Daniela Agneta Kalb

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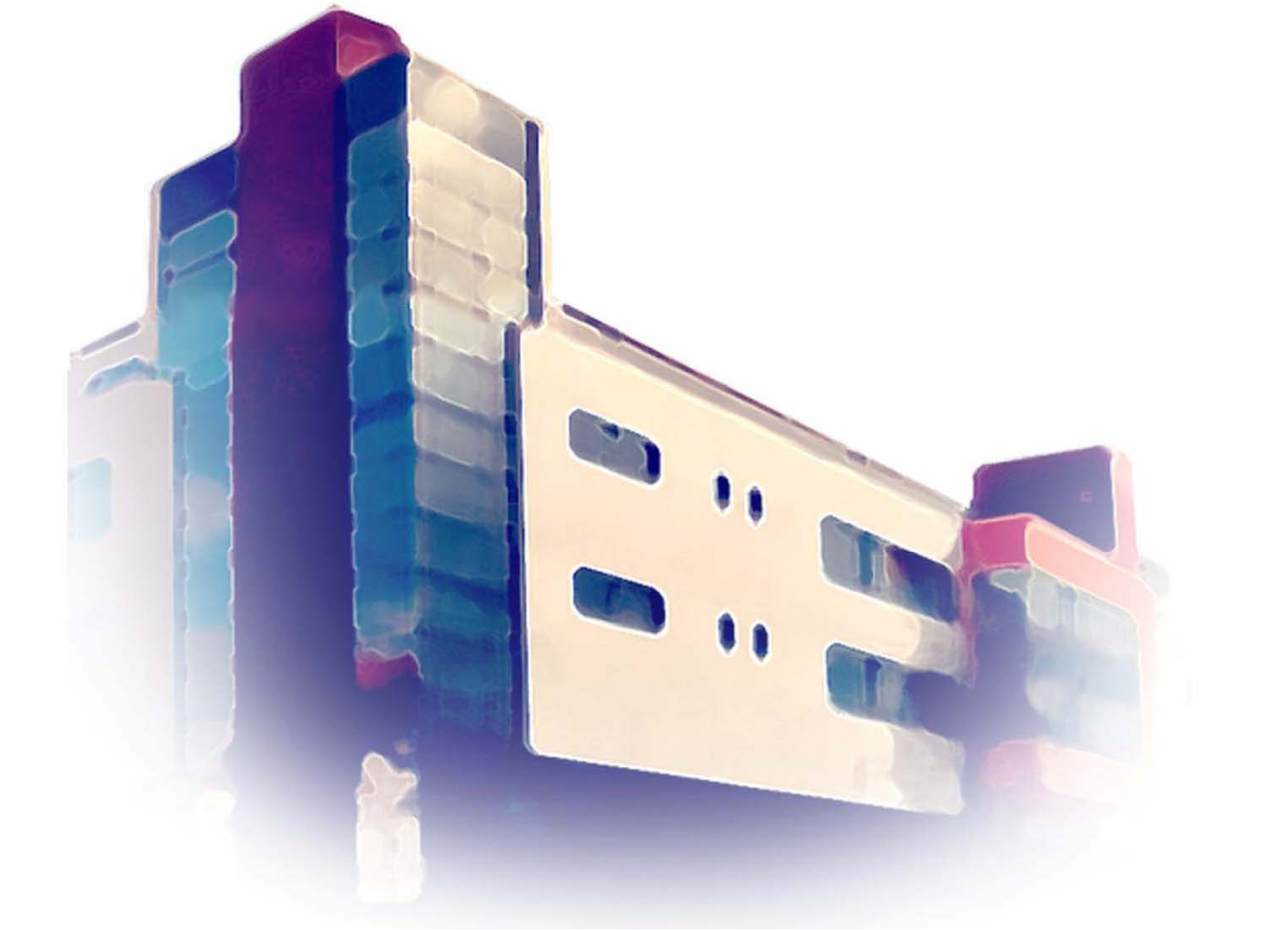

PICS

Publications of the Institute of Cognitive Science

Volume 4-2005

ISSN: 1610-5389

Series title: PICS
Publications of the Institute of Cognitive Science

Volume: 4-2005

Place of publication: Osnabrück, Germany

Date: March 2005

Editors: Kai-Uwe Kühnberger
Peter König
Petra Ludewig

Cover design: Thorsten Hinrichs

Bachelor's Thesis

Interaction of Hippocampus and Cortex - Evidences from Semantic Dementia

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16th August 2004

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Contents

1 Introduction

Long-term memory is a vital component of life. It allows us to store and retrieve facts and events, behavioural responses and procedures. Several psychological dissociations exist for memory systems responsible for different aspects of memory. The semantic memory system and the episodic memory system are both long-term stores, which are thought to interact with each other and other memory systems to ensure normal overall long-term memory performance. Semantic dementia is a disease affecting only the semantic memory component, and spares episodic memory capabilities. Semantic dementia can therefore offer an interesting access to investigate the interaction of episodic and semantic memory processes and their mutual contributions. Moreover, the search for localized neural substrates of memory is facilitated, as patients exhibit limited atrophies in specific temporal lobe areas, which are thought to be highly important in long-term memory.

This bachelor thesis intends to highlight the contributions to memory processing of different brain regions of the medial temporal lobe and the neo-cortex. In particular, the brain regions contributing to semantic and episodic memory and the process of consolidation[1] will be examined. For that, a short introduction to memory systems and an overview of semantic dementia, including some reports of patient cases, are given. Several important medial temporal lobe and cortical regions are presented in more detail in order to show their contributions to semantic and episodic memory. Finally, the computational model TraceLink is introduced, which substantiates some findings from neuro-psychological research on semantic dementia, and may be a valid model for memory acquisition and consolidation.

2 Memory - Basic Information

Memory is the ability of an organism to acquire and retain new information and to utilize that information during behavior in an environment (Tulving [1995a]). Memory compresses time. This means that long bygone events can be remembered now and also in the future, and that future events can be simulated and anticipated in the present, so that an organism can remember and behave more appropriately in subsequent situations similar to the initial learning experience (Tulving [1995a]).

Memory and learning are closely-related concepts; on the one hand learning requires some information-storing facilities and retention mechanisms like a memory, on the other hand a memory always entails learning.

Memory is always biased by internal factors such as the individual's arousal level, intelligence and motivational and emotional status. Memory is additionally influenced by external factors, such as the physical stimulus conditions, interference effects and familiarity with the material presented (Markowitsch [1995]).

