Long-term memory disorders: measurement and modeling
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CHAPTER 2
A BRIEF REVIEW OF AMNESIA

In the past decades, many once agreed-upon characteristics of amnesia have become the focus of controversy. Nevertheless, this review will argue that most evidence still favors classic findings such as the Ribot gradient in retrograde amnesia. Newer findings will also be discussed. For example, it has become clear that isolated forms of both retrograde and anterograde amnesia do exist. Moreover, implicit memory has been found to be spared in amnesia. After reviewing these topics, the chapter concludes with a list of main characteristics of amnesia and of the neuroanatomy underlying memory and amnesia. All comprehensive model of amnesia must account for these.

Memory loss is one of the most common neuropsychological complaints. It is a hallmark of major neurological diseases and psychiatric disorders, which affect millions of people worldwide. Nevertheless, its causes and characteristics remain mired in controversy. This is unfortunate, as amnesia offers a rare view into the neural bases of memory. For example, without cases such as H.M. (Scoville & Milner, 1957), neuroscience would probably not so soon have discovered the role of medial temporal lobe structures in memory. Since then, lesions in other parts of the brain have also been reported to cause various forms of amnesia. A careful review of memory disorders after brain damage may shed light on the exact functions of these brain areas, as well as on their interactions.

Some characteristics of amnesia have been known for over a century, such as Ribot's Law (Ribot, 1881), which states that recent memories are more vulnerable to brain damage than older ones. Others are relatively recent discoveries, such as the sparing of implicit memory. These findings are reviewed in this chapter. The primary focus will be on organic amnesia in humans. Psychogenic amnesia is not addressed, while findings in experimental animals are only briefly discussed. Psychiatric syndromes will also not be discussed.

The chapter starts with a look at some important functional characteristics. Then we will briefly review a number of prominent patient populations with amnesic syndromes. After that, two specific topics will be covered in some depth: the relation between retrograde and anterograde amnesia, and implicit memory in amnesia. The chapter ends with a listing of target data that a model of amnesia, such as the TraceLink model presented in later chapters, must explain.

Jaap Murre contributed thoughts and structure to this chapter.
2.1 CHARACTERISTICS OF AMNESIA

Anterograde amnesia

Amnesia has two main aspects, retrograde amnesia where existing memory traces are unavailable, and anterograde amnesia where the capacity to form new memory traces is lacking. In patients with anterograde amnesia one finds normal intelligence, working memory, reasoning and consciousness, combined with an inability to learn or retain new information (Baddeley, 1990; Bauer, Tobias, & Valenstein, 1993; Reed & Squire, 1998; Rempel-Clower, Zola, Squire, & Amaral, 1996). The diagnosis is often made when there is an abnormal difference between the score of the patients on IQ tests or attention tests, and the score on memory tests (O'Connor, Verfaellie, & Cermak, 1995). Anterograde amnesia can be very debilitating, preventing the patient from holding a job or having a normal social life.

The tests with which anterograde amnesia is demonstrated usually involve verbal learning (e.g., the popular Rey Auditory Verbal Learning Test), or learning sets of pictures (e.g., The Warrington Recognition Memory Test, subtest faces). This does not mean that amnesia is limited to these forms of learning. The Rivermead Behavioural Memory Test was developed specifically to sample a broad range of activities in which memory is displayed. Nevertheless, this test can diagnose amnesia and correlates substantially (r=0.62) with a simple verbal recognition memory test (Wilson, Cockburn, Baddeley, & Hiorns, 1991). Once material is acquired, the forgetting rate in amnesic patients of various underlying pathologies is comparable to that in normal subjects (Baddeley, Harris, Sunderland, Watts, & Wilson, 1987; Huppert & Piercy, 1978; Kopelman, 1985). This has lead to the belief that anterograde amnesia is foremost an acquisition deficit (Kopelman, 1985).

Not all forms of learning are equally affected in anterograde amnesia. Priming and other forms of implicit memory are often intact (see later section). It has been suggested that semantic memory is also spared in amnesia (Cermak, 1984; Kinsbourne & Wood, 1975; Tulving, 1983). Recently, a report appeared that demonstrated nearly normal semantic learning in four children with dense episodic amnesia caused by hippocampal damage (Vargha-Khadem et al., 1997). In two adult cases, semantic learning was evidenced by knowledge of neologisms that entered the language after the onset of amnesia (Kitchener, Hodges, & McCarthy, 1998), and from a sense of familiarity for faces of people who recently had become famous (Kitchener et al., 1998; Verfaellie, Koseff, & Alexander, 2000). However, amnesia is seldom complete, and it may be that the acquisition of semantic knowledge depends on residual episodic memory capacity. Consistent with this possibility, the amount of new semantic knowledge covaries with episodic memory function (Squire & Zola, 1998).

The format of the test with which learning is assessed has also been proposed as an important variable. Some researchers have claimed that recognition memory is spared if lesions are restricted to the hippocampus (Aggleton & Brown, 1999). Others have claimed that this is not the case, that recognition and retrieval are both affected (Reed & Squire, 1997). Recently, it was proposed that the exact format of the recognition test may be the determining factor (Holdstock et al., 2002; Stark & Squire, 2001).

