposed to normal storage — a function that is more passive [45].

A major problem with this research is a failure to discriminate between lesions in different frontal regions. Comparisons are made between a group with a very specific and restricted lesions — medial temporal — and group with very heterogeneous lesions — dorsolateral, orbital, polar and superomedial — which may have greatly different roles in memory. Stuss et al. [46] have investigated this question and demonstrated substantially different effects on memory depending upon specific frontal lesion site. Patients with left dorsolateral frontal lesions are particularly impaired on list learning, and this deficit is highly correlated with deficits in lexicosemantic capacity measured by verbal fluency and naming tasks. Right frontal patients are particularly prone to perseverative errors in recall tasks. All frontal patients are defective in the application of strategies to improve learning.

Patients with frontal lesions also have a number of specific impairments in memory. They are defective in recall of temporal order, that is, recalling the context of learned items, even when they can remember these items [47]. Finally, they have defective metamemory, that is, they are very poor judges of knowing what they remember and how well their memory functions [48]. In summary, patients with frontal damage are impaired
in ‘the process involved in planning, organization and other strategic aspects of learning and memory that may facilitate encoding and retrieval of information’ [45]. Some of these defective strategies may be specific to the frontal lesion site.

There is one other important point about the effects of lesion site on memory. Lesions in brain regions critical for any aspect of information processing will produce deficits in learning that is dependent upon that process. Thus, aphasics will have learning and ‘memory’ deficits for material that requires specific language processes to be encoded. These learning and ‘memory’ impairments will be specific to disturbed language processes [49,50]. Patients with phonological deficits will be impaired in verbal short-term memory; patients with lexical-semantic deficits will be impaired in verbal long-term memory. The same phenomenon is seen in patients with perceptual deficits for visual memory. Many patients complain of ‘memory problems’ that are due to processing deficits and not actually due to impaired memory. Demonstration of ‘memory problems’ (usually verbal) in neuropsychological tests in patients with aphasia (even if mild) are not informative and may not reflect a patient’s real experiential memory capacity.

5. Assessment of memory disorders

Clinical assessment of memory is not difficult. Patients have to be alert, attentive, cooperative, motivated and neither anxious nor depressed, or the assessment is meaningless. Short-term memory is best assessed with a simple forward digit span. Long-term memory is best assessed with a multiple trial list learning task which includes recall after a several minute interval filled with distracter activity. Recognition can be tested by mixing items from the learned list with similar items not on the list. Remote memory is not easily tested at the bedside although the standbys — naming the most recent presidents or describing recent and remote historical events — are reasonable, if coarse, estimates. Semantic memory is also not easily tested at the bedside although questions about commonly known facts may offer an approximate measure. Notice that these are all verbal tasks and give no information about visual or spatial memory.

Neuropsychological testing can provide much more detailed and standard measures of memory. There are numerous reliable standardized assessments of memory — verbal and visual, short-term and long-term, remote, semantic, procedural and implicit [51–53]. All rehabilitation settings should have competent neuropsychological services that can provide these assessments. Raw neuropsychological data can be misinterpreted. Patients with attentional impairments (head injury, thalamic strokes, acute frontal lesions, etc.) will test more impaired than they actually are. Patients with mild language deficits will appear amnesic on traditional verbal tasks such as story recall when they are clearly not amnesic. Semantic memory and motor learning may not be routinely tested and thus overlooked. Nevertheless, accurate measurement of memory and learning requires collaboration with a neuropsychologist.

6. Common neurological causes of amnesia in the rehabilitation setting

There are many reasons why patients on a neurorehabilitation unit may have memory problems. They may have a neurologic disorder unrelated to their rehabilitation admission, such as Alzheimer’s disease or (most common in our experience) multi-infarct dementia. Neurologic disability is often accompanied by depression or anxiety; both have potent effects on memory. Their illnesses may cause pain, requiring analgesics, and both the pain and the medication may affect memory. Some patients (surely too many) may be receiving hypnotics, tranquillizers, sedative antidepressants, centrally-active antihypertensives or other medications that affect mental processes. Systemic medical disorders — chronic respiratory disease, renal failure, etc — may blunt mental capacity. For this review, however, we will focus on primary neurological disorders that are seen on rehabilitation units and may cause amnesia.