In this chapter, the basic knowledge on memory and its psychological and biological substrates is presented. Finally, a short overview of memory-affecting

[1] Consolidation is the term for the process of the transfer of memories into long-term stores.

diseases is given.

2.1 Memory Systems and Processes

In 1972, Endel Tulving spotted a theoretically far-reaching dissociation of long-term memory: the distinction between episodic and semantic memory. He thought of these two memory systems as psychologically and neurologically distinct. Since Tulving's discovery, studies of the neural and cognitive relationships in these different long-term memory subsystems have been undertaken by many researchers, and there are still controversial debates on how these systems might interact (Simons, Graham, and Hodges [2002]).

Episodic memory is thought to be the memory system responsible for storing personally-based memories and experienced events. The remembering of such information is accompanied by the conscious retrieval of the temporal (subjective time on a bi-directional time axis, "when") and spatial (space/location, "where") setting of those events and experiences. As in a mental time travel, events of personal experience are somehow re-lived. For example, remembering episodes of one's own school-time or recognizing previously-seen persons and objects are episodic memory processes.

Semantic memory describes our general knowledge of the world and is retrieved without knowing when and where it was acquired. That is, no temporal or spatial contextual setting is remembered concurrently with a fact. Semantic memory contains the meaning of words and all other vocabulary (but not language!), grammatical and arithmetical factual knowledge, and is therefore a store of facts and concepts. The semantic system provides the material on which cognitive operations are performed; hence it is a basis for what we perceive as thinking. The external world is modeled in the semantic system, which allows us to reflect on it without perceiving the respective external inputs. The semantic system is often assumed to be hierarchically organized (Murre et al. [2001], Simons et al. [2002], Graham et al. [2000], Markowitsch [1995], Tulving [1995b]).

The major dissociations of all human memory systems have been used to associate specific learning and remembrance phenomena with specific memory systems. These dissociations are widely accepted, but there still exist some subtle differences in clustering and naming those systems. Two roughly-drawn separations are a content-based division (implicit and explicit memory) and a division along the time axis based on the age of memories (long-term and short-term memory). Implicit memory systems are: the procedural system, responsible for motor skills, simple conditioning, simple associative learning and skill-based operations; the perceptual representation systems, which makes possible priming through structural descriptions of stimuli; and the semantic memory system characterized above. Explicit memory systems are: the working memory system, also named primary and, for historical reasons, short-term memory - pointing to the short maintenance period of visual and auditory information held here; and the

episodic memory system for personal autobiographical event memory. All systems except for the procedural memory system, which is more of an action system, are thought to be representation systems (Tulving [1995b]). The semantic and episodic memory systems are together also called the declarative or propositional memory system. Recall and recognition are functions *inside* this declarative system (Aggleton and Brown [1999]).

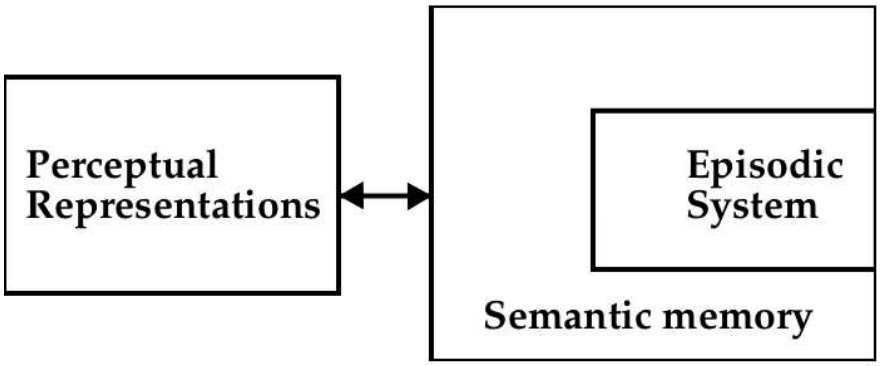
As a competing view to that of localized memory *systems*, where performance and impairments can be described by interactions or lesions of specific brain areas, it has been useful to analytically separate encoding, storage, and retrieval *processes* (Tulving [1995a,b]). Performance and impairments in memory can then be ascribed to interaction of memory processes (encoding, storage, and retrieval deficits).

Tulving proposed an influential psychological model on how episodic and semantic memory might interact, combining cognitive memory systems and memory processes. The central assumption in this SPI (serial - parallel- independent) model is that interaction between different cognitive systems are process-specific. The cognitive systems in this model are perceptual and encoding areas, as well as episodic and semantic memory. The specific processes are serial encoding, parallel storage and independent retrieval. Serial encoding means that information can only be encoded in another system if its preceding system outputs processed information as input contingent to the subsequent processing in this other system. With parallel storage, Tulving described the fact that storing pre-processed information chunks is parallel to and distributed across the memory systems, and the stored information in each system and subsystem is different, even if all the information originates from the same perceptual event. With respect to retrieval, the different systems are independently accessible. Retrieving information from one system does not involve corresponding retrieval from another or from all other systems (Tulving [1995b]).

In Tulving's initial model (Tulving and Donaldson [1972]), the formation of episodic memories was based on the correct output of the semantic memory system as the input to the episodic system, as the systems were organized in a serial fashion. Later, Tulving revised his model and made the episodic memory system a subsystem of semantic memory (see Figure 1 on the following page). Episodic memory was therefore largely dependent on the integrity of semantic knowledge, and with impaired semantic memory it should not be possible to form new episodic memories.

Semantic dementia challenges this view of an impossible double-dissociation of episodic and semantic memory, as patients show strongly-impaired semantic memory but are still able to store new episodic information. Graham et al. provided some convincing experiments contradicting Tulving's SPI theory and confirming the observations made in semantic dementia. They proposed that the formation of new episodic memories is not solely dependent on a functioning semantic system as input to the episodic memory system, but also on processed perceptual information as additional input to the episodic memory system (see section

Figure 1: Diagrammatic view of Tulving's revised SPI model. The episodic memory system is a subsystem of the semantic system.



4.4; Graham et al. [2000]).

2.2 Biological Memory Systems

Although a lot of research has been conducted in this direction, it is not clear that a biological distinction follows from a psychological distinction of memory systems. In any case, the goals of the cognitive neuro-sciences are to find correlations between neural mechanisms and memory processes, as well as to find the neural substrates of memory systems. Nevertheless, one should not forget that the term "memory" is an abstraction and does not depict a single activity or place in the brain. Rather, memory is a compound of inter- and intra-connected brain regions and associated processes (Tulving [1995a]). Memory research should therefore investigate bio-chemical and bio-electrical processes, as well as transmitter activities in the regions of synapses and the more overall influence of hormonal and electrophysiological changes in an organism. The study of brain-damaged patients, electrophysiological recordings, and neuro-imaging techniques have supported this research (Markowitsch [1995]).