Both intact semantic learning and intact recognition memory are features of damage limited to the hippocampus. Broader lesions in the medial temporal lobe, including parahippocampal regions, do severely affect recognition (Aggleton & Brown, 1999), and seem to eliminate semantic learning (Verfaellie et al., 2000).
Retrograde amnesia is characterized by an impaired retrieval of pre-onset memories. In very severe cases the loss of memories extends to all memories and the whole knowledge base of the patient. Loss of personal identity rarely occurs, however, which forms a marked contrast with psychogenic retrograde amnesia accompanying fugue states, where loss of personal identity is typical (e.g., Pratt, 1977).

In some patients, only specific types of information are lost in retrograde amnesia, sparing other types of information (Kapur, 1999). Semantic memories are relatively spared as compared to episodic memories (Cermak & O'Connor, 1983), though it is not the case that they are normal (Verfaellie, Reiss, & Roth, 1995). Cases reviewed by Butters and Cermak (1986), Kapur (1993) and Kopelman (1993) support the notion that memory for autobiographical facts and public knowledge may both be selectively impaired. Other dissociations have also been found, such as between knowledge of people and events (McCarthy & Warrington, 1992). With respect to such dissociations Warrington and McCarthy (1988) speak of the 'fractionating of retrograde amnesia'. It is not clear what these material-specific dissociations imply for a model of retrograde amnesia. Some groups of memories may be preserved because they escape the lesioned site. Alternatively, they may have stronger traces either because of their nature or frequency of occurrence. The facts do not immediately support the latter hypothesis (McCarthy & Warrington, 1992) and the evidence for the former hypothesis is at best confused (see discussion of isolated retrograde amnesia below).

A form of memory that seems generally spared in retrograde amnesia is procedural knowledge. Complex perceptuo-motor skills, such as piano playing, may be preserved in patients with dense retrograde amnesia (Kapur, Ellison, Smith, D.L., & Burrows, 1992). In hippocampectomized animals, simple forms of memory are generally intact, such as discriminating between novel and seen objects (Sutherland et al., 2001). It is not known to what extent priming is preserved in retrograde amnesia, though one study did find effects on word stem completion after electroconvulsive therapy of a list learned before the ECT. Patients in the study had no explicit memories for the list (Dorfman, Kihlstrom, Cork, & Misiaszek, 1995).

The Ribot gradient

Ribot's Law states that there is a time-gradient in retrograde amnesia, whereby recent memories are more likely to be lost (Ribot, 1881). Since the turn of the century, this time gradient, which is called the Ribot-gradient, has been reported time and again. Not all studies report the Ribot gradient in retrograde amnesia, and the steepness and extent of the gradient may vary considerably from case to case.

The Ribot gradient has, in the last decade or so, become a source of much controversy. Nadel and Moscovitch challenged in several papers the view that the Ribot gradient is the typical pattern seen in retrograde amnesia (Nadel & Moscovitch, 1997; Nadel, Samsonovitch, Ryan, & Moscovitch, 2000; Rosenbaum, Winocur, & Moscovitch, 2001). Nadel and Moscovitch (1997) list several cases of ungraded amnesia, and additional cases have been reported since (Cipolotti et al., 2001). There are also many studies in which a Ribot gradient was found. The situation is not helped by the fact that retrograde amnesia is difficult to measure. Construction of retrograde amnesia tests is a painful process, with many caveats threatening interpretability of the data (reviewed chapter 3).

This, and the fact that patient data necessarily results from experiments of nature (with all associated interpretation problems), led to a new approach in which medial temporal
lobe lesions were performed in experimental animals. After the lesion, memory is tested for behavior acquired before the operation. Such experiments started in the '80s. At the onset, they neatly seemed to support the existence of a Ribot gradient in retrograde amnesia after medial temporal lobe lesions (Squire, 1992). However, since then the literature on animal retrograde amnesia has become as muddled as that on human retrograde amnesia (Knowlton & Fanselow, 1998; Nadel & Moscovitch, 1997). While perhaps a small majority of experiments have found Ribot gradients (e.g., Kim & Fanselow, 1992; Kubie, Sutherland, & Muller, 1999; Zola-Morgan & Squire, 1990), others have not (e.g., Sutherland et al., 2001). Moreover, several methodological issues unique to the animal experiments have made firm conclusions more difficult (Murray & Bussey, 2001). When retrograde amnesia is graded and when not, is thus still contested.

The field awaits a careful meta-analysis. Nevertheless, the large variety of patient types, tests and laboratories in which the Ribot gradient has been found, inspires trust that the Ribot gradient is real and not an artifact of the way retrograde amnesia is measured. Ribot gradients seem to be found more often than flat gradients in many syndromes accompanied by retrograde amnesia (see Figure 1 for a non-exhaustive set of studies, and following sections for further discussion). For example, patients with Korsakoff’s disease typically show Ribot gradients, as do patients after ECT, head trauma, and during transient global amnesia. Patients with discrete lesions have typically only been the subject of single case studies (Figure 1 only lists group studies), but most of these have yielded graded amnesia. The Ribot gradient has been found often enough to require explanation. This is acknowledged even in the paper which started the controversy over Ribot’s law (Nadel & Moscovitch, 1997; the explanation they came up with is discussed in a following section, and more in detail in chapter 8).