Amnesia due to stroke is usually the result of a thromboembolic event in the posterior circulation of the brain. The vertebrobasilar circulation feeds the posterior cerebral and posterior communicat-
ing arteries which supply critical memory structures; the posterior two-thirds of the hippocampus and other temporal lobe structures, and the thalamus. Thus, the most common stroke pattern associated with amnesia is infarction in the territory of the posterior cerebral artery (PCA) [54,55]. The PCA supplies the posterior hippocampus and adjacent areas including parahippocampal gyrus and critical pathways that link other structures with the hippocampus such as the fornix and the cingulum. As with all neurologic causes of memory impairments, there will be modality and severity effects depending on the site of the lesion; left sided lesions causing verbal and visual memory impairments, right sided causing visual memory impairments alone, and both sides causing total amnesia. In a careful study of unilateral PCA infarctions, von Cramon showed that lesions limited to the left collateral sulcus affecting the posterior hippocampal gyrus and collateral isthmus was sufficient to cause a significant verbal memory impairment [56]. It is postulated that this lesion is critical because it damages a bottleneck of bi-directional fibers between the posterior hippocampal gyrus and unimodal and multimodal cortical association areas. Thus, the hippocampus is deprived of its main afferent projections and cannot provide input into widespread neocortical areas. Infarction in the region of the retrosplenial cortex, also supplied by the PCA, can also cause amnesia probably through a similar mechanism, damage to cingulate bundle projections to the hippocampus [57]. The PCA also supplies the medial occipital and inferior temporal regions. Depending upon lesion extent amnesia may be accompanied by visual field deficits. With a left sided lesion there may be alexia, visual agnosia, and semantic memory impairments [58,59], and with a right sided lesion, prosopagnosia [60].

A less common cause of amnesia due to stroke is secondary to thalamic infarction. As previously discussed, the critical thalamic nuclei involved in memory are the anterior nucleus which receives projections from the mammillary bodies via the mammillothalamic tract and the dorsomedial nucleus which receives projections from the amygdala [22,23]. These critical structures are supplied by two arteries: the tuberoinfundibular (or polar) artery, a branch of the posterior communicating artery, and the paramedian thalamic artery, a branch of the basilar artery. The arterial supply to the thalamus however is quite variable and there is overlap in the distribution of territory supplied among individuals. Persistent amnesia is caused by thalamic damage that interrupts projections from both the hippocampus and amygdala to the anterior and dorsomedial nucleus. A single origin for both paramedian thalamic arteries is relatively common, and thus can lead to bilateral medial thalamic infarction. This infarction results in an acute onset of hypoarousal or coma followed by a severe amnestic syndrome affecting both verbal and nonverbal memory [61,62].

Rupture of anterior communicating artery aneurysms (ACoA) often results in amnesia. This artery interconnects the two anterior cerebral arteries and is the most common site for cerebral aneurysms, accounting for 30–40% of all aneurysms [63]. It supplies the region of the basal forebrain. Following ACoA aneurysm rupture, the basal forebrain region can be damaged unilaterally or bilaterally as a result of vasospasm causing decreased blood flow or as a result of direct damage of the hemorrhage.

In the acute state following ACoA rupture, patients have a severe confusional state, anterograde and retrograde amnesia and confabulation. The memory impairments seen after ACoA rupture are not uniform. Some patients are densely amnesic with a pattern similar to KS; others are less impaired and may even have normal recognition memory. Many patients with and without amnesia are impaired on 'executive' function tasks, such as the Wisconsin card sorting test, verbal fluency and cognitive estimation [64]. If amnesic, retrograde memory is usually similar to KS [65]. Confabulation seems particularly common after ACoA rupture. Extraordinary confabulation [66] and severe retrograde amnesia [67] are seen in patients who have both dense amnesia and marked 'executive' impairments. At least in the first few months of illness all of these deficits are highly correlated with the extent of frontal infarction. In the population of ACoA patients as a whole, the deficit profiles can be quite variable, reflecting a mixture of lesion profiles in both
basal forebrain and left, right or bilateral frontal structures.

Closed head injury (CHI) may compromise memory in several ways — diffuse axonal injury, hypoxic-ischemic injury, or focal intracranial lesions such as intracerebral hematomas and contusions [68]. Severe diffuse axonal injury may cause marked memory impairment without any demonstrated focal lesion. Also, ischemic necrosis caused by reduced cerebral perfusion secondary to raised intracranial pressure and/or by hypoxia, a frequent systemic complication of closed head injury, can lead to memory impairment due to direct hippocampal damage [69]. A predilection for injury (contusions) of orbitofrontal and anteromedial temporal lobes is most often responsible for memory impairments [70]. For patients with contusions, the extent of memory impairment correlates with the size of temporal lobe lesions [71].