The search for the neural substrates of memory has brought some prominent brain regions into the discussion. As early as 1957, Scoville and Milner supported the idea of the importance of the medial temporal lobe and in particular the hippocampus in the episodic memory system. Today it is widely accepted that the hippocampal complex plays an important role in acquiring episodic and semantic memories. The neo-cortical infero-lateral areas of the temporal lobe are supposed to be the neural substrate for storing prolonged semantic memories (repository of enduring memories). It is exactly these aspects of the temporal lobe which are highly likely to be damaged in semantic dementia. The hippocampal complex, temporal lobe areas and other cortical regions seem to be strongly linked to each other, in order to allow the encoding and association of memory constituents, for example, including visual and/or olfactory information in the memory. The limbic system and some diencephalic structures have also been associated with memory

(Graham et al. [2000], Tulving [1995a]). A more detailed description of certain brain structures and their involvement in memory is given in chapter 4.

2.3 Disturbances of Semantic and Episodic Memory

A wide variety of diseases, substances or brain lesions can lead to memory impairments.

Impairments of the semantic memory system can be identified in diseases like semantic dementia, herpes encephalitis and Alzheimer dementia, and occasionally in head injuries. Semantic impairments are frequently not the only memory deficits present in such diseases. It is therefore important to distinguish the different underlying pathologies of the different diseases. Semantic dementia is especially interesting in research, since it is almost exclusively the semantic system which is impaired, at least at the early stages of the disease. (A detailed overview on semantic dementia is given in the next chapter.)

Atrophies in medial temporal lobe areas are most often the cause of memory loss. The hippocampal complex is actually among the first structures to decline in Alzheimer's disease, as well as during normal aging. Semantic impairments are rarely caused by cerebro-vascular disorders, such as strokes, due to the dual blood supply to the left infero-lateral temporal lobe from the middle and posterior cerebral arteries (Kopelman [2002]). Dementias due to fronto-temporal damage occur with two different sets of characteristics. While the temporal variant is the same as semantic dementia, the frontal variant of fronto-temporal dementia does not lead to semantic memory deficits, but is indicated by changes in behaviour and personality, such as apathy, loss of empathy, impulsivity, disinhibition, stereotyped or ritualistic behaviours, planning and organizational problems, and attentional and executive control loss. In their progression, both variants of fronto-temporal dementia equalize, so that it is more difficult to differentiate between them if a patient presents at a late stage of her/his disease.

Amnesia is the transient/temporary or persistent/permanent loss, failure or lack of memories or memory processes. This may include episodic as well as semantic memories. It may have a psychic or organic cause, such as herpes encephalitis, severe hypoxia, vascular lesions, head injury, deep midline tumors, basal forebrain lesions and occasionally early dementia[2]. Additionally, there exist some kinds of amnesia caused by diencephalic brain damage, for example in Korsakoff's syndrome (Shimamura [1995], Gluck and Myers [1997]). In diseases like Alzheimer, the amnesia is progressive, involving more and more memory capacities.

Medial temporal amnesia lobe as well as diencephalic amnesia both have striking similarities in symptoms, such as analogical forgetting rates or spatial memory abilities. This and the high anatomical interconnectivity between both these regions led to the assumption that diencephalic structures and the medial temporal

[2] In Markowitsch [1995] a list of amnesia related disorders can be found (page 766, Table 84.1).

lobe form a single functional system which contributes to memory (Squire and Knowlton [1995], Kopelman [2002]).

The primary causes of amnesia have not yet been identified, but may possibly be one of the following: impairments in the initial encoding of episodic memories; a failure of consolidation into long-term memory; faulty encoding and storing of contextual information; speedy forgetting of information; or deficits in retrieval processes.

There are two expressions of amnesia, classified according to the subjective time of the memories affected by the amnesia with respect to its triggering event. Anterograde amnesia refers to the inability to store new information long-term, so that memories which have been acquired *after* the impact are involved. Retrograde amnesia is the loss of *previously* acquired and experienced memories. The loss of memories often shows a time gradient (Markowitsch [1995], Kopelman [2002]).

In 1957, Scoville and Milner investigated patients who had bilateral lesions of the medial temporal lobes and extensive and persistent loss of their memories. Additionally, it was reported that patients with atrophied hippocampal complex showed temporal graded loss of memory with a clear Ribot gradient[3] (Murre et al. [2001]). Retrograde amnesia caused by damage to the hippocampal complex, subiculum and entorhinal cortex has been associated with long-term memory loss, whereas limited lesions to some specific hippocampal sub-regions result in amnesia in which only a short-time period of memories is affected (Hasselmo [1999]).

Patients with different patterns of anterograde and retrograde amnesia offer the possibility of investigating the different roles and aspects of memory systems and their interaction. For example, Tulving saw the cause of amnesia as arising from a damaged episodic memory system. In contrast, semantic dementia is characterized by a damaged semantic system. Other diseases of memory involve both the episodic and semantic systems and/or other memory systems.

Research on specific memory-impairing diseases and the alignment of the results obtained there offer the possibility of getting a complete picture of which specific neural substrates are involved in memory processing. Research on semantic dementia, concomitantly to research on amnesia, allows the investigation of interaction between episodic and semantic memories as well as the determination of the specifically involved brain regions, especially in the medial temporal lobe.

3 Semantic Dementia

Semantic dementia is a clinical syndrome resulting in the impaired performance of tasks requiring semantic knowledge. The disease first came into discussion in 1975 when Warrington presented a study of three patients with progressive anomia and reduced word comprehension resulting from a selective impairment of semantic memories. A similar pattern had been described several decades ago in Japan.

[3] A Ribot gradient in memory retrieval describes the fact, that recent memories temporally near to the amnesia inducing event are more likely to be lost than old memories.

The term "gogi" was used which means ("word-meaning"-) aphasia (Mummery et al. [1999]). Radiological and functional imaging studies revealed structural and functional disruption of the temporal lobes in patients with semantic dementia (Graham et al. [2000]).