Shrinkage

In cases of closed-head injury or other types of (partially) reversible damage, the patient may recover from retrograde amnesia. This is usually called ‘shrinkage’ of retrograde amnesia, because the recovery of lost memories follows a roughly chronological sequence, with the oldest memories recovering first and only later the more recent ones (Russel & Nathan, 1946). This suggests that the total time period for which memories have been lost shrinks. There are numerous exceptions to this rule. In many cases, continuous memory is recovered suddenly, for example, after a night’s sleep, and in some cases isolated ‘islands’ of memories return before continuous memory is eventually resumed (Whitty & Zangwill, 1977). Recovery is usually not complete; a residual retrograde amnesia is typically found, often showing a Ribot gradient. Shrinkage implies that part of the memories in retrograde amnesia had not been lost completely, but rather that their retrieval was interrupted temporarily. In accordance with Ribot’s Law, this interruption may somehow affect recent memories more than old memories.
Figure 1: Examples of retrograde amnesia time gradients found in the literature. Ribot gradients are evident in most figures. Tests used are: a, b, m, p: picture naming (famous faces and events); d, e, n: cued picture naming (famous faces and events); f, i, q, s: public events questionnaire; c: public events or famous faces recognition tests, 3AFC; j, r, t: same, 4AFC; g, h, k: autobiographical tests; u: naming of one-season TV series; n,o: means of several tests. Data are from a: Albert et al. (1979); b, c: Albert et al. (1981); d,e: Beatty et al. (1988); f, g, h: Kopelman (1989); i, j: Kritchevsky & Squire (1989); k: Levin et al. (1985); l, m: Parkin et al. (1990); n, o: Reed & Squire (1998); p: Salmon et al. (1988); q, r, s, t: Squire et al. (1989); u: Squire et al. (1975).
2.2 CAUSES OF AMNESIA

Discrete lesions

Both retrograde amnesia and anterograde amnesia in humans can be the result of a variety of diseases and trauma, such as closed-head injury (post-traumatic amnesia), Korsakoff's disease, Alzheimer's disease, lesions in the brain caused by infections, lack of oxygen (anoxia) or blood flow (ischemia), electrical current, vascular accidents, toxic states, pressure from tumors, or surgery. Most of these affect several regions of the brain at once. Several conditions lead to relatively focal pathology, however, and these have substantially formed our views on the neurobiology of memory. A number of sites in the brain have now been identified where lesions can lead to amnesia: the hippocampus and further medial temporal lobe structures, the diencephalon, and the basal ganglia. Frontal lobe lesions can also lead to memory loss, though it is still debated whether this is a genuine amnesic syndrome or secondary to executive problems (Baddeley & Wilson, 1988; Della Sala, Laiacona, Spinnler, & Trivelli, 1993; Kopelman, Stanhope, & Kingsley, 1999).

Amnesia has traditionally been associated with lesions of the medial temporal lobe (Bekhterev, 1900; Grünthal, 1939), which here is taken to refer to the hippocampus and entorhinal and perirhinal cortices. In H.M., the textbook case of amnesia, these structures were surgically removed to end untreatable epilepsy. After bilateral removal of the medial temporal lobes, he suffered from a severe anterograde amnesia (Scoville & Milner, 1957); in his forty years of hospitalization after the surgery, he never learned the names of the staff he dealt with on a daily basis. He also had substantial retrograde amnesia (Corkin, 1984).

Damage limited to the hippocampus often results from ischemia, a condition whereby the brain receives insufficient blood. The hippocampus, and especially its area CA1, has an exceptionally low extracellular volume (McBain, Traynelis, & Dingledine, 1990), which may lead to a high likelihood of damage after ischemia or hypoxia (lack of oxygen). Several patients with hippocampal lesions after ischemia or anoxia have now been investigated, most of which had moderate to severe anterograde amnesia and some measure of retrograde amnesia, in the absence of other deficits (Reed & Squire, 1998; Rempel-Clower et al., 1996; Squire, Haist, & Shimamura, 1989). In some patients, the lesion could be investigated in great detail post mortem during autopsy. The severity of both the anterograde and the retrograde amnesia seemed to covary with the extent of the lesion. Patients R.B. (Zola-Morgan, Squire, & Amaral, 1986) and G.D. (Rempel-Clower et al., 1996), with bilateral lesions limited to the CA1 field of the hippocampus, all had a moderate anterograde amnesia and retrograde amnesia for about a year. Patients W.D. and L.M. (Rempel-Clower et al., 1996), both of whom had lesions extending to all fields of the hippocampus, the subiculum, dentate gyrus and entorhinal cortex, had more severe anterograde amnesia and retrograde amnesia for up to fifteen years. In all cases, the temporal lobe of the neocortex was found to be intact. This strongly suggests that the hippocampus is important for normal acquisition of new memories, something that is also clear from the animal literature (Squire, 1992). Damage to the temporal lobe that extends beyond the hippocampus and surrounding structures has been shown to lead to severe anterograde amnesia and extended retrograde amnesia (e.g., Reed & Squire, 1998; Scoville & Milner, 1957). It should be added that only bilateral lesions cause such pronounced anterograde amnesia (Warrington & Duchen, 1992).
Nadel and Moscovitch (Nadel & Moscovitch, 1997; Nadel et al., 2000) have questioned whether graded retrograde amnesia is a genuine feature of hippocampal damage. They accept that public knowledge tests (public events questionnaires, famous faces tests) typically reveal a Ribot gradient, but assert that patients with damage encompassing the whole hippocampus have a flat, ungraded loss of autobiographical memory. Graded retrograde amnesia in the autobiographical domain would only occur in cases where hippocampal damage is "confined only to one subfield" (Nadel & Moscovitch, 1997).