Initially after emerging from coma, patients have a severe anterograde amnesia, referred to as post-traumatic amnesia (PTA), attentional impairments and behavioral deficits. Duration of coma and duration of PTA strongly correlate with one another and with eventual functional outcome. During the period of PTA, CHI patients exhibit a more rapid forgetting rate than patients with CHI whose PTA has resolved. Deficits in anterograde memory, however, commonly persist even after the resolution of PTA. Again, there may be modality-specific impairments in verbal or visual memory depending upon the site of focal temporal lobe damage. Even CHI patients with good recovery are found to be highly susceptible to interference during free recall tasks and underutilize strategies such as semantic clustering during verbal learning [72, 73]. Short-term memory is relatively intact after resolution of PTA [68].

CHI patients frequently have a retrograde amnesia for events prior to the accident. As PTA resolves, retrograde amnesia (RA) also recovers in parallel, so called ‘shrinking’ RA [74]. Investigation of the pattern of RA has revealed that there is a temporal gradient for autobiographical events but rather poor recall across all decades for public events [75]. These investigators have interpreted this dissociation as relative sparing of early personal semantic knowledge in patients with CHI. Recently there has been a series of reports of patients with severe impairments in retrograde amnesia with relatively intact anterograde memory due to anterior temporal lobe damage [76]. It is not known if this region is critical for storage or retrieval of remote memories.

The herpes simplex virus is the most common cause of sporadic encephalitis. It often causes severe focal necrosis predominantly in the medial temporal lobes, insula and orbitofrontal cortex. This distribution of lesions almost perfectly encompasses the critical memory structures of hippocampus, amygdala and basal forebrain. Damage is often bilateral, but it is not unusual for damage to be restricted to one hemisphere. In the acute phase, patients are often confused, severely amnesic, and have a profound behavioral disturbance which resembles the Kluver-Bucy syndrome, characterized by hyperorality, increased sexual behavior and loss of normal anger and fear responses [77]. Mortality is high. Survivors are usually mostly disabled by amnesia.

One of the best studied cases of herpes encephalitis (HSE) is patient ‘Boswell’ [78]. Neuroimaging demonstrated complete bilateral destruction of entorhinal cortex, hippocampus, amygdala, temporal poles, insula, orbitofrontal cortices and the basal forebrain. The pattern of anterograde amnesia in Boswell is almost indistinguishable from other patients with bilateral medial temporal lobe damage such as HM. Also similar to patients with bitemporal damage, HSE patients have normal implicit memory including procedural learning, classical conditioning, and priming [79]. Severity of ‘frontal’ cognitive impairments is variable and will depend on the extent of frontal damage.

Boswell (like many other HSE patients) differs from HM because Boswell has a severe retrograde amnesia involving all decades of his life history, perhaps due to additional extensive damage to anterior temporal lobes (Brodmann’s area 38) and insula. This pattern of damage is nearly identical to the case reports of isolated retrograde amnesia following a closed head injury. Other patients with HSE have severe deficits in semantic memory [80,81], often category-specific,
probably due to lesion extension to lateral temporal and inferior parietal cortex. For example, one study documented the selective preservation of knowledge of non-living things but severely impaired knowledge of living things. Warrington [82] has proposed that this apparent category-specific semantic impairment is due to distinctions between cerebral knowledge bases organized around function and use (objects), and those organized around their perceptual processes (animals, flowers, etc).

Anoxia can be the result of a variety of causes such as cardiac arrest, systemic hypotension, carbon monoxide poisoning, status epilepticus, failed suicide by hanging and near drowning. Anoxia usually causes widespread cortical damage due to laminar necrosis. If the patient survives, global impairments in cognition including amnesia, are significant. Because the CA1 region (Sommer's sector) of the hippocampus is especially vulnerable to anoxia, some patients have selective hippocampal damage. Damage of this region may be due to release of glutamate during ischemia. This excitatory neurotransmitter acts on N-methyl-D-Aspartate (NMDA) receptors which are found in high concentration in the CA1 region of the hippocampus [83]. There is a single well documented case of dense amnesia in which the patient had a selective lesion in CA1 of the hippocampus, leaving other areas of the hippocampus as well as the amygdala intact verified by autopsy [84]. The pattern of amnesia that resulted was similar to the case of HM. Patients with specific amnesia after anoxia have severe anterograde amnesia with limited retrograde amnesia [85,86]. Confabulation is sometimes also present perhaps due to frontal neuronal loss.