Another pattern of selective language deficits without the additional disturbances of dementia existed parallel to semantic dementia. Both syndromes were referred to as progressive aphasia, until it became clear that they were indeed different syndromes with the common symptom of progressive aphasia. Progressive aphasia without dementia was now labeled *progressive non-fluent aphasia*, indicated by a breakdown in the phonological and syntactic aspects of language, and Warrington's patients were labeled as having a *progressive fluent aphasia*, indicated by a non-impaired speech structure and the inability to produce the names of people, objects and places (Murre et al. [2001]). The terms *semantic dementia* (originally introduced by Snowden, Goulding and Neary, 1989,Nakamura et al. [2000]), *temporal variant of fronto-temporal dementia* and occasionally *focal temporal lobe form of Pick's disease* are synonymous formulations for progressive fluent aphasia (Murre et al. [2001], Simons and Graham [2000]).

3.1 Symptoms

Overall semantic dementia is characterized by the progressive deterioration in semantic knowledge with the relative preservation of episodic memory. Patients with semantic dementia have a selective and progressive impairment of semantic memory, manifested in the progressive loss of expressive and receptive vocabulary and general verbal and non-verbal knowledge. They no longer know previously familiar objects, places and people, responding "I've never seen him/her", show obvious problems in recognizing and using familiar tools, and fail to assign characteristic sounds to relevant pictures or to match corresponding items (for example typical colors of objects) (Nakamura et al. [2000], Mummery et al. [1999], Lambon Ralph et al. [2001], Moscovitch and Nadel [1999]). Patients cannot name pictures or match them to the words representing the content of those pictures. They also fail to sort pictures or words according to categories. Other striking symptoms are severe anomia and general difficulties in word production (Simons et al. [2002], Lambon Ralph et al. [2001]). Some researchers stressed that the anomia was more often manifested during confrontation naming than during spontaneous speech (Nakamura et al. [2000]). Nevertheless, the patients can produce fluent, effortlessly grammatically correct speech, but it is content-less and lacks substantives. Moreover, they can still repeat words and sentences well (Nakamura et al. [2000], Kopelman [2002]). Finally, at the early and late stages, serious comprehension problems are a salient trait of the disease (Simons et al. [2002], Lambon Ralph et al. [2001]). Auditory and reading comprehension are both impaired. Patients cannot follow conversations or TV programs, fail to understand questions, and react as being totally unfamiliar with the meaning of common words. They are, however, still able

to understand grammatically complex structures (Nakamura et al. [2000]). The language impairments seen in patients with semantic dementia all seem to be due to failure of lexico-semantic processing, whereas syntactic and phonological processing both appear largely unaffected (Mummery et al. [1999]). Patients can recall recent autobiographical and semantic memories much better than such memories in the distant past (Murre et al. [2001]). Category-level (superordinate) semantic knowledge is relatively well-preserved compared with fine-graded (subordinate) semantic knowledge. However, both are impaired and both decline further as the disease progresses (Murre et al. [2001], Kopelman [2002]), until only minimal categorization (for example living/non-living things) is possible.

In short-term memory tests, measuring forward and backward digit spans, patients usually perform well. It is only at very late stages of the disease, when the atrophy has spread throughout the temporal lobe and neighboring cortical and subcortical areas, that both digit spans may drop (as seen in patient A.M.; see 3.7.1 on page 16). Visual object and space perception are preserved in patients with semantic dementia, reflecting their intact visuo-perceptual and spatial abilities. In the non-verbal domain, problem-solving is relatively unaffected, whereas in verbal problem-solving tasks the patients often fail to understand the question due to their comprehension difficulties (Murre et al. [2001]). Patients are well-oriented in time and space until the late stages of the disease (Nakamura et al. [2000]).

It has been found that patients show some retention of new learning. New episodic learning, which appears to be intact in semantic dementia (as evidenced by patients' normal recognition performance after learning objects and faces from pictures and their preserved recall of recent autobiographical memories), seems to be based largely on good perceptual processing as input to the episodic memory system (Murre et al. [2001], Simons and Graham [2000], Simons et al. [2001]). This was also suggested by Graham et al. [2000], who found, contrary to the predictions made by Tulving's SPI model, that new learning may be possible due to a combination of sensory/perceptual and semantic information of an event as input to the episodic memory system (see 4.4 on page 30 for more on perceptual input to memory systems). Patients with semantic dementia could therefore still rely on sensory/perceptual information to encode episodic memories. In the SPI model, it was proposed that the learning of new episodic information is dependent on an intact semantic memory system and the processed output of that system. Nevertheless, the patient's capacity for new learning declines during the progression of the disease (Meeter and Murre [2002]). Furthermore, there is little evidence that patients with semantic dementia can re-learn lost semantic knowledge. New verbal learning is also generally very poor in semantic dementia (Simons et al. [2001]).

An experiment carried out by Moss et al. investigated category coordinate priming and functional priming in their patient P.P.. They found no priming effect for category coordinates, but P.P. showed normal priming for functional relations. Priming effects were also found in patient A.M.. A.M. initially showed priming for perceptual and functional properties of stimuli, but not for category coordinates or

category labels. After an 11-month delay he had preserved priming only for functional properties, and in another final testing session he showed no priming in any condition. Other researchers found no evidence of semantic priming (Nakamura et al. [2000]) or priming for words from the same category in lexical decision tasks (Murre et al. [2001]).

3.2 Pathology

The most commonly reported pathology in patients with semantic dementia is the unilateral or (preferentially) asymmetrical bilateral focal atrophy (mostly with more left-hemispheric than right-hemispheric damage) of the anterior, lateral and inferior aspects of the temporal lobes. Additionally, the temporal pole, the inferior and the middle temporal gyri (BA 38/20) are affected, in most cases bilaterally (Simons and Graham [2000], Simons et al. [1999], Mummery et al. [1999], Lambon Ralph et al. [2001], Simons et al. [2001], Marr [1998], Murre et al. [2001]). The most significant atrophy found consistently among the patients was in the left polar and inferior temporal lobe.

The atrophy of the temporal lobes spreads from the pole to more posterior, medial and superior regions, and may also involve the ventro-medial frontal areas near the temporal pole. During the progression of the disease, the atrophy is nearly always evident bilaterally, but mostly asymmetrically, with most cases having more left than right cortical shrinkage (Lambon Ralph et al. [2001], Simons and Graham [2000]).

Typically, the structures of the hippocampal complexes as well as the parahippocampal gyri are not atrophied (Simons et al. [2001]), although damage to the left hippocampus and bilateral parahippocampal regions was reported in certain patients (Meeter and Murre [2002], Murre et al. [2001]). The variability in degree and size of hippocampal and parahippocampal damage may be due to the fact that semantic dementia is a progressive disease (Nestor et al. [2002], Murre et al. [2001]).