A problem with this interpretation is that the patients they see as having a total hippocampal lesion typically had lesions extending to temporal lobe regions outside the medial temporal lobe. This offers the alternative explanation that extended, flat retrograde amnesia results from damage to neocortical temporal areas (Squire & Alvarez, 1995). Moreover, since autobiographical memory tests typically have poor temporal resolution, graded retrograde amnesia might be difficult to capture (Knowlton & Fanselow, 1998). For example, Reed and Squire (1998) report on a patient with damage concentrated in the medial temporal lobe, who had a performance within the control range for the "young adult" period of the Autobiographical Memory Interview (Kopelman, Wilson, & Baddeley, 1990), and a clear amnesia for the "recent" period (patient E.P.). Because the patient was 74 at the moment of testing, these periods might be 50 years apart and the extent of the autobiographical retrograde amnesia thus remains unclear. Another patient of Reed and Squire's (1998), however, with damage supposed to be limited to the hippocampus (patient A.B.), could be established to have retrograde amnesia on autobiographical memory tests of about 10 years. Clearly, more patient studies are needed, but up to now the evidence does not point unequivocally to a difference between autobiographical and public events tests in the retrograde amnesia gradient.

Another brain area that can be involved in amnesia is the diencephalon, which is severely affected in Korsakoff's disease. Discrete lesions to diencephalic regions, without the widespread damage that is found in Korsakoff's patients, can occur through thalamic infarction and through tumors in the third ventricle. Hodges (1995) found eleven patients in the literature who suffered a thalamic infarction and in whom both anterograde and retrograde amnesia were assessed. Most of these patients had severe anterograde amnesia and long-term retrograde amnesia. In some cases, Ribot gradients were found (e.g., patient M.G. of Squire, Haist & Shimamura, 1989).

Damage to the basal forebrain can also lead to memory disorders. Gade and Morteson (1990) compared the anterograde and retrograde amnesia of a group of twenty so-called ACoA patients (patients who suffered aneurysm of the anterior communicating artery) with twenty dementia patients and a group of patients with amnesia through varying etiology. ACoA patients have damage to the basal forebrain. They could not find any differences in the pattern of retrograde and anterograde amnesia of the three groups of patients; for example, their ACoA patients showed a Ribot gradient in their retrograde amnesia comparable to the other groups. This opens the possibility that the basal forebrain has a function in memory comparable to that of the medial-temporal lobe or the diencephalon.

Aggleton and Saunders (1997), however, suggest that the amnesia shown by ACoA patients is not due to basal forebrain damage, but instead to damage to the fornix and the anterior thalamus that is often a feature of such lesions. They propose that diencephalic and temporal lobe structures together form an "extended hippocampal system", and that any lesion to this system causes similar functional deficits. Their theory of ACoA patients is supported by case reports, one of a patient who had only a small
aneurism, resulting in damage to the basal forebrain but sparing the diencephalon. This patient had severe verbal anterograde amnesia, but his remote memory was within the normal ranges (Abe, Inokawa, Kashiwagi, & Yanagihara, 1998). Another patient had lesions restricted to the basal forebrain and part of orbitofrontal cortex. This patient also combined significant anterograde amnesia with almost no retrograde amnesia (Tranel, Damasio, & Damasio, 2000). Transsection of the fornix, cutting basal forebrain inputs to the hippocampus, has also been reported to cause anterograde amnesia with minimal retrograde amnesia (Hodges & Carpenter, 1991).

Up to now, no clear qualitative differences have been uncovered in the patterns of memory deficits caused by lesions in these distinct areas. Lesions in the medial temporal region and the diencephalon seem to cause more or less the same impairments. Several explanations are possible for this finding. One is that we have thus far not used fine-grained enough measures to uncover possible differences. Another is that the variance inherent in patient data — both because of the differences in the location and extent of the lesion and because of general individual differences — obscures any pattern that may exist in the data (suggested by Gade & Morteson, 1990). A third possible explanation is that all sites discussed here are part of one functional memory system such as the ‘extended hippocampal system’ of Aggleton and Saunders (1997), and that a lesion in one spot causes a breakdown of the whole system. Though these matters are far from being resolved, it seems accepted that at least several of the areas discussed here indeed have functional relationships that make it possible to speak of one medial memory system.

How damage to the basal forebrain fits into this picture is also not resolved. Gade and Morteson’s (1990) series of patients seems to point to a similar pattern in amnesia as after for example medial temporal damage. However, damage to the diencephalon may explain these findings. A few cases with more limited damage point to disproportionate anterograde amnesia when only the basal forebrain is affected.

**Korsakoff’s disease and Alzheimer’s disease**

The two most prevalent groups of amnesic patients are those with Wernicke-Korsakoff syndrome — or Korsakoff’s disease as its chronic stage is more often called — and those with Alzheimer’s disease (Hodges, 1995). Both syndromes have a gradual onset, which leads to interpretative difficulties when assessing retrograde amnesia. It is not always clear whether loss of certain memories should be considered a form of retrograde amnesia or anterograde amnesia. The reasoning here is that any lost early memories might simply not be preserved due to early acquisition impairments (i.e., anterograde amnesia).