7. Recovery of amnesia

An optimistic view about recovery of memory impairments following brain injury would be that some natural recovery occurs in almost all disorders. The extent of recovery can range from minimal to complete. There are three important clinical questions. First, how does memory recover? Second, are there early predictors of who will recover and who will not? Third, are there treatments that extend or accelerate recovery. All three must be considered to provide support for the patient and family as they struggle with the demands of living with brain damage.

There are several proposed physiological mechanisms for how the brain may recover. Most evidence for these mechanisms is derived from animal work and a review of this literature is beyond the scope of this paper. However, these studies warrant further review by all rehabilitation professionals who are involved with patients with memory disorders (for review, see [87]). One possible mechanism for recovery of function, called diaschisis, refers to the detrimental effect of a lesion on the functioning of remote regions. Early recovery observed in patients may be due to the re-establishment of function in these intact regions of the brain that were disrupted by the primary lesion [88].

Another mechanism of recovery is regeneration of neural elements. Regenerative sprouting from transected axons and collateral sprouting from intact axons does occur. For example, experimental destruction of entorhinal cortex on one side resulted in sprouting of axons from the contralateral entorhinal cortex to the hippocampus on the side of the experimental lesion. The onset of this sprouting correlated with the recovery of a function subserved by these structures [89,90].

A promising mechanism for recovery of function would be that an intact brain region can reorganize to assume the function of a damaged region. Preliminary evidence for reorganization in humans has been reported. Several functional neuroimaging studies have now shown that novel brain regions activate during performance of a function that was traditionally performed by a damaged cerebral region. In one PET study, in a patient with semantic memory impairments following a left posterior parietal stroke, homologous areas in the right posterior parietal lobe activated during a semantic memory paradigm [91].

Most studies of recovery in humans have been disease-specific and only descriptive, documenting the percentage or extent of recovery in a specific group of patients [92]. We recently reported an analysis of what cognitive processes might actu-
ally account for recovery in a single group of amnesies [67]. Retrograde amnesia, but not anterograde amnesia, improved in a group of ACoA patients in parallel with recovery of ‘executive’ functions. With recovery, the slope of the retrograde temporal gradient became less steep. The combination of ‘executive’ impairments and amnesia produces the phenomenon of temporally graded retrograde amnesia, and as one — ‘executive’ function — improves, the other improves. There is a great deal to be learned about recovery of memory. Some mechanisms may be specific to one disease, to one lesion site, to one point in recovery or to one aspect of impairment.

There is also scant information available to predict memory recovery. It is clear, however, that lesion site and laterality do have some predictive value. Bilateral damage to hippocampus, surrounding cortex and the amygdala will lead to permanent amnesia, as seen in patient HM. The permanence of amnesia after bilateral medial temporal lesions has also been observed in HSE, PCA strokes and anoxia. This notion of bilateral damage to critical memory structures is also seen after lesions of the fornix and the thalamus. Unilateral lesions (HSE and PCA strokes predominantly) allow much recovery of modality-specific memory and day-to-day experiential memory. Lesions in the basal forebrain are usually bilateral, but in these patients, the combination of damage to basal forebrain, striatum and frontal lobes results in persistent, dense amnesia. Damage to basal forebrain alone is compatible with an excellent recovery [93].

After stroke, aneurysm rupture, herpes encephalitis and some cases of closed head injury, focal lesions produce amnesia and the bilaterality and extent of lesions determines prognosis. For disorders without lesions demonstrable by neuroimaging there are, however, other clinical factors that predict recovery of memory function. In patients with subarachnoid hemorrhage from any vessel, the magnitude of subarachnoid blood is an important predictor of recovery presumably because increased subarachnoid blood increases the risk of ischemia due to vasospasm. The Glasgow outcome scale score (which measures global functional impairment) at discharge from the neurosurgery unit is the best predictor of persistent cognitive impairment [94]. In diffuse axonal injury due to closed head injury, the lowest post-resuscitation Glasgow Coma Scale score is predictive of verbal memory 1 year later [95]. Similar relationships can be found in patients who have suffered hypoxic-ischemic injury [96]. Finally, in all memory disorders, a patient’s age, gender, education, socioeconomic level, ethnic background and cerebral dominance are important factors in memory recovery [88].

