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Chapter 7

Amnesias

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As to the memory ... no other human faculty is equally fragile: injures from, and even apprehension of, diseases and accident may affect in some cases a single field of memory and in others, the whole.

Pliny the Elder [1]

Introduction

Memory is one of the most fascinating abilities of the human faculties. It makes us unique and gives rise to our individuality. Memory can store everyday experiences so that they can be recalled in future occasions to help us face the changes that occur in the environment. Because of this crucial role in adaptation to complex environments, memory deficits can be extremely harmful to our health and well-being, inflicting serious problems in our relationship with the external world.

The importance of memory has attracted human attention for centuries. In Greek mythology memory was associated with the goddess Mnemosyne, who was married to Zeus, the king of the gods. She was the mother of nine muses, who presided all the arts and sciences. The importance of memory during this time can also be illustrated by the fact that citizens from ancient Greece and Rome were educated in "memoria", as part of the formal training in rhetoric. It was during this period that Aristoteles wrote: "De Memoria Reminiscentia", a historical landmark in the study of memory. In this book, Aristoteles

[1]Pliny the Elder, whose real name was Gaius Plinius Secundus, was a Roman natural philosopher who lived during the first century (23-79).

proposed the first set of laws of association between stimuli to explain voluntary recollection: contiguity, similarity and contrast [16].

Artists have also been interested in the concept of memory. "The Persistence of Memory" is one of Salvador Dali's earliest masterpieces of modern art. **Figure 7.1** depicts this surrealistic painting from 1931, in which Dali expresses the fragile dependence between memory and time. Indeed, abundant multidisciplinary research conducted over the years indicates that rather than being a perfect record from the past, memory involves a constant interaction between previously acquired knowledge and current incoming information. These highly dynamic temporal processes suffer several forms of modulations which ordinarily lead different memory imperfections [7].

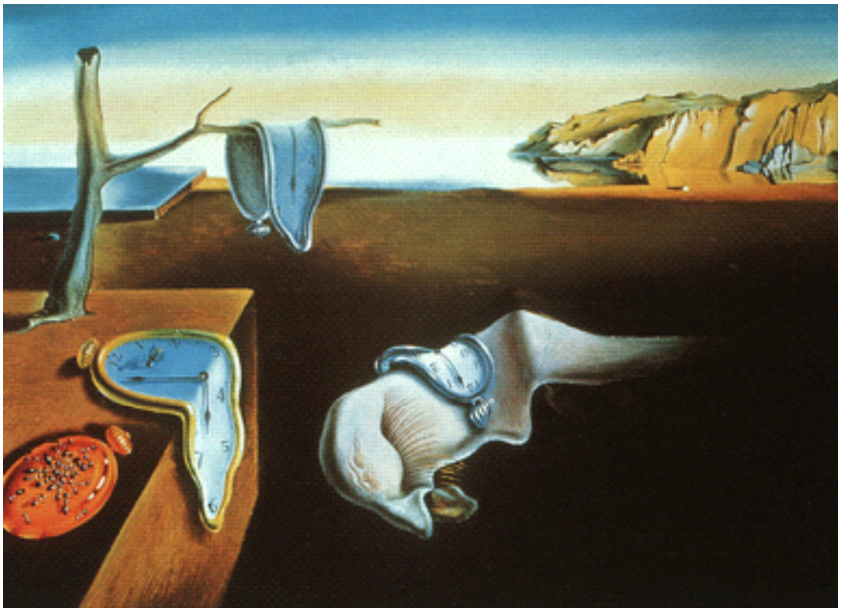

Figure 7.1. The Persistence of Memory by Salvador Dali.

Schacter [43] pointed out that some of these memory imperfections can be classified into two major categories: one related to memory omission, observed when the information is not available to our consciousness and another related to memory commission, observed when the information is retrieved in a rather incorrect or unwanted form. These omission and commission modulatory processes in memory retrieval have important adaptive value in our daily life. For example, it is easy to see how forgetfulness might help to strengthen our social relationships, or to deal with traumatic experiences. **Box 1** presents an example of the problems that might happen when forgetting fails to occur. The imprecise nature of our memory appears to be so important that it has been suggested that there are specific brain structures responsible for active forgetting mechanisms [2].

However, memory flaws can become so frequent that the person fails to recall important information involved in everyday activities. In this case, forgetting loses its function and becomes a disorder known as amnesia.

Amnesia has a wide spectrum. It can be highly specific, affecting only a limited aspect of memory, or it can be a life long devastating disorder. A common way to classify amnesia is by referring it to the time when the information was learned. As can be observed in **Figure 7.2**, retrograde amnesia refers to a deficit in recalling old events acquired prior to the onset of the amnesia. In contrast, anterograde amnesia is a deficit in recalling new information, acquired after the beginning of the amnesia.

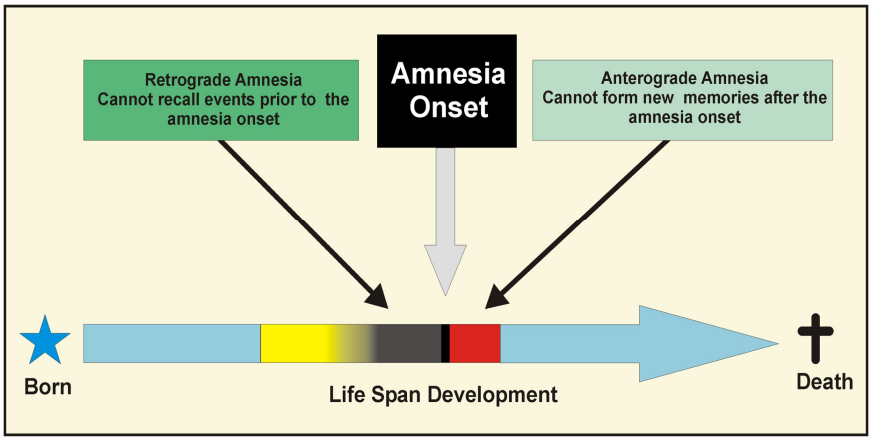

Figure 7.2. Description of retrograde and anterograde amnesias.

Retrograde and anterograde amnesia are dramatic events, and usually occur simultaneously in the same patient. These descriptive symptoms can have different etiological causes, ranging from organic causes, such as brain damage resulting from stroke, or neurodegenerative diseases such as Alzheimer's disease, to functional causes, such as psychological traumatic events. Before getting into the underlying mechanisms related to the different forms of amnesia, first it is important to understand the basic concepts involved in the structure and organization of different memory systems and their respective areas within the central nervous system.

Different Memory Systems

The experimental study of memory departed from an early concept of a unitary process, and evolved to a more recent view, which suggests that there are different memory systems. For a long time prevailed the notion that memory consisted of two major serial stages: a temporary storage system named short-term memory (STM) and a more enduring system termed long-term memory (LTM). This temporal fractioning of memory was probably based on Donald Hebb´s distinction between an ephemeral or transitory electrical activity of the nervous system and a more permanent change in synaptic transmission [20].

An illustration of this model, which was formally proposed by Atkinson and Shiffrin [4], is presented in **Figure 7.3**. Accordingly, sensory information enters STM from the external world, where it is initially encoded. It is assumed that STM has the capacity to hold a limited amount of information for a short period of time. This transient memory system is contrasted

with a more permanent LTM, which can hold a seemingly unlimited amount of information for eventually the entire life.

As it can be observed in **Figure 7.3**, the relationship between the STM and the LTM is mediated by two different mechanisms: consolidation and retrieval. Consolidation comprises the processes of transferring the information from a transitory STM system to a more permanent LTM. It starts at the time of the learning experience and leads to a certain stabilization of the information. When consolidation occurs and the information has entered the LTM, it fades away from awareness. However we know that the information has been successfully stored in LTM because we can bring it back to our consciousness through a retrieval mechanism. Therefore, retrieval comprises the search for specific information stored into the LTM, and the act of bringing it back to the STM.

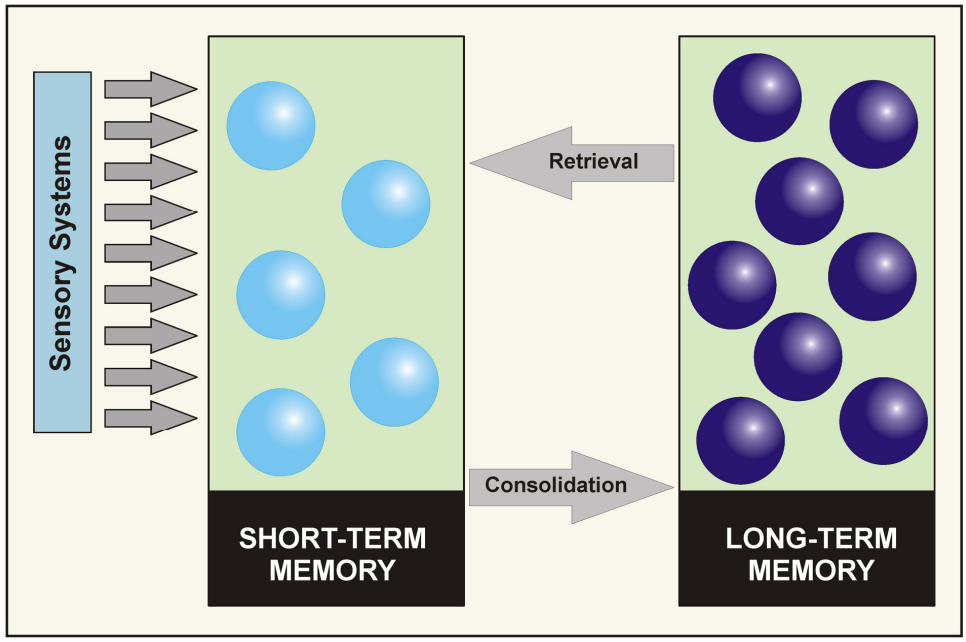

Figure 7.3. The two-stored memory system proposed by Atkinson and Shiffrin[4].