Korsakoff patients usually show an amnesic syndrome that involves both anterograde and retrograde amnesia. The anterograde amnesia can be very dense, and the retrograde amnesia tends to be extensive. A group study by Kopelman (1989), using a News Events test for public events from 1930 to 1980, showed retrograde amnesia for Korsakoff patients extending over 15 to 25 years, with a relatively steep Ribot gradient. Similar findings were reported by Albert, Butters and Levin (1979), Albert, Butters and Brandt (1981), Parkin, Montaldi, Leng and Hunkin (1990), and Squire, Haist, and Shimamura (1989). Kopelman’s (1989) study also included a matched group of Alzheimer patients. These patients had a low performance on all decades; though a Ribot gradient was clearly present in their retrograde amnesia, it was less steep than that of the Korsakoff’s patients. A clear, steep time gradient in retrograde amnesia on the Famous Faces Test in ten Alzheimer’s patients has been reported by Moscovitch (1982), but
Wilson et al. (1981) found a uniform loss with a flat time-gradient. From these and other group studies a picture emerges whereby weak temporal Ribot gradients are found for Alzheimer patients, and generally steeper ones for Korsakoff patients (Kopelman, 1993; see figure 1). Kopelman (1989) has suggested that part of the added steepness of the gradient might have arisen from consistent, high alcohol intake which often extends back for periods of over 25 years. Though it has been thought that retrograde amnesia in Korsakoff’s disease could be fully explained by the prolonged alcoholism, the case of P.Z. (Butters & Cermak, 1986) has discredited this theory: it is now generally accepted that patients with Korsakoff’s disease show genuine retrograde amnesia (Meudell, 1992).

The neural mechanisms producing anterograde and long-range retrograde amnesia (covering several decades) in Korsakoff’s disease and in Alzheimer’s disease involve diffuse damage, which makes it difficult to interpret deficits associated with these diseases. Some areas, including the diencephalon, medial temporal lobes, and frontal lobes, seem to be more involved than others. In Korsakoff’s disease, the diencephalon – and in particular the mamillary bodies and the medial nuclei of the thalamus – is seen as the critically damaged structure (Bauer et al., 1993; Hodges, 1995). In Alzheimer’s disease, damage is initially concentrated in the medial temporal lobe, while later fanning out to preferentially the temporal and frontal neocortex (Braak & Braak, 1991). Another area that is preferentially damaged in Alzheimer’s disease is the basal forebrain (Whitehouse et al., 1982). Nuclei in the basal forebrain have cholinergic projections to the hippocampus and the neocortex. The depletion of acetylcholine in the hippocampus has been proposed as one of the causes of the memory problems associated with Alzheimer’s (Bartus, Dean, Pontecorvo, & Flicker, 1985; Fibiger, 1991; Kopelman, 1986; Kopelman & Corn, 1988).

Non-Alzheimer forms of dementia also lead to memory impairments. In so-called subcortical dementias (associated with Huntington’s or Parkinson’s disease), patients often have moderate anterograde and also retrograde amnesia (Hodges, 1995). Their performance on memory tests, and especially the improvements seen with better cueing, points to a retrieval deficit as the main cause of their anterograde amnesia (Deweer, Pillon, Pochon, & Dubois, 2001). Consistent with this interpretation, their retrograde amnesia tends to have a flat temporal gradient, suggestive of a general deficit in retrieval (Albert et al., 1981; Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Hodges, 1995; see Figure 1b, c, d, e).

Transitory forms of amnesia

Amnesia can only be judged relative to normal forgetting by a suitable control group on a similar task. In retrograde amnesia, such a group is rarely available, and considerable ingenuity is required by the experimenter to assess the extent of the memory loss. This problem does not apply, however, in the case of transient forms of amnesia, such as Transient Global Amnesia (TGA) and the amnesia induced by electro-convulsive therapy (ECT). Retrograde amnesia during TGA or after ECT can be investigated by comparing recall of remote memories during the TGA episode with similar recall later on, when remote memory has returned back to normal. After the amnesia has resolved, the patient can thus function as her own control subject.

Transient global amnesia (TGA) is an attack of amnesia resolving within 24 hours, without disturbance of consciousness, neurological signs or symptoms. The official diagnosis requires that someone has witnessed the beginning of the episode (Caplan, 1985; Hodges & Ward, 1989; Kritchevsky, 1992). Both retrograde amnesia and anterograde amnesia can occur under TGA. The onset is usually sudden without known
external causes. The study by Hodges and Ward (1989) is one of the few in which extensive neuropsychological testing took place under TGA. In the five cases investigated by them, they found severe anterograde amnesia, and retrograde amnesia with a clear Ribot gradient (see also Kritchevsky & Squire, 1989). The extent of the retrograde amnesia varied not only from patient to patient but also from test to test. Patients showed evidence for abnormal memory for at least the two decades preceding the attack on a public events questionnaire, but on an autobiographic memory test the problems seemed to be restricted to the five preceding years. The severity of the retrograde and anterograde amnesia during the TGA were not closely correlated.

After a rapid partial recovery within 24 hours, further recovery of anterograde amnesia occurred which was not yet complete one week after the attack. In the first 24 hours, there was also a rapid shrinkage of retrograde amnesia. Some isolated memory deficits may have been present after this period, and one of their subjects continued to improve on remote memory for six months. In all five cases tested, there was a persistent, dense retrograde gap of around one hour (30 min to 2 hrs) prior to the apparent onset of the attack.