8. Memory rehabilitation: does it work?

The third question about recovery is whether treatment is effective in improving recovery. There are two general approaches to improve memory after brain damage; pharmacotherapy and cognitive remediation therapy. Neither approach has had, thus far, a profound impact on the recovery and rehabilitation of memory disorders, perhaps because both types of therapies are still quite primitive. Pharmacological interventions aim at simple replacement or augmentation of a neurotransmitter that is presumed to be critical in memory function. Cognitive therapeutic interventions attempt to ‘exercise’ the weakened memory system. Over the past few years, critical appraisal of these approaches has guided investigators to new innovative ways of treating memory disorders.

The neurotransmitter most closely linked to memory function is acetylcholine. Early studies observed that healthy young subjects developed impairments on immediate and delayed free recall of word lists following the administration of the anticholinergic preparation, scopolamine. [97,98]. Further, anticholinergics impair episodic memory only, leaving semantic, procedural and short-term memory intact [99]. This pattern of memory deficits in normal subjects is similar to that observed in dementia and could be alleviated by physostigmine, an cholinesterase inhibitor, which prolongs acetylcholine action within the synapse [100,101]. This observation led to numerous investigations of acetylcholine replacement and augmentation therapy as a means of improving memory function in patients with dementia,
especially Alzheimer’s disease, in which a dominant cognitive impairment is amnesia [102]. The possibility that cholinergic therapy could be beneficial was supported by several findings in Alzheimer’s patients. The synthetic enzyme choline acetyltransferase is markedly reduced in the amygdala, hippocampus and neocortex [103]. Enzyme reduction correlated with senile plaque formation and the mental status test scores. There is a severe loss of neurons in the nucleus basalis of Meynert; an area that provides a large proportion of the cholinergic input to the cortex [26].

Overall, clinical trials with cholinergic medications in Alzheimer’s disease (AD) have been disappointing since improvement in memory function has not been dramatic or sustained (for review, see [102]). Investigations have utilized lecithin, the precursor of acetylcholine; physostigmine, a cholinesterase inhibitor; and arecholine, a cholinergic agonist. Only tacrine, another cholinesterase inhibitor, has been approved by the FDA for use in AD because of its beneficial effects on behavior and cognition [104]. However, close scrutiny of these clinical trials suggests that the benefits, although statistically significant, produce only modest functional gains in these patients.

Using these results in AD patients as a rationale, there have been a handful of single case studies in which cholinergic drugs were administered to patients with memory impairments due to acute brain injury. A patient with temporal lobe damage from HSE and another from a penetrating injury showed improvement on long-term memory tasks after administration of cholinergic agonists [105, 106]. A third patient with a lesion limited to the diagonal band of Broca in the basal forebrain after surgical resection of a low grade glioma had modest improvement in supraspan immediate recall with physostigmine during the dose-finding phase. However, no benefit was found during a six-day double-blind placebo controlled trial [107]. SPECT showed decreased blood flow in the medial temporal region ipsilateral to the lesion during baseline and increased blood flow in this region after a physostigmine dose. Placebo-controlled clinical trials of neurotransmitter drugs are necessary to determine their ultimate effect in patients with acute brain injury.

These pharmacological studies have focused on episodic long-term memory, much less work has addressed short-term memory. Elegant work by Goldman-Rakic in nonhuman primates has shown that the dorsolateral prefrontal cortex, which is a critical component of the neural network that subserves spatial short-term memory, contains the highest concentration of dopaminergic receptors in nonhuman primate cortex [108]. The functional importance of dopamine to spatial short-term memory has been demonstrated in several ways. Depletion of dopamine in the prefrontal cortex or pharmacological blockade of dopamine receptors induces impairment in spatial delayed response tasks [109,110]. Furthermore, administration of dopaminergic agonists to these monkeys reversed the delayed-response impairments [109]. Expanding on these findings in humans, recent investigations from our laboratory [111] and others [112] have demonstrated that a dopaminergic agonist, bromocriptine, improves performance on short-term memory tasks when given to normal young subjects.