Early experimental evidence indicates that STM and LTM may have different temporal gradients. Preventing information from being consolidated into the LTM, in fact induces a rapid and irreversible loss of the recently learned information. This time dependent decay of information has been an important argument in favor of a short memory stage. This permanent loss of information is dissociated from a different sort of forgetting mechanism. In this case, information is allowed to enter LTM but can not be properly recalled, due to an interference process.

It is now clear that there are two forms of interference. Proactive interference occurs when previously stored information disrupts the ability to recall new information. Retroactive

interference occurs when recently learned information disrupts the ability to recall old information.

A New Perspective in Short-Term Memory

Results coming from investigations with healthy subjects, and from neuropsychological studies with brain damaged patients, started to pose serious problems to this serial model of memory. Among them is the fact that STM memory does not need to be activated as a whole before the information could be consolidated in the LTM. For example, Craik and Lockart [13] found that information stored in LTM depended on how the information was processed. Deeper processing based on the complex characteristics of a stimulus, such as its meaning or its relationship to other stimuli, results in a more elaborate, longer lasting, and stronger memory, when compared to shallow visual or phonological processing. It has also become clear that patients with specific deficits in STM are able to acquire new LTM outside the range of their specific STM deficit [46].

These results have challenged the idea that STM was a single storage system that needed to be activated as a whole, in order to transfer new information to LTM. To deal with these problems, different concepts of STM model, envisioning different storage mechanism within this system, started to emerge. A very successful attempt was made by Baddeley and Hitch [6], who proposed a multi-component model of working memory as a system used for short-term storage and manipulation of information, required for different cognitive operations.

The Working Memory System

Working memory (WM) has been operationally defined as the ability to keep information in a conscious level over a relatively short period of time in order to perform a certain cognitive task. **Figure 7.4** presents an illustration of this model. As it can be observed, auditory and visuospatial information are the main sensory inputs to the WM.

The visuospatial scratch pad is responsible for the processing and storage of visual or spatial information. A good example of the manipulation of visual or spatial information in the WM is what happens when driving on a foggy road. We are constantly aware of the location of the cars, but as we continue to drive, we are unable to recall where each car was on the road. Another example of how the visuospatial information employed by the WM is handled by the scratch pad component of the WM is the popular concentration or memory game. The purpose of this game is to find out the location of pairs of pictures facing down after they had been reversed, memorized and put back facing down again. When a pair of figures is matched, it becomes difficult to remember where these figures were located.

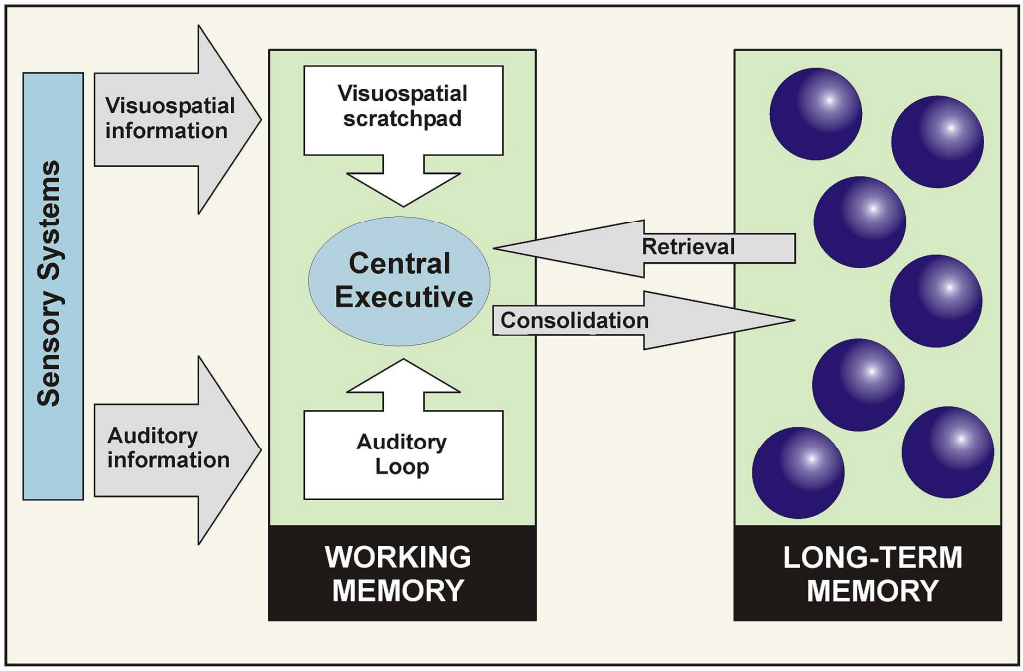

Figure 7.4. The Working Memory system proposed by Baddeley and Hitch (1974).

The phonological loop is responsible for temporal storage of auditory information, such as words or any other type of auditory stimuli. An example of this function is the problem that we usually face when we have to memorize a phone number before we call it. A few minutes after doing that, we can not remember the numbers any more.

The phonological loop and the visuospatial scratch pad operate in a parallel fashion. For example, maintaining verbal information in WM can be disrupted by a concurrent verbal task, but not by a visual or spatial activity. In the same vein, visual or spatial information within the WM can be selectively affected by visuospatial distractions, but not by a verbal task. Therefore, both visuospatial and phonological processing and storage components of the WM, can be activated independently.

Besides a phonological loop and a visuospatial scratch pad, Baddeley and Hitch [6] also proposed that WM has a central executive component which integrates information from the phonological loop and the visuospatial scratch pad, as well as information from LTM. The central executive component lies at the center of the WM model, and is the most complex, yet the least understood, element of the system. It is involved in the control of the flow of information to and from visuospatial and phonological inputs. For these reasons, the central executive component is the main part of the WM, responsible for solving cognitive tasks.

This multicomponent notion of the WM, which has replaced that old concept of a single STM, has proven to be an extremely useful model. The importance of this model is further substantiated by the fact that there might be neural structures responsible for this memory system. Some of these possible neural circuitries involved in WM are presented next.

Neural Substrates of the Working Memory System

WM is a sort of interface between perception, attention and LTM. Therefore it is conceivable that neural structures involved in WM might be related to these high cognitive functions. A flow diagram of possible brain structures underlying WM is presented in **Figure 7.5**. The first step for the functioning of WM is a sensory-perceptual mechanism necessary to process different stimuli modalities coming from the environment. Visual and auditory stimuli are the main sensory components of WM. Auditory stimuli related to verbal information are processed by the primary auditory cortex located in the temporal lobe on the posterior half of the superior temporal half of the superior temporal gyros. Visual stimuli, such as spatial location, are processed by the primary visual cortex, located around the calcarine sulcus in the occipital lobe.

The posterior portion of the parietal lobe plays an important role in integrating sensory information from various senses. Visual and auditory information reach this polymodal sensory area through occipital-parietal and temporal-parietal pathways respectively. The convergence of these different stimuli modalities appears to be processed by different regions within the posterior parietal cortex. There is evidence indicating that the ventral aspects of the posterior parietal cortex (VPPC) is associated with auditory encoding, especially in speech processing, such as phonological discrimination and identification task. Conversely, the processing of visuospatial information seems to be more restricted to the dorsal portion of the posterior parietal cortex (DPPC).

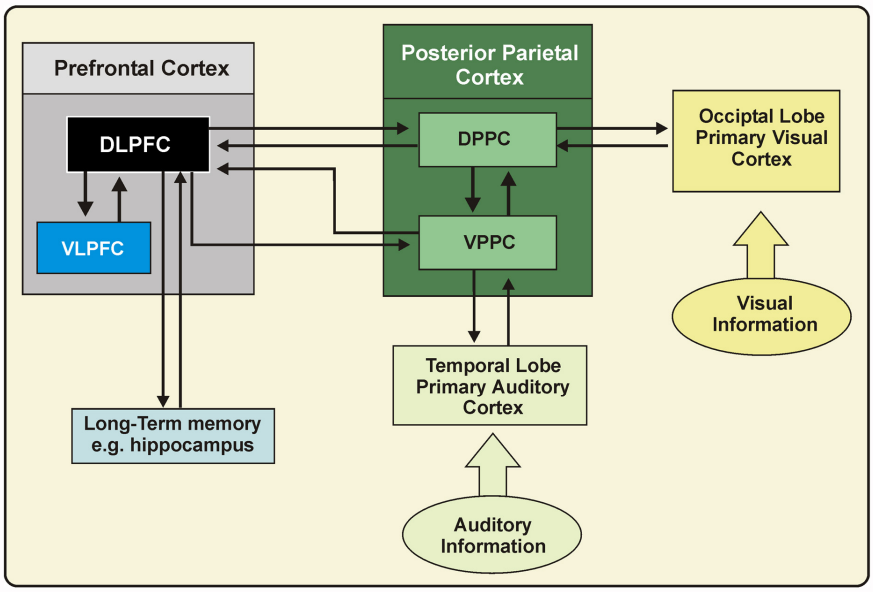

Figure 7.5. A circuit diagram showing the information flow in the working memory system. VPPC= ventral aspects of the posterior parietal cortex (VPPC). DPPC = dorsal portion of the posterior parietal cortex. VLPFC= ventrolateral prefrontal cortex. DLPFC= dorsolateral prefrontal cortex.