A study by Evans, Wilson, Wraight, and Hodges (1993) gives clues about the neuropathology underlying TGA. They conducted a SPECT scan of a patient whilst suffering from a TGA attack. During the TGA episode reported by Evans et. al (1993) there was severe anterograde amnesia, and a modest retrograde amnesia mainly confined to autobiographical memories. The scan revealed bilateral posterior medial temporal hypoperfusion, which resolved after the attack. This was also found in two other SPECT studies of TGA (Stillhard, Landis, Schiess, Regard, & Sialer, 1990; Tanabe, Hashikawa, Nakagawa, & Ikeda, 1991). Though is not possible to assess from the SPECT studies to what extent the affected regions could still function during TGA, these studies suggest that TGA has similar neuroanatomical origins as amnesia caused by permanent lesions of the medial temporal lobe.

A comparable form of temporal amnesia is that seen after electroconvulsive therapy (ECT). It is not easy to interpret the effects of ECT on memory. The patients receiving treatment are most often depressed and may use anti-depressant drugs. ECT is usually administered under (brief) anesthesia. Furthermore, ECT usually alleviates the depression. All of these factors by themselves have an effect on memory, so that any difference in memory performance after ECT must be interpreted with great caution. In addition, it is ethically undesirable to compose good control groups. Finally, it is not exactly known what brain structures and processes are most affected by ECT. Nevertheless, the evidence suggests that directly after ECT, a patient may show both retrograde amnesia and anterograde amnesia which recovers in the ensuing weeks (Cahill & Frith, 1995). With retrograde amnesia under ECT, Ribot gradients may be observed (Squire, Slater, & Chace, 1975).

The retrograde amnesia found during TGA-attacks and after electroconvulsive therapy is reversible. The implication of this is that retrograde amnesia can occur as a retrieval deficit alone and need not be caused by either encoding or consolidation problems (this is also implied by the fact that retrograde amnesia sometimes shrinks during recovery).
2.3 THE RELATION BETWEEN ANTEROGRADE AND RETROGRADE AMNESIA

The correlation between anterograde and retrograde amnesia in clinical groups

In most amnesic patients anterograde and retrograde amnesia occur together. However, several studies have shown that the correlation between the two forms of amnesia is far from perfect. Its exact size is not known, as few studies have reported correlations. The ones who did have used different measures and patient populations, and most have only used small patient samples. The correlational patterns are nevertheless important, since low correlations between measures of anterograde and retrograde amnesia may indicate that the two forms of amnesia have different causes.

Russell and Nathan (1946) tested large groups of closed-head injury patients, and found sizeable covariance between anterograde and retrograde amnesia. They did not compute a correlation between their two measures of severity, the duration of the anterograde amnesia, and the period for which there was retrograde amnesia. As these were only coded in categories, we calculated the Gamma correlation between these two measures, a nonparametric measure of association suitable for ordinal data (Goodman & Kruskall, 1954). It is 0.77 for the data reported in their table 4, and 0.68 for the data in table 5.

Retrograde amnesia and anterograde amnesia are less strongly correlated in populations of patients with Alzheimer’s and Korsakoff’s disease (Kopelman, 1989, 1991; Schmidtke & Vollmer, 1997; Shimamura & Squire, 1986): the reported correlations range from 0.30 to 0.60. Correlations of around 0.50 are in general hard to interpret; this is made even more difficult by measurement caveats for retrograde amnesia (see chapter 3), and by the fact that tests of anterograde and retrograde amnesia use dissimilar items and recruit dissimilar processes (Kapur, 1993). Both problems can be expected to lower the correlation between the two forms of amnesia.

Perhaps because of this uncertainty, the data reviewed above has led authors to very different conclusions: Meudell (1992) concludes from the data reviewed above that “little correlation...has been reported [in alcoholic Korsakoff patients]”, and Kopelman (1989) sees the correlational pattern as indicating a partial independence of the two forms of memory impairments. Squire and Alvarez (1995), on the other hand, see the correlation between retrograde and anterograde amnesia as rather strong, and as indicative of a common deficit behind both forms of amnesia. Only extensive, ungraded retrograde amnesia has in their view an independent cause, namely damage to neocortical temporal areas.

Squire and Alvarez’ (1995) view predicts a very high correlation when the damage is limited to the medial temporal lobe and does not extend to neocortical areas. Too few such patients exist to do meaningful correlational analyses. However, when one looks at the in total eight patients with hippocampal damage reported by Rempel-Clower et al. (1996) or by Reed and Squire (1998), there does indeed seem to be a strong correspondence between the severity of anterograde and that of retrograde amnesia (and of both with the size of the lesion): whether one ranks the cases by the severity of the anterograde amnesia or by the severity of retrograde amnesia, the same rank order appears.

An interesting study that supports Squire and Alvarez’ (1995) view is that of Schmidtke and Vollmer (1997). They contrasted two predictors of performance on tests for
retrograde amnesia: tests of anterograde memory, and tests of semantic memory. They found different correlational patterns for retrograde amnesia for different time periods. Retrograde amnesia for periods 5 to 10 years before the onset of amnesia correlated highest with anterograde memory performance. Retrograde amnesia for the more remote time periods, on the other hand, correlated highest with the semantic memory test. This was the case both for a famous faces test, and for an autobiographic memory test. Schmidtke and Vollmer interpreted this finding as indicating that two memory systems contribute to performance on retrograde amnesia tests: a hippocampal system and a neocortical system. Lesions to the hippocampal system contribute to anterograde amnesia, and to retrograde amnesia for the periods 5 to 10 years before the lesion. Lesions to neocortical areas lead to semantic deficits and to amnesia for more remote time periods. Though this explanation clearly goes beyond the correlational data, it fits in with data from patients with discrete lesions. Damage limited to what could be called the hippocampal system (perhaps including certain diencephalic areas; Aggleton & Saunders, 1997) causes anterograde amnesia and retrograde amnesia for at most 15 years. Damage beyond these structures, and specifically to the temporal lobe, causes more extensive retrograde amnesia (Squire, 1992).