Neuro-radiological investigations confirmed the atrophy of some aspects of one or both temporal lobes and the sparing of the hippocampal complex (hippocampus proper, parahippocampal gyrus, and subiculum). Functional neuroimaging studies measuring regional cerebral blood flow during a semantic decision task in semantic dementia patients showed a significant reduction in activity in the left posterior inferior temporal gyrus (BA37) (Graham et al. [2000]).

Generally, the pathology of semantic dementia in the polar and inferolateral temporal cortex spreads from anterior and inferior temporal regions to more posterior, medial and superior regions as the disease progresses.

3.3 Histology

Semantic dementia is presumed to be a non-Alzheimer degenerative brain disease (Nakamura et al. [2000]), either with underlying classical Pick's disease pathol-

ogy or with accompanying non-specific neuronal loss without characteristic Pick or Alzheimer histological markers (Graham et al. [2000], Simons et al. [1999]). Very common features are a loss in weight of the brain and micro-vacuolar histopathological changes in the atrophied temporal lobe regions (Marr [1998]). Atrophied regions may show a shrinkage or loss of nerve cell bodies and their dendrites. The loss occurs preferentially in the outer cortical laminae, whereas in the inner laminae the nerve cells are more likely to shrink. The hippocampus is usually histologically normal; sometimes there may be cell loss in region CA1. Occasionally, neurofibrillary tangles in, for example, the entorhinal cortex have been found (Marr [1998]). Gray and white matter are usually well maintained. In cases at very late stages of the disease there may be evidence of axon and myelin loss, and the white matter may become brownish in colour (Marr [1998]). An enlargement of the lateral ventricles can often be observed, triggering squeezing in their neighboring areas (Marr [1998]).

3.4 Diagnosis

To diagnose semantic dementia, tests which target certain aspects of the pattern of known symptoms of memory deficits can be carried out.

Various verbal and non-verbal semantic memory tests can be applied in investigating the most prominent deficit in the disease: the breakdown of semantic knowledge. Picture-naming and word-picture matching tests reveal the severe anomia of patients with semantic dementia. Picture-sorting tests highlight their inability to assign categories to presented items. In category-fluency tests they produce a much smaller number of category examples than a healthy subject would produce. When asked to generate verbal descriptions from spoken labels or, vice versa, to name an item after they have been given a description, the patients are deficient. Furthermore, synonym judgment tasks can be useful in investigating the patients' still available semantic knowledge.

In non-verbal tests, patients reveal deficient capabilities when asked to select the appropriate colour for a black-and-white line drawing of a familiar object (for example, yellow for a banana). When asked to produce drawings of animals or objects from memory, to use previously familiar objects and tools or to match common object and animal sounds to the appropriate picture, the patients fail. In the picture version of the Pyramid and Palm Trees test, a test to examine semantic associative knowledge (for a detailed procedure description see the Methods section in Simons et al. [2002]), semantically demented individuals are impaired as well (Murre et al. [2001]).

A useful test for investigating episodic memory in semantic dementia is the delayed Rey Complex figure recall. Patients have to copy the figure immediately after seeing it, and again after a 45- minute delay. Generally, they perform in the control mean range in both conditions, demonstrating their relatively good episodic memory for the recent time period.

The Warrington Recognition memory test for faces and for words consisting of two sub-tests, one testing face recognition, the other word recognition, has been useful in investigating perceptual contributions to recognition memory. As words do not provide the rich sensory information that faces do, patients with semantic dementia are generally better at recognizing faces than at recognizing words built up from letters. However, they seem to be impaired in both sub-tests of the Warrington Recognition memory test, as compared with matched control subjects (Murre et al. [2001]).

The Autobiographical Memory Test (AMI) inspects the patients' autobiographical retrieval, which is cued by family photographs distributed across their lifetime. Five criteria are used to classify how much and how well the patients retrieve events: (i) their sense of recognition ("I remember"); (ii) the patients' knowledge of temporal context (year); (iii) their knowledge of spatial/situational context; (iv) their expression of emotions during retrieval (smiling, laughing); and (v) the narrative structure of the patient's report (describing the sequence of events) (Nestor et al. [2002]).

Other accompanying deficits can be detected with a wide range of experiments from neuro-psychological and memory research.

3.5 The Temporal Course of Semantic Dementia

Over time, the behaviour of semantic dementia patients deteriorates and the memory deficits and brain pathology become worse. Most patients presents with uni- or bilateral temporal lobe atrophy. At later stages, bilateral involvement of the temporal regions is very common. Although medial temporal lobe structures seem unaffected (at least on one side of the brain) early in the disease, the atrophy in the lateral anterior and inferior areas of the temporal lobe becomes more severe and other neighboring areas become affected during the disease's progression. Medial, posterior, and superior temporal lobe areas become atrophied, as well as the hippocampi and related structures and the parahippocampal gyri. Generally, the pathology spreads from the lateral to the more medial areas in the brain.

Whereas the patient's recognition memory in the early stages of the disease is observably preserved, with the pathological progression a deterioration in recognition memory occurs. This may be due to concurrent perirhinal cortex damage, an area recently held responsible for recognition memory contributions (see 4.2.1 on page 26 for more on the perirhinal cortex and its role in memory) (Murre et al. [2001], Simons and Graham [2000], Simons et al. [2002, 2001]). Visuo-spatial abilities remain intact throughout the course of the disease and cannot be made responsible for the recognition memory deficits seen at the late stages of the disease (Simons et al. [2002]).

Other cognitive domains, such as non-verbal problem solving and working memory, remain unimpaired until the late stages. Phonological and syntactic aspects of language are still processed relatively well, although the patient's compre-

hension steadily declines (Simons et al. [2001]).

3.6 Semantic and Episodic Memory in Semantic Dementia

Difficulties in investigating patients with semantic dementia arise because their pathological pattern is a progressive one. This means the disease has no fixed profile of symptoms and pathology. Psychological impairments increase according to the ongoing damage to brain tissue. This means that semantic and episodic memory impairments in semantic dementia are along a continuum, making it difficult to explain how far one system is still functionally involved in memory processes.