Besides this DPPC and VPPC dissociation, according to the nature of the WM material that is being processed, it has been also reported that a hemispheric specialization might also

be an important issue. In this case, the right DPPC is preferentially activated during a non-verbal spatial task, whereas the left VDPPC is more active during a verbal task [55].

Reciprocal projections between DPPC and VPPC are important for the multisensory integration within the parietal lobe. In fact, these projections might translate visual processed information in verbal or phonological code, such as in reading tasks. Moreover, projections from these regions within the posterior parietal cortex to their respectively primary sensory areas might be responsible for stimuli selection and general attentional components of WM.

Neuroimage and neuropsychological studies have indicated that the prefrontal cortex (PFC) is one of the most important neural substrates for the central executive component of the WM [14]. The participation of the PFC in WM has also been confirmed by experimental studies employing lesions and electrophysiological recordings from PFC neurons in primate and rodent models of WM [17].

The PFC can be subdivided into separate regions based on citoarchitectural properties and connectivity to cortical and subcortical regions. Among these regions, the dorsolateral (DLPFC) and the ventrolateral (VLPFC) regions of the prefrontal cortex clearly have distinct neuronal specialization and might be associated to different domains of the WM.

There have been a number of interesting findings suggesting that DLPFC might be responsible for the central executive function of the WM [1]. For example, it has been shown that the DLPFC is important for maintaining information in WM, by directing and changing attention to internal representation of sensory stimuli. This function is probably accomplished by bidirectional projections that the DPFP maintains with the DPPC and VPPC. These projections might be important for holding information on consciousness when they are no longer available in the environment, but necessary to perform a certain cognitive task.

Although WM and LTM can work independently, these two systems are constantly interacting under normal conditions. In fact, one of the main features of the WM is its ability to recall information from LTM, integrating it with incoming information that is being continuously processed. Neural functional imaging studies have shown that DLPFC is activated during a retrieval task [55]. This is an important finding because the DLPFC has bilateral projections to the hippocampus, a well-know structure involved in LTM.

The DFPFC also plays a role on the rehearsal mechanisms through projections that it maintains with the VLPFC. Neuroimage results indicate that the left VLPFC, which correspond to the Broca area, is highly activated in WM tasks when those require subvocal rehearsal. Moreover, it has also been found that the left VLPFC is more active during verbal tasks, whereas the right VLPFC is more active during visuospatial tasks [14]. Therefore, a lateralized system in the VLPFC appears to be responsible for maintaining different types of information within the WM during a brief period of time. The phonological loop is associated with the left hemisphere functioning, whereas the visuospatial scratch pad is associated with the right hemisphere functioning [51].

Deficits in the Working Memory System

As already mentioned, WM consists of three main components: the phonological loop for maintaining and rehearsing verbal information; the visuospatial scratch pad for holding and

manipulating visual or spatial information; and a central executive element, which is an attention controlling system, responsible for coordinating different cognitive functions.

Deficits in WM can be associated with a particular component of this system. Problems in the phonological or visuospatial WM, generally observed during the child's development, are related to learning disorders, such as reading, spelling, or calculation poor performance, in the absence of mental retardation. Weakness in the central executive component is implicated in more serious cognitive disorganization, usually observed in mental retardation and schizophrenia, including attention problems, reasoning ability, and the capacity to maintain and manipulate information in abstract tasks.

Specific language impairment (SLI) is a language development disorder in the absence of any other medical disorders. It does not include children who have language difficulties related to mental or physical disability, such as hearing loss, emotional problems or severe environmental deprivation. Therefore, SLI refers to children with normal nonverbal intelligence, and a deficit in expressive and/or receptive language.

Children with SLI have reduced capacity in the WM phonological loop. They do not present any impairment in their perceptual discrimination of auditory stimuli, but have significantly greater difficulty in repeating three and four syllable nonwords than matched control children. These results suggest that SLI is due to poor processing or holding phonological information in WM. Indeed, it has been proposed that tests that measure phonological WM deficits might be employed as reliable and culture-free markers of SLI [39].

Reading problems also appears to be related to impairment in the capacity of the phonological component of WM. Children who present reading comprehension problems also display deficits in phonological loop but intact visuospatial scratch pad and central executive functioning. It is assumed that poor readers present deficient phonological processing skills which in turn might impair the comprehension of written material. In agreement with this view, it has been shown that as the child develops the phonological processing capacity, reading problems start to disappear [18].

Learning disability in mathematics also appears to be a consequence of a poor WM functioning. Different components of the WM play a crucial role in calculation and in solving arithmetic problems. For example, children with mathematical leaning problems, when compared to same-age peers, have poor performance in several WM tasks, such as the visual or the auditory digit spans [54]. In agreement with these findings, it appears that the visuospatial representation of numerical information and the phonological aspects necessary to decompose and understand the mathematical problem might underlie the poor performance among children with mathematical learning disability.

Deficits in the central executive component of WM might also be an important factor responsible for mathematical problems. A lack of coordination of the many activities involved in counting and in solving arithmetic word problems, might be one of the consequences of a poor central executive part of WM. For example, it has been observed that individuals with low performance in mathematical tasks, due to the high anxiety elicited by these tasks, present a smaller capacity in WM central executive processes [3].

Deficits in WM have also been associated with more severe problems in cognitive capacities. It seems clear that certain genetic conditions that lead to cognitive developmental disorders appear to be associated with specific deficits in WM. For example, deficit in

phonological memory is a well-established feature of Down's syndrome. It has also been shown that children with Prader-Willi's syndrome – a genetic disorder characterized by delay in language development – have a relatively intact central executive component and visuospatial scratch pad, but present a deficit in the phonological loop, probably related to the capacity of the phonological store [5]. These finding are consistent with the assumption that the phonological loop plays an important role in the general development of aspects of language, especially in vocabulary acquisition.

The opposite pattern has also been observed among patients with William's syndrome, a rare genetic condition resulting from abnormalities on chromosome 7. This genetic condition is characterized by a relative competence in language ability and hypersocial behavior, with intense conversation, despite the deficits in overall intelligence and visuospatial processing. Neuropsychological results indicate that individuals with William's syndrome have a preserved phonological loop, but a serious impairment in the visuospatial component of the WM [24].

General failure in the three components of the WM has also been observed in more pervasive developmental mental disorders, such as the fragile-X syndrome and severe autism cases. Children with these disorders exhibit deficits in a wide range of cognitive functions including speech and language capacity, communication skills, visuospatial ability and abstract reasoning.

There is considerable evidence that WM impairment is a common feature in schizophrenia and seems to persist throughout the course of the illness. The association between schizophrenia and WM deficit has been demonstrated in medicated, non-medicated and naïve-medicated patients [32]. Thus, the WM deficits observed among schizophrenic patients appear to be relatively resistant to pharmacotherapy .

The DLPFC is a main structure associated with the central executive WM (see **Figure 7.5**). Structural and functional abnormalities of the DLPFC in schizophrenic patients have been repeatedly described [23]. In fact, several problems in executive functions leading to drastic cognitive disorganization have been observed in patients suffering from different forms of schizophrenia. Finally, the poor performance of schizophrenic patients on these tests can not be explained by non-specific factors, such as poor effort or motivation or even instruction misunderstanding of the cognitive task (see **Chapter 4**).

The Explicit and Implicit Long-Term Memory Systems

Besides the transient WM operational system involved in cognitive problem solving, there is another memory system known as LTM which can store a large amount of information for a considerable period of time defined. A clear dissociation between WM and LTM can be illustrated in HM's case described in **Box 2**. The fact that HM was able to carry a normal conversation and accurately repeat back a telephone number indicates that his WM was functioning normally. However, if HM was distracted, he could not remember any of the events that were occurring, indicating a selective deficiency in LTM.

HM's case also revealed a very surprising fact. He was able to learn new motor skills in the absence of any consciousness. This result points out that certain information that is acquired and consolidated into the LTM, can be retrieved without any conscious or deliberate recollection of the previous experience when the information was acquired.

Philosophers such as René Descartes during 17th century and Gottfried Leibniz during 18th century had already made reference to unconscious processes that could influence behavior [44]. During the late 19th and early 20th century, neurologists such as Sergei Korsakoff [28] and Edouard Claparède [11], dealing with amnesic patients, as well as psychiatrists such as Josef Breuer and Sigmund Freud [10] and Pierre Janet [22], working with hysterical patients, provided empirical evidences and insightful contributions supporting the notion that unconscious processes could affect the functioning of normal and pathological memory.

Experimental studies of memory storage and retrieval in the absence of any consciousness started in the late 1950´s, when the results from HM had clearly indicated the existence of at least two forms of LTM: one dependent and the other independent of consciousness recollection. The LTM dependent on conscious recollection is known as explicit or declarative memory, whereas the LTM which does not depend on the person's awareness is called implicit or non declarative memory [[2]]. The classification of LTM into explicit and implicit memory is displayed in **Figure 7.6**.

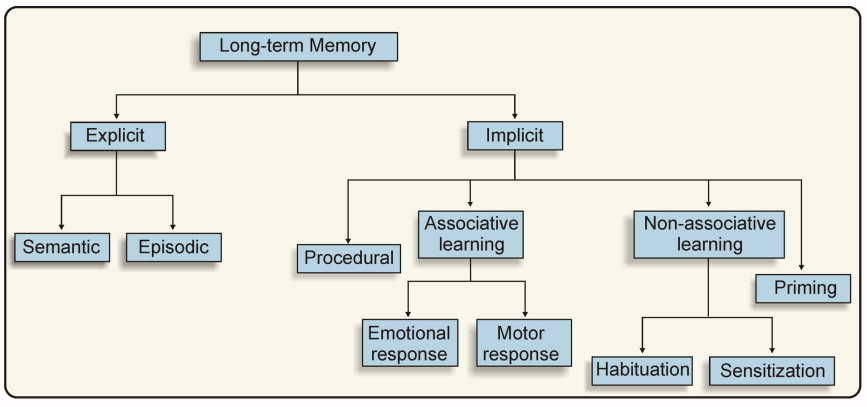

Figure 7.6. Classification of different long term memory systems. (Adapted from Knowlton et al. [26]).