Investigations of this type in humans and other primates suggests the first faint outline of a pharmacological model of human memory. Acetylcholine may be one neurotransmitter that is critical for episodic long-term memory, and dopamine appears to modulate short-term memory. Abundant evidence from the animal literature demonstrates that the picture will be, however, much more complex than this simple view. Many other neurotransmitters, such as GABA, serotonin and norepinephrine also play a role in memory function [113]. Neuromodulators, such as neuropeptides (i.e. opioids and vasopressin) are also involved in memory processes [114]. The operation of memory systems is likely the result of the interaction of multiple neurochemicals. It is naïve to believe that treatment directed at a single neurotransmitter can affect memory significantly. Thus, an innovative approach for improving memory function would be to influence several neurotransmitters systems, especially systems that are less affected but nevertheless interact in memory.
processes. For example, in rats, there is a high concentration of GABA receptors in the basal forebrain and GABA antagonists (i.e. benzodiazepines) cause a decrease in acetylcholine release, and cause memory impairments. In contrast, GABA agonists, reverse the memory impairing effects of anticholinergics [115]. In another study, rats depleted of acetylcholine and norepinephrine exhibited improved memory performance with administration of a combination of low dose cholinergic and noradrenergic agonists. Administration of a low dose of either agonist alone could not produce memory improvement [116]. This finding challenges the single drug therapy approach that is in common practice in clinical trials today attempting to improve cognition. To our knowledge, clinical trials using combinations of different neurotransmitters have not been performed.

In addition to the uncertainties about the critical mix of neurotransmitters involved in memory processing, it is not known if different lesion sites influence the extent that even the correct treatment (whatever that may turn out to be) will be effective. Extensive bilateral damage to hippocampus is likely to leave little substrate left to be influenced by pharmacotherapy. It is possible that lesions that damage pathways (i.e. fornix, cingulate bundle, collateral isthmus, etc) might respond better to drug treatment because receptor neurons would be intact. Future aims of investigations of this type must choose specific neurochemical agents, study specific cognitive processes and control for extent and location of brain damage. It should be possible, and it should be a high priority of research, to discover and dissociate the different neurochemical substrates from the different components and mechanisms of memory. In this way, pharmacological investigation of memory in animals, as well as investigations in disorders not commonly treated in rehabilitation hospitals (i.e. Alzheimer’s disease), can shed light on possible rational therapies for patients on neurorehabilitation units.

Cognitive remediation approaches to memory rehabilitation have developed along three general lines; re-training a damaged memory system through exercises and drills, using compensatory strategies such as memory aids and mnemonics, and tapping residual learning abilities. The notion that practice improves memory was pervasive and led to the domination of retraining techniques in early memory rehabilitation programs. Evidence that this notion still exists among rehabilitation workers was found in a survey of occupational therapists in which many believed that memory could be improved simply by repetitive practice [117]. There is no scientific evidence that such repetitive practice effectively generalizes to real life situations despite numerous hours of intensive training [118,119]. An illustration of this important point is an individual who increased his digit span from seven to 80 by repetitive practice, but when switched to a memory span task using letters, his performance dropped to seven items, the standard span performance [120]. Unlike a weakened muscle, damaged memory processes show little recovery through repetition training. The proliferation of inexpensive software for personal computers that allows endless memory drills increases the likelihood that patients will be exposed to memory rehabilitation paradigms that have no therapeutic value which will ultimately lead to continued failure [121,122].

The alternative to repetition re-training is to develop strategies to compensate for impaired memory abilities. The goal of memory rehabilitation is not to restore the unrestoreable but to produce improvements that will allow amnesic patients to understand and cope with these difficulties in a way that will lead to a more normal life [123]. One such compensatory strategy for improving amnesia is to train patients to perform more elaborative encoding during the learning of new information. The assumption is that ‘deeper’ encoding can improve recall performance. For example, a patient with a right hemisphere lesion was taught a ten-word shopping list by learning a phrase that used the first letter of each item on the list [124]. Although recall for the tested lists improved, the patient was not able to use this encoding strategy spontaneously for other lists. Other cueing techniques that facilitate recall also appear not to generalize [125].