Semantic memory is slightly impaired in the early stages of the disease, but continues to diminish until it breaks down completely. In contrast, only episodic memory functions highly dependent on semantic input seem to be implicated in producing episodic memory deficits. Episodic memory functions such as picture recognition are relatively well-preserved. For example, this behavior is disclosed by patients who perform completely normally in recognizing real and non-real animals (preserved episodic memory), but significantly fail to classify (by naming or pointing) the animals into real and non-real ones (highly impaired semantic memory; Murre et al. [2001], Simons and Graham [2000], Simons et al. [2002]). In forced-choice non-verbal recognition memory tests, patients with semantic dementia perform well, irrespective of whether or not they have semantic knowledge of the items (Simons et al. [1999], Simons and Graham [2000]). Nestor et al. even reported two cases[4] in which past episodic memory retrieval was significantly unaffected by semantic knowledge loss (Nestor et al. [2002]).

Minimally compensating their semantic memory loss, patients often retain at least the semantic facts concerning their individual lives, on the basis of their still functional episodic memory system. It was observed that the "semantic" memories of patients have autobiographical qualities, for example when they give definitions of concepts. Personally relevant or familiar places, faces and names are far better remembered than other facts, and even in conversations their comprehension is often limited to aspects of their own current life. Snowden et al. proposed that this is due to the effects of the interaction between episodic memory and preserved semantic knowledge, that is, autobiographical experiences facilitate the maintenance and/or retrieval of semantic information (Kopelman [2002]).

As impairment is restricted almost exclusively to the semantic system, with hardly any impairment in other memory tasks and systems (non-verbal problem-solving, perceptual and visuo-spatial abilities, working memory), patients with semantic dementia offer the possibility of investigating episodic memory behavior in the absence of semantic contributions (Simons et al. [2002]).

[4] L.P. and V.H.

3.6.1 Remote and Recent Memories in Semantic Dementia

Despite all the episodic capabilities mentioned above, episodic memory in patients with semantic dementia is not as normal as it is in healthy subjects. Experiments using public and autobiographical knowledge domains demonstrated that the patients have a retrograde amnesia for episodic memories which extend back in time, but their episodic memories of information which was encoded in recent time is unaffected (Meeter and Murre [2002]). In 1994, Snowden et al. were the first to discover that patients with semantic dementia made better familiarity judgments for proper names from the current time period than with names from the more distant past. They drew the conclusion that time is an important factor in episodic memory. In 1996, they used the Autobiographical Memory Interview (AMI) to investigate the episodic memory of the patient's whole life-time. And again it became clear that the patients were significantly better at memory retrieval from the recent time period than from childhood or early adulthood, which was impaired (Murre et al. [2001]).

Although memory retrieval is somewhat impaired for *all* time-periods in patients with semantic dementia as compared to healthy individuals, it crystallized that memory retrieval for episodic and semantic information from the past two to three years is much better than retrieval of distant events, as it the case, for example, in patients J.H. and A.M. (see the patients' case reports starting in the next section;Nestor et al. [2002], Simons and Graham [2000], Simons et al. [2001]).

This temporal gradient in memory retrieval is called *reverse* Ribot effect; it is opposite to the Ribot gradient typically found in amnesics, whose distant memories are retained better than the recent ones (Aggleton and Brown [1999], Graham et al. [2000], Kopelman [2002]). Murre et al. and Simons et al. suggested that the reverse Ribot effect is not a gradient in that memory retrieval continously decreases from recent to more distant time periods, but that the Ribot effect in semantic dementia is rather a step-like function. They identified a performance drop in memory retrieval for memories older than approximately two or three years in the majority of cases (Simons et al. [2002], Murre et al. [2001]). This step-like pattern of performance was found in episodic memory retrieval for the person's own history and for the memory of famous people and events (Nestor et al. [2002]).

Various explanations exist as to why this temporal step-function might occur. It is evident that patients who suffer a retrograde amnesia extending far into their past often experience severe atrophies which are not just situated in the medial temporal lobe and diencephalic structures. A shorter retrograde amnesia for only a brief period of time prior to the brain injury is associated with specific lesions in the medial temporal lobe and diencephalic structures. For this reason, damage to these brain regions cannot be responsible for the reverse Ribot effect in semantic dementia. In this disease the temporal neo-cortex is atrophied, whereas the medial temporal lobe areas remain relatively spared. Distant memories are lost, whereas recent ones are preserved (Kopelman [2002]). These premises lead researchers to

the conclusion that the destroyed temporal neo-cortex was the location of the lost long-term memories, and that the hippocampus and related medial temporal lobe structures play a time-limited role in the initial formation and maintenance of recent memories (Simons and Graham [2000]).

To explain the step-function, the medial temporal lobe structures also have to execute memory retrieval for these recent memories, as well as to care for the transfer of these memories to stores in the neo-cortex (consolidation). This may take two years or longer and finally makes the consolidated memories independent of the medial temporal lobe (Kopelman [2002]). This means that the hippocampal complex is responsible for the acquisition and retrieval of recent memories, but not involved in the retrieval of older memories (Nestor et al. [2002]). This retrieval of older memories takes place in neo-cortical storage sites.

This is different from the scientific view arising from research into amnesia. The multiple trace theory (see page 35) proposes that the hippocampi are important in the retrieval of all (at least episodic) memories, independent of their age. In this theory, the size and exact location of the hippocampal lesion correlates with the amount of memory loss and the form of the temporal gradient.

It has also been suggested that the reverse Ribot effect may be due to deficits in frontal lobe processes, for example for memory organization. Patients with semantic dementia (temporal variant of *frontal* temporal dementia) often have accompanying atrophies in their frontal lobes. Frontal lobe damaged patients have shown to be impaired in autobiographical and semantic retrieval as well. But memory deficits induced by frontal lobe damage correspond more to an amnesic profile, with a poorer performance on more recent decades. Nestor et al. therefore concluded that the reverse-step function seen on the test of autobiographical memory in semantic dementia is not caused by impaired strategic (frontal) retrieval processes (Kopelman [2002], Nestor et al. [2002]).

3.7 Patient Cases

3.7.1 Patient A.M.

A.M. was born in 1930 and was a well-educated manager with a wide range of sporting and academic interests. He presented with progressive problems in word-finding and comprehension. His speech was fluent but was devoid of content. Nevertheless, he made few phonological or syntactic errors. He showed minimal general knowledge and impaired single-word comprehension. When his semantic knowledge was tested he could only produce a small number of category members. This selective impairment of semantic memory in A.M became more and more pronounced over time. His recent episodic memories seemed to be preserved, whereas his episodic memories from more distant time periods seemed lost or to be fading away.