The Explicit Memory System

In 1972, Elding Tulving divided explicit memory into an episodic and a semantic component [52]. Episodic memory is a system responsible for storing and retrieving consciously

[[2]] A distinction between implicit and explicit learning was also made in 1967 by Arthur Reber [41] in his classic experiments with artificial grammar learning. In this case, implicit learning is defined as the acquisition of new information in the absence of any intention or awareness. The distinction between implicit learning and implicit memory relies on a technical distinction between learning and memory. Learning is defined as the processes involved in the acquisition of new information whereas memory is related to the storage and the retrieval mechanisms of information previously acquired.

context and time dependent experiences mostly of autobiographical nature. Semantic memory describes our general knowledge of the world, including the meaning of the words.

Examples of episodic memory, also known as autobiographic memory, are any personally experienced events, such as meeting a certain person or buying a particular product like an old Luiz XV chair. An example of semantic memory is the general world knowledge on the concept of a chair that we all share. Note that the semantic memory process that underlies the concept of a chair is different from the episodic memory system responsible for the recollections of the particular chair you bought. This semantic and episodic subdivision of the explicit memory is presented in the left portion of **Figure 7.6.**

Neural Substrate of the Explicit Memory System

The profound memory impairment that occurred after HM's brain surgery (see **Box 2)** suggests that the medial temporal lobe system along with the hippocampus and its substructures (CA1-CA4, dentate gyrus and the subiculum) are intimately associated with explicit memory. More recent results, employing neuroimage techniques, as well as experimental results with animal models of amnesia (**Box 3**) indicate that three medial temporal cortical area – the parahippocampal, the perirhinal and the entorhinal cortices - have reciprocal neuroanatomical connections with the hippocampus forming a functional module known as "the medial temporal lobe memory system" [50].

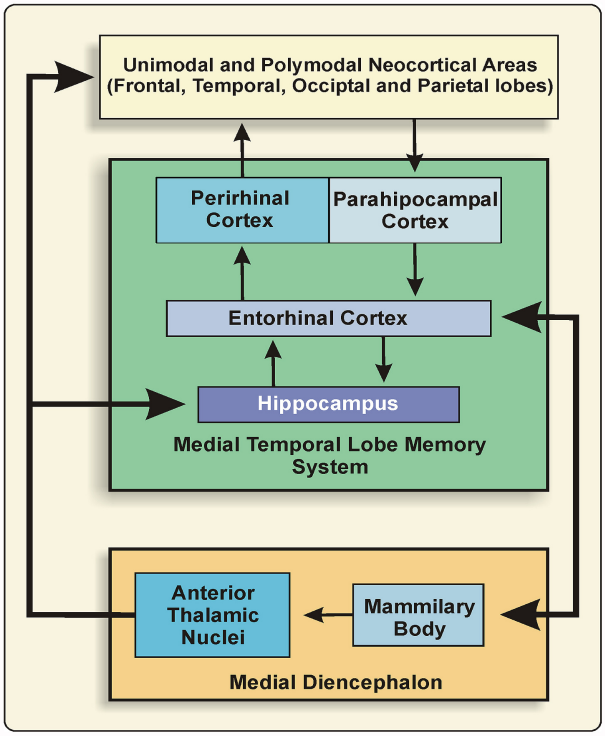

Figure 7.7. A circuit diagram showing the information flow in explicit memory.

As it can be observed in **Figure 7.7**, bilateral projections between unimodal and polymodal neocortical areas, flow first to the parahippocampal and the perirhinal cortices, and then to the entorhinal cortex, reaching finally the hippocampus. Once in the hippocampus, information starts to flow in the reverse order, going from the hippocampus to the entorhinal cortex, reaching the perirhinal and parahippocampal cortices, before returning to the cortical area where the information originally arose. These projections might be responsible for the conscious nature of the explicit memory, since neocortical areas can process the activity that is occurring in the hippocampus [38].

Besides the medial temporal lobe memory system, diencephalic structures have been associated with explicit memory. Amnesic patients suffering from Korsakoff´s syndrome (see **Box 4**) have memory deficits similar to HM's, although neural structures within the temporal lobe are not affected by this disease. In this case, lesions are found in the medial diencephalic region, including the mammillary body and the anterior thalamic nuclei.

The remarkable similarities between memory deficits of Korsakoff´s patients and individuals with hippocampal damaged are not so surprising, given the heavy connections between the medial temporal lobe and the medial diencephalic structures through several pathways. The main one is the fornix, which conveys bidirectional connections between the hippocampal formation and the mammillary bodies. The anterior thalamic nuclei receive direct projection from the mammillary body through the mammillo-thalamic tract. Finally, there are bilateral projections among the anterior thalamic nuclei and the hippocampus, as well as the neocortical areas (see **Figure 7.7**).

The Dynamics of the Explicit Memory System

The availability of an explicit memory is highly related to the passage of time. In order to explain this finding, it is assumed that the hippocampal and medial diencephalic areas encode events and places where they occur, and combine them together, composing an episodic or autobiographic memory. This constitutes a fast and temporary consolidation mechanism which will eventually be replaced by a more permanent one. Once the memory is permanently stored in the neocortex, the hippocampal area and medial diencephalic structures are no longer required. That is why amnesic patients with hippocampal or medial diencephalic lesions, typically present severe anterograde amnesia (they cannot form new explicit memories), but time limited retrograde amnesia (old memories are fully accessible to consciousness), a phenomenon known as Ribot's law (**Box 5**).

The neural substrate responsible for the permanent storage of explicit memory appears to be related to neocortical areas. The neocortex is a brain area with large capacity to store for a much longer period of time the information that was temporarily maintained in the medial temporal-diencephalic area. In the neocortex, the information can be integrated into a higher level and probably it is where a series of episodic memory events may be transformed into semantic memory knowledge.

According to this model, explicit memories reach the neocortex where they are firstly handled by the WM system, and then rapidly incorporated into a temporary system which

appears to depend on neural structures lying in the medial temporal lobe, and in the medial diencephalic area. This is a fast consolidation mechanism with little integration with previous stored information. This temporary storage mechanism characterizes the highly personal pattern of an episodic memory.

Further processing of different episodic memories and their association with previously integrated knowledge common to a group of people, might give rise to a much slow, but more enduring consolidation mechanism, in which different neocortical areas might have being called into action. This is exactly what constitutes a semantic memory.

Therefore, the permanent storage of explicit memory in the neocortex might involve a first step, in which information is initially stored as an episodic memory event within the medial temporal-diencephalic regions, and then permanently stored in the neocortex in the form of semantic memory (**Figure 7.7**). At this point, episodic memory within the medial temporal-diencephalic region starts to disappear, although residual episodic memory might still persist for a much longer period of time within these areas.

Deficits in the Explicit Memory System

A deficit in explicit memory is what people generally mean when referring to amnesia. This type of memory complaint highlights the importance of consciousness in memory function and its disorder. Since memory encompasses three general stages - encoding, storage and retrieval – explicit memory deficits involve at least a dysfunction in one of these stages. Encoding deficit usually jeopardizes the WM functioning and its several mechanisms have already been discussed in the beginning of the chapter. Storage and retrieval deficits are associated with LTM and will be discussed below.

There are several criteria to classify explicit memory disorders. As already mentioned, amnesia can be classified according to its temporal course. Inability to establish new memory after the beginning of the amnesia is called anterograde amnesia, whereas the difficulty in retrieving previously established memory prior to onset of the amnesia is called retrograde amnesia (see **Figure 7.2**).

Since explicit memory can be subdivided in episodic and semantic memory, it is also possible to classify amnesia into episodic and semantic. Episodic amnesia is by far the most common form of amnesia. It refers to a deficit in remembering events personally experienced, in a highly temporal fashion (see **Box 5**). Semantic amnesia, also known as semantic dementia, is characterized by a progressive deterioration of semantic knowledge with the relative preservation of episodic memory.

Patients with semantic amnesia present atrophies in neocortical areas, where the semantic knowledge is permanently stored, whereas patients with episodic memory display damage in neural areas responsible for temporarily storing episodic memories, such as structures in the medial temporal lobe and the medial diencephalic area. Interestingly, episodic amnesia follows Ribot´s Law (**Box 5**), whereas semantic amnesia follows the reverse order of the temporally graded retrograde effect [21].

Global or selective amnesia is another form to classify memory deficits according to the content that the patient failed to retrieve. Global amnesia affects all sorts of information,

regardless of its nature. It is associated with a dysfunction of the medial temporal-diencephalic region. Therefore, Global amnesia involves severe anterograde as well as temporally graded retrograde amnesia of episodic memories.

Selective amnesia is a content-specific memory deficit of a particular event or a cognitive domain previously acquired. Selective amnesia of a specific event is an episodic memory deficit associated with a malfunctioning of the medial temporal-diencephalic region. Selective amnesia of a cognitive domain is a semantic memory problem related to specific damage of the neocortical area. It might jeopardize recognition of familiar faces, objects or words, usually observed in other cognitive disorders, such as different sorts of agnosias, acquired dyslexias and anomias.

Amnesia can be also classified according to its duration. In this sense, amnesia can be transient or permanent. Transient amnesia is a brief loss of memory. Its most common expression is known as transient global amnesia. It has an abrupt onset and results in a period of amnesia lasting for 4-24 hours. Although consistently aware of their own identities, patients are often perplexed and confused with their surroundings.