The correlational pattern thus seems to favor a single cause for anterograde and retrograde amnesia (at least for recent periods). An important source of evidence for multiple causes of retrograde and anterograde amnesia, however, comes from cases of either anterograde amnesia without retrograde amnesia (isolated anterograde amnesia), or retrograde amnesia without anterograde amnesia (isolated retrograde amnesia).

### Isolated anterograde amnesia

Patients who show anterograde amnesia and no retrograde amnesia seldom appear in the literature. Meudell (1992), in a review of dissociations between anterograde and retrograde amnesia, could find only one case of isolated anterograde amnesia. This case, patient R.B. described by Zola-Morgan, Squire and Amaral (1986), had in fact a retrograde amnesia that may have covered the two years before the onset of his amnesia. Though his retrograde amnesia could be called mild compared to his anterograde amnesia, it is not true that pre-onset memories were unaffected. The same holds true for other patients with unusually short retrograde amnesia, such as patient G.D. discussed by Rempel-Clower et al. (1996), and patient L.J. discussed by Reed and Squire (1998).

The closest to a real isolated anterograde amnesia come patients with damage to the basal forebrain, or to the fornix bundle that, among other things, connects the basal forebrain to the hippocampus. One patient with basal forebrain damage had severe anterograde amnesia (Abe et al., 1998). He performed within the normal range on tests of remote memory, though he was said to have some retrograde amnesia, and a notable loss of the ability to date events and put them in order. Two patients discussed by Hodges and Carpenter (1991) had lesions to the fornix. Both had mild anterograde amnesia, and were said to have retrograde amnesia for approximately four weeks before the surgery that led to the amnesia. These patients were not formally tested, however. Lesions to the basal forebrain or the fornix thus seem to cause near-isolated anterograde amnesia.

An artificial form of isolated anterograde amnesia can be created by injections of a cholinergic blocker such as scopolamine. This impairs new learning, but spare the retrieval of information learned before the injection (Kopelman, 1986; Kopelman & Corn, 1988). Scopolamine injections thus cause anterograde but not retrograde amnesia in
normal human subjects. The same seems to be true for benzodiazepines such as Midazolam (Masuda et al., 2000), though more research is needed on this.

**Isolated retrograde amnesia**

A few cases have been reported of isolated retrograde amnesia. Usually this is an amnesia in which the initial anterograde component resolves nearly completely with time, leaving the patient with only a substantial retrograde amnesia (Carlesimo, Sabbadani, Loasses, & Caltagirone, 1998; Goldberg et al., 1981; Kapur et al., 1992; Roman-Campos, Poser, & Wood, 1980). One case has been reported with dense, widespread retrograde amnesia without any initial anterograde amnesia (Andrews, Poser, & Kessler, 1982), but the retrograde amnesia in this patient may have been psychogenic in nature (Kapur, 1993). Kapur (1993) reviews several other cases of isolated retrograde amnesia. In most patients, the hippocampal system is spared. The invariant neuroanatomical factor in many of these cases is a dysfunction or lesion of the temporal lobes, in particular the anterior and to a lesser extent ventral portions. This is in accord with an early study by Bickford et al. (1958), where the electrical stimulation of the anterior temporal lobe structures in humans (i.e., during operations) resulted in periods of isolated retrograde amnesia.

Hunkin et al. (1995), however, report a patient with seemingly fully intact temporal lobes and hippocampi (in MRI scans) but with damage to the right parieto-occipital and the left occipital lobes. This patient shows isolated retrograde amnesia without a Ribot gradient.

Squire and Alvarez (1995) explain isolated retrograde amnesia by stating that temporal lobe neocortical lesions damage the knowledge base itself, leading to dense retrograde amnesia with a flat Ribot gradient. Such amnesia is indeed found in some patients (as in the case of Hunkin et al., 1995), but others have limited, temporally graded retrograde amnesia (such as the patient of Carlesimo et al., 1998). Kapur (1993) lists eight patients. As far as reported, 2 out of 5 cases show evidence of a Ribot gradient for public knowledge and 3 out of 7 for autobiographical memory. One case shows 'patchy retrograde amnesia'. Thus, Ribot gradients are found in around 40% of the cases of isolated retrograde amnesia, with over 50% showing dense retrograde amnesia with a flat gradient.

In conclusion, the data from correlational studies and cases with isolated amnesia only partially support the view of Squire and Alvarez (1995). Anterograde and retrograde amnesia, especially for the first decade preceding the onset of amnesia (Schmidtke & Vollmer, 1997), are substantially correlated. This suggest a common cause for both, such as damage to the medial temporal lobe and medial diencephalon. In agreement with the Squire and Alvarez view, more extensive retrograde amnesia and isolated retrograde amnesia seem to be caused by neocortical damage. The fact that the correlation between the two forms of amnesia is far from perfect, and that isolated anterograde amnesia can be induced, however, suggest that multiple causes may underlie anterograde amnesia.