Due to his dramatic loss of semantic knowledge, A.M. was greatly disabled in his ability to live his everyday life. He misused objects, inappropriately se-

lected items and mistook various food items, such as putting sugar into a glass of wine or pouring orange juice over lasagna. Normal and previously familiar situations contained new, occasionally frightening and distressing qualities for him. In November 1996, A.M. could still remember that someone had rung the telephone while his wife was away, he could still find his way around his town and he could remember golfing appointments, which shows preservation of the recent component of his autobiographical memory. His semantic memory performance was at chance at this time. Since 1997 A.M. has generally deteriorated. He became time-obsessed, withdrawn and disinhibited and even lost his sense of time in late 1997. But he continued playing golf and learned to play dominoes (Murre et al. [2001]).

A.M. had a severe left temporal pole atrophy, where the right temporal lobe seemed to be less affected. The temporal lobe atrophy on the left involved the infero-lateral region. The superior temporal gyrus may also have been affected to a lesser extent (Murre et al. [2001]). Entorhinal and perirhinal left cortices appeared affected, too,as a result of a gross enlargement of the collateral sulcus, which contains the perirhinal cortex (Murre et al. [2001]), and, in the medial and lateral banks, the lateral border of the entorhinal cortex (Mikkonen [1999]). A.M.'s hippocampal complex seemed relatively well-preserved. This pathology correlates highly with A.M.'s episodic and semantic memory deficits.

A.M. participated in various experiments semiannually over a few years (1994-1997), thus his neuro-psychological profile could be described in time and quality (Murre et al. [2001]). In semantic tests in April 1994, A.M. showed severe impairments. In picture-naming tests, he could only name three out of 48 drawings of familiar objects and animals. His performance in word-picture matching was slightly impaired (36 out of 48, controls performed 47.7+-1.1). In the picture version of the Pyramid and Palm Trees test, disclosing associative semantic knowledge, A.M. scored 39 out of 52, with the controls scoring close to the ceiling. In non-semantic tests, A.M. performed as well as the controls. His copying of the Rey Complex figure was error-free, and after a 45- minute delay he reproduced the figure in the control mean range. In tests on non-verbal problem-solving, A.M. showed no impairments. Measuring his auditory and verbal short-term memory with forward and backward digit spans initially revealed no impairments (forward span: 7; backward span: 6).

In 1997, Graham and Hodges tested A.M.'s episodic memory. A.M.'s performance in retrieving autobiographical memories from the last five years of his life was much better than the retrieval of autobiographical memories from the other 60 years of his life (Murre et al. [2001]). In another episodic memory experiment, A.M. had to retrieve autobiographical memories from four different time-periods of his life. It was found that memories from the last five years were *qualitatively* better than those from the other three more distant time-periods. The retrieval performance was similar when he was cued with words or family photographs (Nestor et al. [2002]). The TraceLink model, which will be introduced in section 5.1.1 on page 39, explains this temporal gradient with specific interaction between the hip-

pocampal region and neo-cortical storage sites.

In priming experiments, A.M. initially showed priming for perceptual and functional properties of stimuli but not for category coordinates or category labels. After an 11-month delay, he had preserved priming only for functional properties, and in another final testing session he showed no priming in any condition.

His short-term memory performance also declined. Forward and backward digit span fell to 4 and zero respectively. Nevertheless, in November 1996 he could still reproduce some parts of the Rey Complex figure in delayed recall (5 out of 36; controls controls 15.2+-7.4).

3.7.2 Patient J.L.

Between March 1991 and September 1992, Hodges et al. investigated J.L.'s semantic knowledge with the semantic test battery (Lambon Ralph et al. [2001]). They found severe impairments in the semantic knowledge of J.L. Only some superordinate semantic knowledge was shown to be preserved, as evidenced by his relatively stable performance in superordinate level sorting tests. Initially, he only made coordinate semantic errors, but his sorting at the subordinate and category level also declined over the testing sessions. Over time, J.L.'s response characteristics progressed from semantically related to more prototypical and stereotypical answers. In the end, reflecting his progressive semantic deterioration, he could only give generic or superordinate responses or high-frequency labels, and he could only name an appropriate broad domain of objects and items presented to him.

Concomitantly to his morbid naming performance, J.L. showed, as do all patients with semantic dementia, severe and declining comprehension problems. Hodges et al. also found a relationship between the preserved naming of an object and its semantic conservation in J.L.'s memory. If J.L. was able to name an object in a naming test, it was likely that he would make no errors with this item in other semantic tests, such as word-picture matching. Symmetrically, if he could not name a picture on one occasion, he was unable to name this same picture in any subsequent testing session(Lambon Ralph et al. [2001]).

3.7.3 Patient D.M.

Patient D.M. was born in 1939 and presented at a very early stage of the disease with first symptoms of mild semantic memory loss in 1995 (Nestor et al. [2002], Simons et al. [2001], Murre et al. [2001]). He was an ex-surgeon and reported an increasing derogation of naming the technical instruments he was familiar with from his profession. His word-finding problems progressed, and increasingly problems in language comprehension also occurred. In the picture version of the Pyramid and Palm Tree test, he was three standard deviations outside of the control range. He also showed significant impairments in picture naming and conceptual knowledge tests, such as synonym judgment and category fluency. D.M.'s executive

abilities and visuo-spatial skills were tested as being normal (Nestor et al. [2002], Simons et al. [2001]).

Conspicuous was a reverse temporal gradient (Murre et al. [2001]) or a reverse temporal step-function (Simons et al. [2001]) that D.M. showed in retrieval during testing the integrity of some aspects of his memory. It was found that his knowledge of famous people and public events across various time periods differed according to the time at which the person had been famous or the event had occurred (Murre et al. [2001]). He was substantially better at giving information about currently famous people than about formerly well-known personalities. Similarly, D.M. could remember public events from the last three years prior to the study (1995-1997) much better than events from two more remote time periods (1989-1991 and 1992-1994) (Murre et al. [2001], Simons et al. [2001]).

In a recognition experiment, D.M. was tested with pictures depicting either objects he was familiar with or objects he had no semantic knowledge of. There were two different versions, showing the object from two different positions. Highlighting the contribution of perceptually-processed input (besides semantic input; see section 4.4) to episodic memory stores, D.M. could recognize objects in pictures as well as the control subjects, unless he had no semantic knowledge of the objects or they were in a perceptually different position from that in the learning session (for example, a picture of a book viewed from the front versus viewed from the spine; Simons et al. [2001]).