Transient global amnesia is generally observed in elderly people in good health conditions. It might be associated with a stressful life event, and probably results from a transient malfunctioning of the medial temporal-diencephalic areas responsible for the initial consolidation process of episodic memories. A transient ischemic attack within the medial thalamus or the hippocampus has been raised as another possible cause for this memory deficit.

Permanent amnesia is a memory impairment that does not disappear with the passage of time. It is generally related to damage of certain brain structures. In fact, another way to classify amnesia is based on its etiology. According to this criterion, amnesia can have psychological or organic causes. Psychological causes are related to traumatic or stressful events and are classified as dissociative disorders. It usually does not involve the destruction of specific neural areas. Instead, psychogenic or functional amnesia is related to synaptic functioning and/or changes in the neuronal metabolic rate [33].

Functional amnesia is usually a temporary retrograde amnesia and can be either global or selective. Global functional amnesia, also known as a dissociative disorder, refers to a sudden loss of all episodic memory. When recovered from amnesia, global functional amnesia patients do not remember what happened during the amnesic period. Selective functional amnesia is restricted to a failure to retrieve emotional or traumatic events.

Organic amnesia is associated with different degrees of destruction of brain structures that underlie the explicit memory systems. Neurodegenerative and vascular disorders, hypoxia, herpes encephalitis and head injury can all damage some brain structures associated within the medial temporal-diencephalic area, leading thus to a particular form of amnesia syndrome.

For example, neurodegenerative disorders, such as Alzheimer's disease, produce serious damage to the hippocampus and associated structures within the temporal lobe. Moreover, vascular diseases, such as infarction or hemorrhage of paramedian arteries can lead to the median diencephalic area destruction, whereas of anterior and posterior choroidal arteries can damage the medial temporal lobe and its substructures involved with memory. Finally, herpes

encephalitis, hypoxia and cardio-respiratory arrest can produce severe bilateral damage of the temporal cortex.

Explicit memory loss can also be observed as a side effect during the treatment of certain mental disorders. For example, tranquilizers such as benzodiazepines can induce amnesia of episodic events that occur while the drug is acting. Chronic use of benzodiazepine drugs might lead to long lasting amnesic problems. Finally, electroconvulsive shock therapy, generally employed for the treatment of refractory depression also induces amnesia which might disappear within 5-10 months after the treatment.

The Implicit Memory System

Implicit memory is a phylogenetic old memory system essentially pre-linguistic and thus not available (dependent) to consciousness. The presence of this form of memory in humans can be inferred after a change in a motor activity performance or in autonomic reactions as the result of previous experience with a stimulus in the absence of any awareness of the experience.

Implicit memory accounts for a common finding among amnesic patients. They can perform certain tasks, although they may emphatically deny having had any previous knowledge of the tasks. It is exactly these neuropsychological studies employing amnesic patients that allow most of the investigations regarding the different forms of implicit memory. The right portion of **Figure 7.6** shows how these implicit memories have been classified so far.

Procedural memory is the prototype of implicit memory. It reflects a memory system responsible for performing a motor skill. Examples of procedural memory are brushing the teeth, riding a bicycle, swimming and walking. All these tasks can be performed automatically without the awareness of its occurrence.

It has also been shown in amnesic patients that non-associative and associative learning can occur independently of consciousness. Non-associative learning can be subdivided in habituation and sensitization. Habituation refers to a response decrease due to stimulus repetition. Sensitization consists of the response increase to a repetitive stimulus due to the occurrence of a different and much more intense stimulus, usually an aversive stimulus, which sensitizes the subject.

Associative learning, also known as Pavlovian conditioning, involves a particular relationship between two stimuli. A neutral stimulus, such as a tone, becomes a conditional stimulus (CS) when it can predict the occurrence of another stimulus, called unconditional stimulus (US), such as food, electrical shocks or any other stimulus with high biological value for the individual.

There are different forms of associative learning. Among them, two types have been widely studied: eye-blink conditioning and fear conditioning. Eye-blink conditioning involves the learning of a motor response of blinking the eye to a tone (CS) after it has been preceded by a painless air puff (US) into the subject's eye. Fear conditioning is an emotional learning which involves the presentation of a noxious stimulus (US) in a certain context, or in the presence of a discrete CS, such as a tone or a light.

There are some experimental procedures, such as priming, in which implicit memory has been amply demonstrated in healthy subjects. Priming is an increase in the speed or accuracy of a decision that occurs as a consequence of a prior exposure to the information in the decision context, without any intention or task related motivation.

Neural Substrate of the Implicit Memory System

As displayed in the right portion of **Figure 7.6**, there are several forms of implicit memory, which in turn might depend on different neural circuitries. In fact, it has been shown that procedural memory seems to be associated with the striatal areas; non-associative learning might involve sensorial pathways; associative learning of motor responses depends heavily on the cerebelum, whereas emotional responses depend on the amygdaloid complex [48].

Explicit and implicit memory system seems to work in parallel. The independence between these two memory systems was demonstrated by an elegant study performed by Knowlton, Mangels and Squire [26]. The study employed Parkinson's disease patients with neuronal degeneration of the substantia nigra and severe disruption of basal ganglia. It also employed amnesic patients with lesions within the hippocampal, temporal, or diencephalic areas. Matched control subjects did not have any memory deficit or lesions. All subjects were required to learn a probability task which depended on associative implicit memory.

Results indicated that both control and Parkinson's patients could remember the training episodes. However, control but not Parkinson's subjects, effectively learned the task. In contrast, amnesic patients were not able to recall the training episodes despite the fact that they learned to perform the task just like the control subjects.

Several results indicate that, besides Parkinson's disease, Huntington's chorea patients with degenerative neurons within the basal ganglia also have impairment in the acquisition of tasks which depend on implicit memory system (see **Chapter 9**). Thus, basal ganglia seem to play an intimate role on implicit memory system.

As it may be seen in **Figure 7.8**, the basal ganglia (caudate and putamen) receive projections from different areas of the neocortex. These cortical projections to the basal ganglia seem to be unidirectional, and thus cortical areas do not receive direct projections from the basal ganglia, accounting for the unconscious nature of the implicit memory. This might be what differentiates the explicit memory, which has bidirectional projections between the hippocampus and neocortical areas [38].

The basal ganglia send projections to several motor structures, such as the substantia nigra, cerebellum, ventral thalamus and premotor cortex. These projections might be involved with different forms of motor activity. For example, neuroimage results indicate that highly skilled responses, but not explicit memory tasks, require a reorganization of the pre-motor and primary motor cortex [40]. The substantia nigra is also involved in the coordination of motor behavior and its malfunctioning leads to tremor during movements observed in Parkinson's disease patients. Finally, the cerebellum might be involved in associative learning, in which the acquisition of an adaptive response to deal with aversive stimuli is required.

The Emotional Memory System

In the beginning of the 20th century, the French psychologist Edouard Claparède demonstrated that an emotional experience could be acquired, stored and recalled in the absence of any conscious process. Claparède attended a female patient who had severe anterograde amnesia, probably suffering from Korsakoff´s syndrome. Whenever introduced to Claparède, she would shake his hand, repeat his name and carry out a normal conversation. But when Claparède went out of the room for a few minutes, and then returned, the patient would behave as if nothing had happened before.

Once, Claparède pinpricked the patient's hand as he shooked it. As expected, she was not able to consciously recall the painful incident. However, she refused to shake his hand again, indicating that she was able to store and recall the aversive experience. These results are similar to the HM´s case (**Box 2**), who was able to acquire several motor skills in the absence of any consciousness. Therefore, besides motor activity, emotional events can be acquired, stored and retrieved in the absence of consciousness, through specific neural circuitry.

It is well-known that the amygdaloid complex plays a fundamental role in emotional learning which relies exclusively on implicit memory [29]. For example, Bechara et al. [9] were able to demonstrate the participation of the hippocampus and the amygdaloid complex in the explicit and implicit aspect of fear conditioning, respectively. In this experiment, two different measurements were employed to monitor the acquisition of fear conditioning task. The conscious recollections of the CS-US pairing were employed as an explicit measurement. The changes in the skin conductance to the CS were the implicit measure.

The results indicated that the control subject acquired both responses. Patients with bilateral hippocampal lesions presented a change in the skin response to the CS, but could not recall the CS-US relationship. In contrast, patients suffering from a rare disease known as Urbach-Wiethe's, which bilaterally damages the amygdaloid complex, were able to consciously remember the CS-US relationship, but had no changes in the skin conductance to the CS. Finally, patients with both hippocampal and the amygdaloid complex damage failed to present the explicit and the implicit measurements of conditioning. This double dissociation result indicates that the hippocampal system is exclusively associated with explicit memories whereas the amygdaloid complex is exclusively involved with implicit memories.

Intense emotions with traumatic characteristics may dramatically change the way episodic memories are encoded, stored and recalled. A traumatic event may either enhance a memory event as in the case of post traumatic stress disorder, or completely suppress this event from conscious recall, as in the case of dissociative disorders. It is still unclear what determines the accessibility of a traumatic event to consciousness. In this regard, according to the psychoanalytic theory, it is possible that protective defensive mechanism might be involved in this modulatory effect of the traumatic event of explict memory [53].

Emotional events without traumatic characteristics are generally better remembered than neutral events. Most of us remember what we were doing during certain emotional circumstances, such as September 11th or when we heard that Lady Diane died. The reciprocal amygdala projections to sensory cortices, together with its projections to

hippocampus, may explain why emotional experiences are so well remembered. In fact, it has been shown that the amygdaloid complex has the ability to enhance the function of the medial temporal lobe structures, responsible for the origins of episodic memory [15]. As noted earlier, the medial temporal-diencephalic memory circuitry incorporates neural structures, such as the hippocampus, the mammillary body and the anterior nucleus of the thalamus, which are also part of the Papez circuitry involved in emotions (See **Chapter 3**).