**2.4 IMPLICIT MEMORY IN AMNESIA**

Graf and Schacter (1985) define implicit memory as that which is revealed when performance on a task is facilitated in the absence of conscious recollection. Implicit
memory is contrasted with explicit memory, which involves the deliberate searching of memory. Similar divisions of memory tests, processes or systems have been proposed by others, such as direct versus indirect testing (Richardson-Klavehn & Bjork, 1998), and declarative versus procedural memory (Cohen & Squire, 1980). Attempts have been made to apply these distinctions to the animal literature as well, notably by Eichenbaum (Eichenbaum, 1992; Eichenbaum, Cohen, Otto, & Wible, 1992).

The literature on dissociations of memory supporting these distinctions is vast and complicated, and is impossible to review here (see Richardson-Klavehn & Bjork, 1998; Roediger & McDermott, 1993). The study of amnesia is important for implicit memory, however, because studies with amnesic patients are a strong source of support for the dissociation between implicit and explicit memory. Patients with amnesia are unimpaired on a host of implicit memory tests. They show normal or near-normal priming (Schacter, 1987, 1992), and are also able to acquire certain novel skills if learning these involves a great number of repetitions of relatively simple subtasks (e.g., the tower of Hanoi, (Cohen, 1984), or if the skills rely heavily on existing ones (e.g., reading transformed script, Cohen & Squire, 1980). Amnesic patients can also learn categories of probabilistic stimuli like random dot patterns (Knowlton & Squire, 1993; Kolodny, 1993) and diagnostic cues for fictitious diseases (Knowlton, Squire, & Gluck, 1994). In these cases, normal subjects also take many repetitions to reach target performance on the task. When learning more complex patterns, such as artistic styles on the basis of selected paintings, normal subjects greatly outperform amnesic patients who, in this particular task, remained at chance level in categorizing the correct style (Kolodny, 1993).

Not only do patients exist whose explicit memory is impaired in the face of normal implicit memory, there are also patients who show the opposite pattern. Gabrieli et al. (1995) and Keane et al., (1995) each describe one patient with lesions in the occipital lobe. Both patients are impaired on perceptual priming tests, but have normal explicit memory (and show normal conceptual priming). This shows that there is a double dissociation between the neurological substrates of implicit and explicit memory: whereas for explicit memory medial temporal and medial diencephalic regions are important, the posterior neocortex is important for priming.

Neuropsychological studies also show that implicit memory is not a unitary system. The patients of Gabrieli et al. (1995) and Keane et al., (1995) were impaired on tests of perceptual priming, but both had intact conceptual priming (e.g., category generation). Patients with Alzheimer’s disease are claimed to show the opposite pattern (Gabrieli et al., 1995), though this may oversimplify the pattern of intact and impaired priming skills in Alzheimer’s disease (Fleischman & Gabrieli, 1998). Moreover, there is a double dissociation between Alzheimer’s disease and Parkinson’s disease on putatively implicit tasks. Alzheimer’s disease patients are impaired on several priming tasks but show intact motor learning, whereas Parkinson’s patients show the opposite pattern (Bauer et al., 1993).

These studies converge on a now common view of implicit memory (e.g., Gabrieli, 1998). Implicit memory has severe limitations; it relies strongly on existing memory representations, such as known words or existing connections between words. Explicit memories involve new associations, in particular with the context of the learning episode. Implicit memory seems to involve incremental learning that is independent of the hippocampal system or other medial memory areas. This learning may occur in neocortical processing areas, with different areas involved in different forms of implicit memory.
2.5 CONCLUSIONS

Our review of the neuropsychological literature has led us to formulate the following list of conclusions, that have to be explained by a comprehensive model of amnesia:

- Though the exact brain areas involved remain unclear, damage to certain medial structures—in particular, the hippocampus, adjacent medial temporal lobe structures and the medial diencephalon—can cause both retrograde and anterograde amnesia. The retrograde amnesia shown by patients suffering such lesions typically shows a temporal gradient in accordance with Ribot’s law: more information is lost from recent periods than from remote periods.

- Anterograde and retrograde amnesia are partially correlated, with the correlation varying from one patient group to the next. Indexes of anterograde amnesia correlate more with retrograde amnesia for the periods right before the lesion than with retrograde amnesia for more remote periods.

- In patients, substantial anterograde amnesia is nearly always accompanied by at least some retrograde amnesia. It occurs in complete isolation of retrograde amnesia, however, after injections of scopolamine, a cholinergic blocker. This suggests that multiple causes may underlie anterograde amnesia.

- Retrograde amnesia for more remote periods, and also isolated retrograde amnesia, appear to be caused by neocortical lesions. ‘Isolated’ retrograde amnesia always involves at least some initial anterograde amnesia.

- Transient forms of amnesia show that amnesia can involve a retrieval deficit; after the amnesia has resolved, the patient is typically able to retrieve most memories that were unavailable during the amnesia episode. The patient is usually left without memories of the episode itself, which suggests that transient forms of amnesia also involve impaired learning.

- During recovery from retrograde amnesia, memories from more remote times tend to come back faster than memories from more recent times; this is referred to as shrinkage.

- Memory impairments in amnesia are probably limited to explicit memory: amnesic patients show normal or near-normal implicit memory. Implicit memory seems to involve incremental learning in neocortical processing areas.