One popular compensatory strategy for memory impairment is the use of visual imagery to
organize information during the time of learning in order to facilitate later recall; again, the assumption seems to be that broader encoding leads to better recall. There is ample experimental evidence demonstrating improvement in memory recall when learned items are linked with visual images. For example, patients with left hemisphere damage showed improved verbal memory after being trained to link each word on a list of ten items with a ridiculous but vivid visual image. For example, 'teacup' is linked with 'radio' by imagining yourself drinking tea from a radio instead of a cup [126]. Training patients to link a list of verbal paired-associates to a visual image resulted in improved verbal recall in left temporal lobectomy patients whereas right temporal lobectomy patients derived no benefit from using imagery [127,128]. These observations suggested that an intact right medial temporal system could produce image-mediated verbal learning to compensate for verbal learning deficits following left medial temporal damage. Other investigators have determined that imagery cues must be provided not only during encoding but also during retrieval in order to aid impaired free recall [125,129]. Patients with more severe amnesia due to bilateral lesions, including patient HM, have shown no benefit from visual imagery. In fact, these patients are unable to even remember the images that were taught to them during initial learning to enhance memory recall [127,130].

Any optimism that is generated from these techniques must be tempered by several limiting factors which likely prevent their practical use outside of the laboratory. First, elaborative encoding by visual imagery or other mnemonics places excessive demands on brain damaged patients who have limited processing capacities [131]. Second, even if amnesic patients were capable of using these strategies many patients are unaware of their memory deficits and, thus, unmotivated to use them spontaneously. Third, it is not clear that even individuals with normal memory use these types of mnemonics when attempting to recall past learned information [121]. Finally, mental imagery may help amnesic patients learn a short shopping list but why not just teach the patient to write the items down on a piece of paper — the ultimate compensatory strategy! [64].

A simple compensatory technique that can be highly effective in helping amnesic patients compensate for their difficulties is the use of memory prostheses. External memory aids reduce reliance on defective memory. notebooks, diaries, nametags and posted signs containing useful information in critical areas around a person's living environment, or simply relying on a spouse all have been useful [132]. Patients and families are often given too little instruction in the use of these aids, and then patients may reject the memory books or not use them correctly. Memory rehabilitation programs must be designed to train amnesic patients to use these external aids. One well-designed program takes at least 2 months to train patients to use a memory book spontaneously [133]. Many amnesics also have other problems — alexia (PCA strokes), poor motivation (thalamic and frontal lesions), etc — that make them poor candidates for external aids. It is our impression that external aids are only valuable for 'forgetful' patients, i.e. most CHI patients, frontal lesion patients, and not for the densely amnesic.

As a complement to memory aids, several investigators have developed 'memory manuals' which are written for patients with a mild memory disturbance and address typical day-to-day problems that patients will likely face and strategies for dealing with them [134,135]. Many centers that treat patients with memory disorders also provide memory support groups to emphasize and reinforce the strategies. These groups may reduce anxiety and depression rather than actually improve memory performance, but this aspect of memory rehabilitation is critical and the efficacy of these groups is affirmed by the continued participation of its members [136].

Another type of compensation for memory difficulties would be the use of residual memory capacities. For instance, amnesic patients have normal implicit memory, and the technique of 'vanishing cues' takes advantage of this observation [137]. The aim is to teach amnesic patients complex domain-specific knowledge that can be used to enhance their day-to-day functioning.
Glisky et al. [137] were able to teach dense amnesics the vocabulary necessary to use a personal computer and carry out simple programs. In this procedure, a definition would be presented and the patient would be provided with as many letters as were needed to elicit the correct word. In subsequent learning trials, letters are gradually withdrawn from the cues until the patient can produce the correct word without the letter cues. The amnesic patients were eventually able to generate the definitions of each word in the absence of letter cues, and this was retained across a 6-week interval. This technique of ‘vanishing cues’ produced faster learning and better retention than techniques without cues given.

In a follow-up study using the same technique, memory-impaired patients were taught the knowledge necessary to actually manipulate information on a computer screen and execute simple computer programs [138]. Further, this knowledge was retained for up to 9 months [139]. Finally, a severely amnesic encephalitis patient was taught how to perform data entry into a computer and was able to demonstrate her skills in the workplace [140].