The Implicit Memory System as a Resource for Memory Rehabilitation

As a rule of thumb, implicit memory systems are generally preserved in classic amnesic syndromes. Implicit memory strategies have been used to rehabilitate some of the competencies that were lost in patients suffering from amnesia. Indeed, there are several reports indicating that rehabilitation procedures which employ a residual explicit memory and a relatively intact implicit memory, successfully restore some of the negative consequences of a deficient explicit memory. Two major memory rehabilitation techniques employ this approach: errorless learning and the method of vanishing cues.

Errorless learning is a technique in which the acquisition or encoding of new information occurs without any error. This form of learning can be contrasted with traditional trial and error learning, in which the person is encouraged to guess, resulting in the occurrence of some errors during the learning situation. It appears that trial and error learning relies on the explicit memory system which enables conscious monitoring and elimination of errors. This form of learning has no value among amnesic patients and in fact might impair learning, since the error might be reinforced by the implicit memory system which is not sensitive to error evaluation.

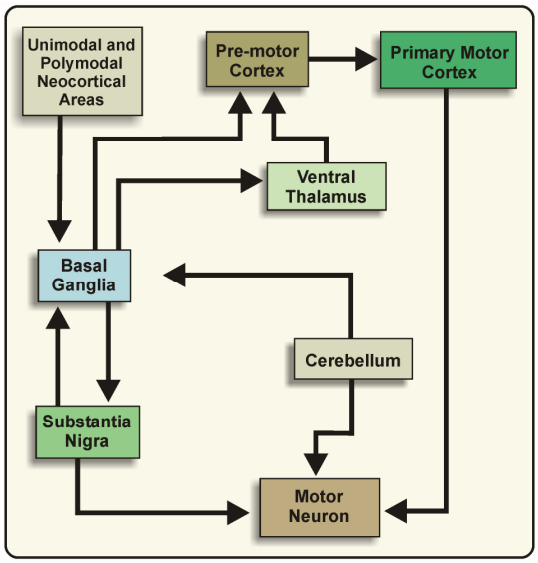

Figure 7.8. A circuit diagram showing the information flow in implicit memory.

The method of vanishing cues is a computer-aid knowledge and skill learning, in which the amnesic patient receives a series of cues in the form of word stems. The cues are gradually removed as the person successfully learns the task. This method was developed by Glisky, Schachter and Tulving [19] and is based on the concept of the teaching machine proposed by Skinner in the second half of the 20th century [47].

A common feature among these training techniques is the fact that implicit knowledge acquisition by amnesic patients is extremely specific and not easily transferable to new situations. This domain-specific knowledge seems to be restricted to the distinctive learning set, which relies on particular stimuli to trigger the appropriate chain of responses. For example, it has been documented that patients with large lesions within medial temporal lobe suffering from severe anterograde amnesia can acquire new habits in the absence of any awareness. This implicit knowledge was extremely rigid, so that when the task format was altered, performance impairment was observed [8].

Conclusions

Memory is not a perfect record from the past and its failure has adaptive value. However, as memory failure increases, it starts to lose its function, turning into a disorder. Memory is not a single process. It is a rather complex series of systems which can be dependent or independent from each other. Consequently memory deficits can be expressed in different ways.

For a long time, it was conceived that memory consisted of a serial processing format, in which information passed through a series of stages, such as STM and LTM. More recent approaches have provided new insights on how memory is organized in different systems which can operate simultaneously or in parallel.

The historical concept of a single STM has been replaced by the notion of a multi-component WM. This memory system has a time and space limited-capacity for the processing and storage of information from the external world. It is also responsible for retrieving information previously consolidated, and for executing a series of reasoning and thinking operations in order to solve a cognitive problem.

It has been proposed that WM has different components, including a central executive system, as well as a visuospatial scratch pad and an auditory loop. Problems in any of these WM components are associated with deficits in solving cognitive tasks. These cognitive deficits can have different degrees, ranging from simple math or language problems to serious mental retardation and schizophrenia. The parietal and frontal lobes appear to be important structures involved in WM.

There are two main memory systems involved in LTM: explicit or declarative LTM, which depends on consciousness; and implicit or non-declarative LTM memory, which does not depend on consciousness and may be expressed through behavior and/or autonomic nervous system activation. Explicit memory can be subdivided into semantic (general world knowledge or facts) and episodic (memories of particular events) memory. There are several

implicit memory systems, including procedural and emotional memory, associative and non-associative learning and priming.

Neural structures within the medial temporal lobe and the medial diencephalic area play an important role in episodic memory whereas neocortical areas might be related to semantic knowledge. Damage or malfunctioning of the medial temporal-diencephalic region causes severe anterograde amnesia and a temporally graded retrograde amnesia. Lesions within the neocortical regions might be associated with memory deficits within a specific cognitive knowledge. Furthermore, these amnesic patients are able to learn a variety of motor skills and emotional experiences in the absence of consciousness.

Implicit memory systems depend on the basal ganglia and its projections to other motor structures such as the substantia nigra, cerebellum and the pre-motor cortex. Previous experience with emotional events can alter behavior through implicit systems which involves the amygdaloid complex. Implicit memory systems are generally preserved in classic amnesic syndromes. Therefore, these systems can be employed as valuable resources to rehabilitate some of the explicit memory deficits found in amnesic patients.

Box 1

S: A Man Who Could Not Forget

Solomon Veniaminovich Shereshevsky, known as "S", was a Russian journalist with a remarkable memory. For many years he thought that everyone had the ability to recall just about everything the person had ever experienced. His uniqueness only came to light when his newspaper editor noticed that he never took notes during his interviews. S was able to recall every single word that had been said by the person he had interviewed. When S realized that he had an overwhelming memory capacity, he left his work and started to perform mnemonics publicly as a professional.

During the shows, S was able to remember quicky and accurately a tremendous amount of information. Standing in front of an audience, he would study long lists of words, figures or nonsense mathematical formulas written in a blackboard besides him. An example of one of these tables is presented in Figure 7A. After a few minutes, he turned his back to the blackboard and started to recite every single piece of information without a flaw. S´s memory was so reliable that it seemed that he was reading instead of remembering the material that he had previously memorized. For example, if the information was poorly written in the blackboard, he would mistake a 3 for an 8 or a 4 for a 9.

6	6	8	0
5	4	3	2
1	6	8	4
7	9	3	5
4	2	3	7
3	8	9	1
1	0	0	2
3	4	5	1
2	7	6	8
1	9	2	6
2	9	6	7
5	5	2	0
X	0	1	X

Figure 7A. Example of a table used by S, during one of his public presentations as a mnemonist (adapted from Kolb and Whishaw [27]).

The Russian neuropsychologist, Alexandra Luria, who met S in 1920, studied carefully his memory abilities in the course of thirty years and published the results in a book entitled *The Mind of a Mnemonist* [31]. Luria was astonished with S´s unlimited memory faculties. He succeeded in all neuropsychological memory tests and could remember every list of words Luria had asked him to memorize. For example, he was able to remember a list of 70 words forward, backward or in any other order. More than that, he could remember this list of words 15 years afterwards.

S suffered from a disease known as synesthesia, in which a certain stimulus evokes sensations usually associated with other stimuli. These symptoms, which are common in some hallucinogenic drugs such as LSD or mescaline, typically produce a mixing of the different senses. For example, when synesthetes people hear some sounds, they can also see an intense color or taste a strong flavor. S took advantage of this condition to enhance his memory capacity. Therefore, when memorizing a long list of items, he associated each item with an image from a place that he knew well. When he had to remember some of these items, he simply had to walk in that place and pick them up as he had imagined. This association technique is generally employed by common people to enhance their memory capacity.

However, S's memory gift was a double-edged sword. His memory ability was so powerful that it was usually impossible for him to forget anything. From time to time, he was flooded by memories he had no desire or needed to recall. For example, when looking at the blackboard during his public presentations, he had problems to forget what he had already memorized. His memory was so powerful that he had to put a lot of effort to forget older information, just like we usually do to remember.

The fact that S could not filter irrelevant information, made him so overwhelmed by the sheer amount of detailed information, that he could not follow a story or even watch simple TV programs. Paradoxically, S had problems to remember familiar faces, since their expressions were constantly changing according to their moods. This deficit was probably related to the fact that he had problems of integrating different stimuli in a more complex representation. Figurative, abstract or metaphorical language was also a problem for S. It was hard for him to grasp the meaning of words whose meaning was not literal, which in turn jeopardize his understanding of poetry or fiction literature. Therefore, S's extraordinary memory was also a somewhat disabling condition, interfering with his daily activities and surely affecting his quality of life.

BOX 2

HM: A Man Who Could Not Remember

Henry M, known as "HM" is without any doubt the most well-known amnesic patient in the history of the study of memory. His case has been studied for more than 50 years now and has provided a large amount of data which has helped to change our current understanding of memory.

HM grew up outside Hartford, Connecticut. He suffered from intractable epilepsy that was supposedly attributed to a bicycle accident when he was seven years old. Since then, he had increasing fits of minor seizures. When he was 16, the seizures started to increase and the symptoms were typical of grand mal seizures which included generalized convulsions with tongue biting incontinence and loss of consciousness. These seizures started to become more often and more intense, remaining uncontrollable despite the variety of medication he took. Indeed, HM was experiencing as many as ten seizures per week, keeping him from working and have an independent life.

In 1953, when he was 27, William Scoville at the Hartford Hospital, performed a bilateral medial temporal lobe resection in HM, in an attempt to stop his epileptic seizures. The idea behind the surgery was that the epileptic seizure was caused by uncontrolled electrical impulses that start in both temporal lobes and then spread throughout the rest of the brain. Therefore, removing the brain areas where the seizures originated might prevent the occurrence of the seizures. In the case of HM, an 8-cm length of the medial temporal lobe, including the cortex, the underlying amygdala and the anterior two-thirds of the hippocampus were removed from both hemispheres. An illustration of these neural structures that were removed from HM´s brain can be found in **Figure 7B-1**.

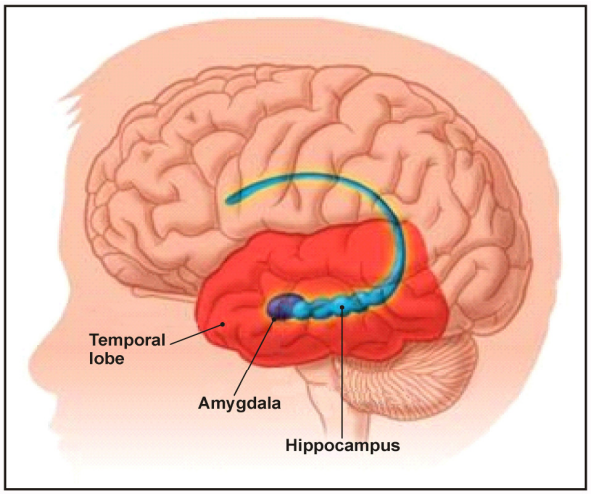

Figure 7B-1. Illustration of the neural structures that were removed from HM´s brain. Surgery removed these structures from both hemispheres. Figure from http://www.brainconnection.com/topics/?main =fa/hm-memory

The surgery had a noticeable beneficial effect on the epilepsy and HM´s seizures became better controlled. However, the bilateral medial temporal lobe resection caused a drastic effect on his memory. HM was unable to remember any new information and events that occurred after his operation. For example, HM would not recognize people he met after the surgery, even when he met them again and again. This meant that he could not form new memories, a pathology known as anterograde memory.

The first formal psychological exams of HM were conducted almost 2 years after the surgery by Brenda Milner at the Montreal Neurological Institute. These results fail to show any personality or emotional disorders. HM had normal social behavior, was always helpful and seemed highly motivated to collaborate during the tests. No deficits were also observed in perception, abstract thinking, reasoning and general intelligence. He had good command of language, including vocabulary, language production and comprehension. HM could find the right words to express himself in daily conversations [45].

When his old episodic memories were tested, HM displayed a temporally graded retrograde amnesia. He was not able to remember some events that occurred before the surgery. For example, he could not recall that his favorite uncle had died three years earlier. However, he performed well on a test of famous people's faces that had become famous long before his brain surgery. Still, most of his general knowledge (semantic memory) was intact. He clearly remembered his name, the jobs that he used to do and the events that occurred during his childhood.

HM was also able to hold information in his verbal and non-verbal working memory. For instance, he could repeat correctly a string of numbers immediately after seeing or hearing it. But if he was distracted, the information was lost for ever. HM had a profound difficulty to consolidate newly acquired information. This severe anterograde amnesia, which has persisted to this day, disables him to recall anything that has happened after the surgery. For example, minutes after he had lunch at the hospital, he would eat another meal if another tray was brought to him, since he would not recall that he had already eaten. When a third tray was brought to him, he limited himself to eat only the desert claiming that he was not very hungry. In fact, HM was never able to recognize Brenda Milner, even though she had met him once a month for 30 years.

Despite the devastating anterograde amnesia, HM could learn new motor skills, in spite of not having any conscious memory of doing so. As it may be observed in **Figure 7B-2**, HM could learn to copy a complex figure, such as a star, only by seeing the mirrored image of the figure. People without memory problems usually need some training before performing well in this task. HM acquired this new skill just like anybody else, although he could not remember that he had been trained to do the task [45].

Suzanne Corking, who was a Milner´s graduate student at that time, trained HM on various other manual tracking and coordination tasks. The results were always

the same: HM was able to improve his performance from session to session but was not able to recall that he was being trained to perform the task [12].

Finally, it is important to mention that HM knows that he has a memory deficit. He says:" *Right now, I'm wondering, have I done or said anything amiss? You see, at this moment everything looks clear to me, but what happened just before? That's what worries me. It's like waking up from a dream. I just don't remember".* This is an important feature of this amnesic syndrome resulting from bilateral destruction of the temporal lobe, but not in the Korsakoff´s syndrome which destroys both diencephalic and frontal lobe neural structures (see **Box 4**)

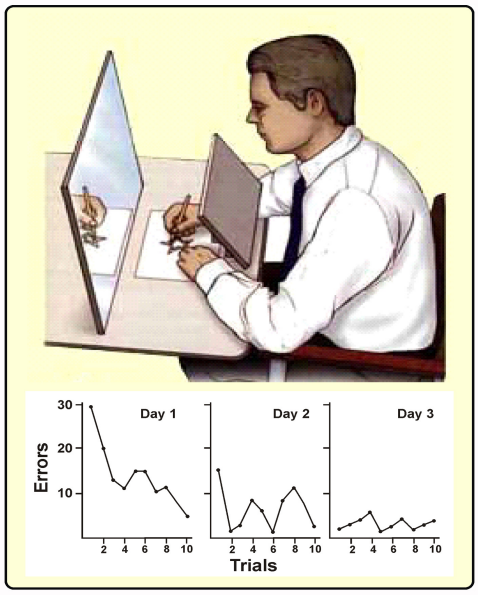

Figure 7B-2. HM´s performance of the mirror-tracing task. **Above**, the illustration of the task. **Below**, HM´s performance of this task on three successive days. It is clear that HM improved his performance, although he could not remember that he was being trained in this task. (Based on Milner [45]).

BOX 3

An Animal Model of Human Amnesia

Animal models are extremely important to understand the underpinning neural mechanism involved in mental disorders in general and in amnesia in particular. Any animal task involving some form of learning can be used to study amnesia. The acquisition, consolidation, retrieval of a behavioral task can be disrupted by experimental treatments such as genetic manipulation, drug injections or lesion in a specific area of the brain. In this case, the behavior of the experimentally manipulated animals is compared to a control group which acquired the behavioral task but did not suffer the experimental treatment.

Since the discovery that a profoundly amnesic patient HM had several memory abilities preserved (see **Box 2**), numerous animal researchers started to develop animal models that would reproduce HM´s condition in a laboratory setting.

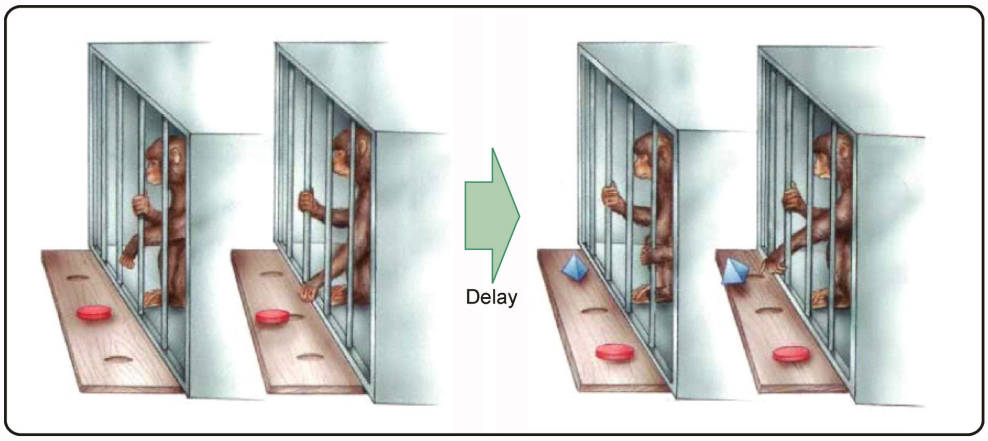

Figure 7C. The non-matching to sample animal model of explicit memory. The model involves two tasks. First, the monkey is trained to displace objects to obtain a reward. Then, the monkey is trained to displace an object that is different from the one presented a few seconds before. (Based on Miskin and Delacour [37]).

In 1978 Mortimer Mishkin, employing Rhesus monkeys as subjects, reported a behavioral procedure which induced striking similarities to HM's deficits [36].This is known as delayed non-matching to sample procedure, and involves several trials, each one composed of two phases. In the first one, the monkey learns to move an object in order to receive a small food reward, such as a half-peanut or a raisin (see **Figure 7C**). This is followed by a delay in which the object is removed from the sight of the monkey, but the animal must keep the object in his memory in order to solve a more complex problem during the second phase of the delayed non-matching to sample procedure. In this second phase, the animal is presented with

two objects: the one he had seen before and a new object.

Now the monkey must choose the new object in order to get the reward. If the animal chooses the original object which was presented during the first phase he is not rewarded. Monkeys are able to learn this task fairly well. They can remember the initial object for long delays of many minutes. Interestingly, bilateral lesions of the medial temporal lobe, similar to HM's surgery, induce a clear cut performance disruption in this task. Importantly, if the delay between the first and the second phases is reduced, then lesioned animals perform normally. These results parallel HM's conditioning, indicating that the object perception and working memory are well preserved, but long-term memory is impaired. Interesting, amnesic patients also demonstrate delay-dependent impairment on versions of this task developed for human subjects.