For amnesics, this technique has a profound limitation; the knowledge learned is ‘hyper-specific’. That is, it is only accessible when the original conditions are reintroduced. This suggests that neither the information or the procedure of learning generalizes. When the patients who were successful in the workplace were presented with novel situations, learning slowed dramatically [122]. As a practical treatment matter, there are additional problems with implicit memory techniques. First, they take an inordinate amount of time and effort for a result with little generalization. Second, the patient is not prevented from making errors during learning, so errors can be endlessly repeated and inadvertently primed [123]. Recent studies have shown that errorless learning paradigms are substantially better when the subject is not allowed to guess during the learning process [123]. Despite these potential limitations, utilization of intact implicit memory systems in amnesic patients seems to have potential but must be investigated further before it can be used clinically.

In summary, a theme for effective memory rehabilitation is beginning to emerge. Efforts to restore memory function are probably futile and efforts should be directed towards compensating for memory impairments. An important adjunct to these ‘cognitive’ remediation therapies are ‘behavioral’ therapies that are aimed at modifying a patient’s attitude or beliefs concerning their impairments [141]. There is a single acid-test for the value of any proposed memory therapy: does treatment generalize to daily living? Wilson describes three types of generalization of rehabilitation strategies; generalization across subjects, generalization across behaviors, and generalization across settings. The last two types of generalization refer to the ability of memory impaired patients to use the external aids spontaneously and apply strategies to other situations than the one in which they were learned. Little evidence exists that the various memory rehabilitation strategies discussed in this paper are effective in to the real-life situations of these patients. Wilson argues that generalization should not be expected to occur and it should be specifically taught in memory rehabilitation programs [141]. Future work should be aimed at systematically evaluating the outcome of these programs.

Since memory deficits are often permanent disabilities, even if generalization can be taught, it must be sustained beyond the rehabilitation program and throughout the patient’s life. Little is known about the long-term prognosis of memory disorders following memory rehabilitation but several recent studies have addressed this issue [142,143]. A group of 54 memory-impaired patients with various etiologies who underwent memory therapy were re-evaluated 5–10 years later. Approximately 60% of these patients showed no significant improvement in memory functioning since finishing formal memory rehabilitation and only 30% showed significant improvement. In the remaining 10% of patients memory function had deteriorated. Fifteen of the 54 patients returned to work but only two of these patients returned to their previous work on a full-time basis. An important finding was that patients were using memory aids and strategies to a greater extent during the follow-up evaluation
than they were during the rehabilitation period. Internal memory aids (mnemonics) were used less often than external aids by these patients. The most common internal aid was mental retraction of previous events, and the common external aids were reliance on notebooks, lists, calendars and wall charts. Overall, these patients were not densely amnesic.

Although this information is helpful in evaluating the long-term prognosis of amnesic patients, conclusions regarding the efficacy of memory rehabilitation must be interpreted cautiously since there was no comparison with patients without formal rehabilitation to evaluate the effects of natural recovery. In a similar study which included a control group of memory-impaired patients that did not receive memory therapy, it was found that only the memory-trained patients showed improvement on objective memory measures at 4 months following the end of therapy. Memory training did not result in improvement on control tasks, reaction time measures, which was taken as evidence that the improvement was due to the memory therapy rather than natural recovery or improvement in general motivation [144].

9. Conclusion

Memory impairments are a common manifestation of many neurological disorders treated on neurorehabilitation units. After discharge, persistent memory difficulties greatly reduce functional independence and limit return to work, school and leisure activities. Memory function is comprised of several processes and different subcomponents of memory may become impaired following brain damage. For example, despite dense anterograde amnesia found in some patients, implicit memory is preserved. Qualitatively different patterns of amnesia are found in patients depending on the location of brain damage within the neural networks that subserved memory.

Understanding the psychological functions and the neuroanatomical bases for memory processes can aid health professionals involved in the rehabilitation of patients with memory disorders in many ways: with appropriate assessment and classification, with understanding of the underlying pathophysiology, and with the role of neuroimaging studies to inform prognosis. Neuropsychological assessment that pinpoints cognitive strengths may provide a route to compensate with memory therapy. Cognitive theories of memory may lead to new therapeutic approaches. Pharmacotherapy must target specific components of memory and use specific neurochemical mediators. Cognitive remediation therapy must abandon the idea that repeated practice and drills will strengthen the weakened ‘memory muscle’ and must use compensatory strategies for overcoming memory impairments. As severe memory impairments are rarely reversible, our attempts to help patients must strive for long-term effects across their disabled life span.

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