BOX 4

Filling in the Past: The Korsakoff´S Syndrome and the Confabulation Effect

Heavy drinking for a long period of time, especially when accompanied by malnutrition, may lead to a severe memory deficit, known as Korsakoff's syndrome. The syndrome was named after the Russian physician Sergei Korsakoff, who in 1880 described a typical memory loss among chronic alcoholic patients. This syndrome is caused by a thiamine (vitamin B1) deficiency, which destroys the neurons located along the midline of the diencephalon, including the mammillary bodies of the hippothalamus and the dorsomedial nucleus of the thalamus, as well as lesions in the frontal lobe.

Korsakoff's syndrome cannot be diagnosed until the patient has abstained from alcohol for at least one month. General intelligence and memory from past events are well persevered. Patients suffering from Korsakoff´s syndrome display clear cut anterograde amnesia. They have serious problems to retain the memory of events occurring after the onset of the condition. They also present a temporally graded retrograde amnesia which affects memories that are close in time to the beginning of the disease. Therefore, Korsakoff´s patients have similar memory deficits to HM's, who suffered a medial temporal lobe surgery to control epileptic seizures (see **Box 2**).

Figure 7D- Picture of Sergei Korsakoff (1853-1900).

Nonetheless, Korsakoff´s patients have a very peculiar symptom. They do not realize that they have a memory deficit and are indifferent to suggestions that they have a memory problem. In fact, one of the hallmarks of Korsakoff's syndrome is the person's complete unawareness of the memory problem and a complete lack of worry or concern when told so. Korsakoff´s patients with great memory gaps may believe that their memory is functioning normally. In order to deal with this paradox, Korsakoff's patients fill in their memory gaps with fabricated or imagined information. For instance, a patient with Korsakoff´s syndrome can report that he spent the weekend fishing, when in fact he stayed at home with his wife. Although he can not recollect the past appropriately, he replaces the missing information with events that never happened. This process of filling in the past with imaginary experiences is called confabulation, and its occurrence among Korsakoff´s patients might be the result of frontal lobe damage.

Confabulation should not be confused with the false memory effect. Confabulation is a clinical symptom resulting from a brain injury, whereas false memory is a phenomenon observed among healthy individuals who can recall an experience that never happened. For example, Loftus and Pickerall [30] were able to convince a group of adult subjects that they had been lost in a shopping mall when they were still children, although this fact did not occur. Once the false memory is induced, the person may strongly believe in its validity, even to the point of ignoring or denying evidence to the contrary. The false memory effect challenges the reliability and accuracy of human memories and shows how they are extremely vulnerable to suggestions.

Box 5

Temporally Graded Retrograde Amnesia and the Ribot´S Gradient Law

One of the main findings about retrograde amnesia is the fact that memory loss of personal experienced events is larger for recent events than for events that occurred during remote periods. This retrograde amnesia pattern is usually referred as the "Ribot´s Gradient Law" or the "Ribot´s Regression Law", named after the French experimental psychologist, Theodore Ribot, who in 1882 first noticed that recent memories might be more vulnerable to brain damage than remote memories. According to Ribot [42], "The dissolution of memory is inversely related to the recency effect".

The fact that older memories are less likely to be disrupted by brain lesions indicates that memories need a certain amount of time to be completely consolidated. Although the precise time course of consolidation is still unclear, there is a fair amount of results indicating that there might be at least two different consolidation processes within the LTM: a temporary one, which can hold information in the range of hours, days or even months, and a more permanent one that can hold information through the course of years (**Figure 7D**).

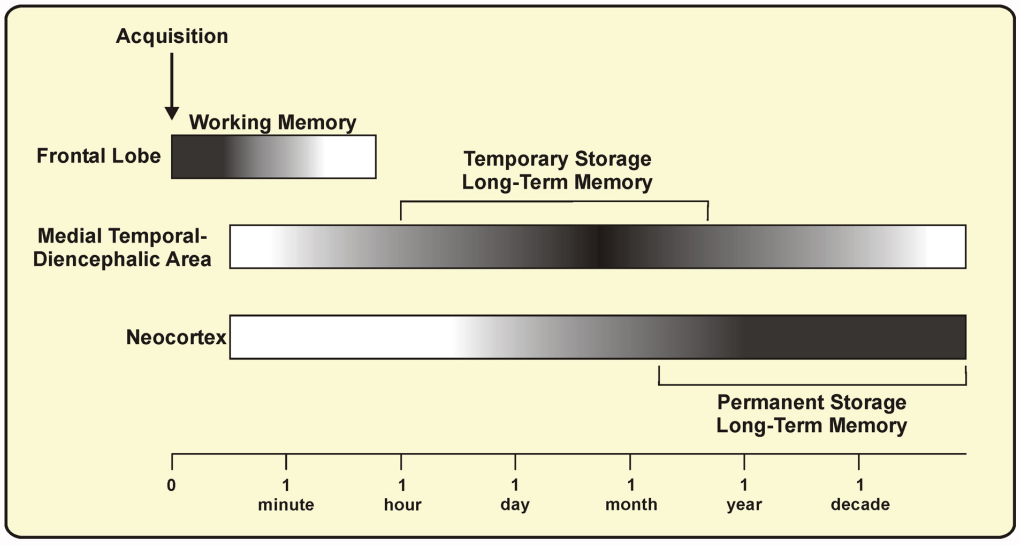

Figure 7D. Representation of the explicit memory consolidation and retrieval mechanisms in a pseudologarithmic time scale. The darkness of the columns represents the memory availability to retrieval. (Adapted from Meeter and Murre [34]).

Animal [25] as well as human [49] results indicate that the temporary storage of the information in the LTM depends on the integrity of the medial temporal-diencephalic area, whereas the permanent consolidation of this information might be associated with the neocortex. This highly dynamic process of memory consolidation is depicted in Figure 7D. As it may be observed in the figure, information is acquired and maintained in WM for a few minutes and then starts to fade way. The frontal lobe appears to be the main neural region responsible for maintaining this information in the WM. From WM, information can be temporarily stored in the medial temporal-diencephalic area. Permanent LTM might occur thereafter, through the strengthening of the information across the neocortex.

In parallel to the strengthening of the information in the neocortex, there is a weakening of this information in the medial temporal-diencephalic region. Therefore, lesions within this region can disrupt recently acquired information, which is temporarily stored in any of these structures, but might not affect more permanent memories which are stored throughout the neocortex. These results strongly suggest that Ribot´s Law observed in retrograde amnesia might be associated with the medial temporal-diencephalic region. Besides the temporally graded retrograde amnesia, lesions within the medial temporal diencephalic region can also induce severe anterograde amnesia, since no temporary storage of recently acquired information from the WM can be accomplished.

BOX 6

A body without a soul: The Alzheimer's disease and other dementia

Ageing is the biggest risk factor for developing memory problems due to the natural decrease in brain size and synaptic activity of the cerebral cortex. Elderly people can present different types of amnesia which in turn has an impact on their performance in all sorts of cognitive abilities.

Dementia is an age-related disorder characterized by a general failure of intellectual activity. The disease has an insidious onset and leads to progressive and drastic cognitive decline. Dementia has become more common in our society since life expectancy increased rapidly during the last decades. Roughly 5% of 65-year-old and as much as 45% of the 85-year-old population have some sort of dementia.

Memory impairment is the most common complaint among patients in the early stages of dementia, followed by deficits in language abilities, visual-spatial orientation, attention and abstract thinking. Personality alterations are inevitable in the course of the disease and dementia patients in later stages may look just like a body without a soul. They do not recognize familiar faces and may become very passive with no interest to become involved with anything. Even the most basic and daily tasks, such as eating, dressing, and grooming, start to disappear.

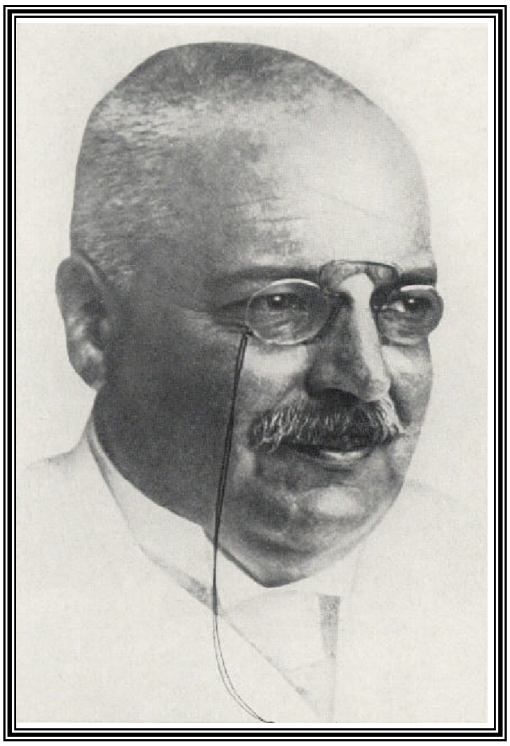

Figure 7F - Picture of Alois Alzheimer (1864-1915).

Alzheimer's disease is the most common form of dementia, accounting for nearly 80% of all the elderly dementia. The disease was named after the German psychiatrist and neuropathologist Alois Alzheimer, who in 1906 described for the first time the clinical symptoms of a dementia and the histopathological findings of this disease. Today, it is clear that Alzheimer's disease is a neurodegenerative disorder with two very distinct patterns of neuronal pathology: neurofibrillary tangles and amyloid plaques. Neurofibrillary tangles are intraneuronal abnormalities of the tubules and filaments that provide the neuron with structure and organization. Amyloid plaques consist of a core of amyloid beta-protein involved in neuronal cell death. The neuronal death starts in brain areas involved in explict memory, such as the entorhinal cortex and hippocampus, progressing then to the neocortex of the frontal and temporal poles, and finally reaching motor areas such as the primary motor cortex. See also **Chapter 9**.

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