Before he presented himself in a clinical context, D.M. had already begun to note down some words he observed as being lost in his spontaneous speech and which he practiced up to five or six hours a day. It was observed that he had significantly better knowledge in the categories he had practiced than in the categories in which he had not practiced. But after he stopped practicing, his knowledge decreased quickly (Simons and Graham [2000]). These observations were tested in a semantic learning experiment, in which D.M. re-learned 160 words from eight separate semantic categories (for example, breakfast cereals, herbs and spices, TV shows, stones and gems), in which he had impairments prior to learning (Graham et al., 1999). D.M. learned the words for two weeks, 30 minutes a day. Three results were obtained from this test: The intensive learning of the vocabulary raised D.M.'s performance in naming those specific category members on a category fluency test up into a normal range. Nevertheless, D.M. did not acquire any semantic facts about the learned words and, after he stopped practicing, he showed a rapid rate of forgetting. He lost almost 60% of his re-learned category knowledge after a 6-8 weeks delay (Murre et al. [2001]). This indicates that his practice was analogous to rote learning of meaningless stimuli. D.M. could not acquire, generalize or maintain any semantic facts (Simons and Graham [2000]).

Imaging techniques, such as MRI and voxel-based morphometry, revealed restricted left temporal atrophy in the pole region and changes in the left anterior temporal lobe with mild left-sided ventro-medial frontal atrophy. D.M.'s right temporal lobe and parahippocampal gyrus and both hippocampi appeared to be

spared from abnormal brain changes (Nestor et al. [2002], Simons et al. [2001]).

3.7.4 Patient S.L.

S.L. was born in 1948 and presented in January 1998 with difficulties in remembering the names of people and things; however, she disputed any comprehension problems. Along with an ongoing detraction of her semantic memory, her personality changed. She became rigid, obsessed, impulsive and disinhibited. In spring 1998, she experienced more and more problems remembering words and the names of friends. Her word production became affected as well.

Furthermore, she showed remarkable deficits on episodic memory tests. As with patient D.M., S.L. was also impaired in naming famous people from their pictures and showed a similar performance profile in recognizing famous people from photographs, whether known or unknown to her, in the conditions of perceptually identical and perceptually different perspectives of the depicted objects.

An MRI study revealed a severe atrophy of the temporal poles bilaterally, with some involvement of the hippocampus, parahippocampal gyrus and lateral temporal lobe on the left. Other temporal lobe structures appeared relatively unaffected (Simons et al. [2001]).

3.7.5 Patient J.H.

Patient J.H. displayed all the common symptoms known for semantic dementia. In the last three years prior to presentation she experienced word-finding difficulties and severe comprehension impairments. Her performance on semantic tests, such as category fluency or picture naming, was deficient. J.H. was good at copying the Rey Complex figure, even after 45 minutes delay, demonstrating some intact anterograde memory (Nestor et al. [2002]). In addition, like patients D.M. and S.L, J.H. had well-preserved recognition memory for perceptually identical depicted items (Simons and Graham [2000]). She also had intact visuo-spatial skills.

MRI scans showed a bilateral temporal atrophy. Accordingly, a voxel-based morphometry disclosed a severe bilateral atrophy of the anterior temporal lobes, with the left side more affected than the right temporal lobe. In spite of the fact that MRI scanning revealed no frontal involvement, voxel-based morphometry showed some degree of ventro-medial frontal involvement. The hippocampi and parahippocampal gyri seemed unaffected (Nestor et al. [2002]).

3.7.6 Patient F.M.

Similarly to all other semantic dementia patients, F.M. showed a severe anomia. She exhibited only slight semantic impairment and excellent single word phonology and few phonological errors in speech, was good at non-word reading and could repeat single words quite well. Over the next few years her state deteriorated. Although her anomia progressed, in contrast to other cases her comprehension abilities remained relatively constant and she scored on tests only minimally

outside the control range. Nevertheless, F.M.'s comprehension abilities declined at the late stages of her disease. Brain scans showed in F.M. an infero-lateral left temporal lobe atrophy (Lambon Ralph et al. [2001]).

3.8 Summary

The previous sections introduced semantic dementia as a progressive clinical syndrome resulting in the complete breakdown of all of the patient's semantic knowledge. Episodic memory for recent time-periods and new episodic learning appear relatively well-preserved in the disease. There exist two possible explanations why this phenomenon in episodic memory occurs. One explanation arises from theories of consolidation (see section 5 on page 34) and another from the multiple input hypothesis (see section 4.4 on page 30). A combined account of both theories may additionally be useful in investigating cued or time-specific retrieval of episodic memories and is introduced in section 6.

Over time the behaviour of semantic dementia patients deteriorates and the memory deficits and brain pathology become worse. Generally, the pathology in the polar and inferolateral temporal cortical regions, which are affected early in the disease, spreads from anterior and inferior temporal regions to more posterior, medial and superior temporal regions as the disease progresses. The patient cases presented exemplify the memory deficits in semantic dementia in more detail.

The memory deficits, especially episodic memory deficits, seen in semantic dementia have often been viewed as opposite to those of amnesia. Whereas amnesics have a severely damaged episodic memory system, patients with semantic dementia show some preserved episodic memory capabilities. Additionally, the temporal gradients occurring in episodic memory retrieval differ in the two diseases. Whereas amnesics have problems with memories from more recent time periods, patients with semantic dementia are impaired in memory retrieval from more distant time periods. The pathologies in the two diseases differ in that amnesia typically has underlying damage to the hippocampus and attached areas, whereas in semantic dementia the temporal neo-cortical areas are mostly atrophied. This might indicate the possibility to distinguish biologically and psychologically between the contributions from different neural (sub-)systems to different (sub-)systems of memory.

This overview of semantic dementia makes it clear that the deficits in episodic and semantic memory seen in the disease not only conflict with previous theories of memory systems, but also highlights the networked state of these systems. It offers a new approach to investigating the interaction between episodic and semantic memory systems[5] in particular and their multiple associated and supporting brain structures. The next chapter describes in more detail the brain areas which are involved in memory processes and are associated with semantic dementia.

[5] From the sparing of recent memories and the impairments in distant memory retrieval in semantic dementia it follows that the interaction of episodic and semantic memory can only occur for recent memories (Murre et al. [2001]).

4 The Medial Temporal Lobe and other Brain Structures contributing to Memory

The medial temporal lobe is a deep brain structure in the temporal lobe. It contains the hippocampus (with all its substructures, like CA1-CA4, dentate gyrus and the subiculum), fornix, amygdala, and the surrounding entorhinal, perirhinal and parahippocampal cortices of the parahippocampal gyrus (Simons and Spiers [2003], Meeter and Murre [2002], Gluck and Myers [1997], Alvarez and Squire [1994], Mikkonen [1999]). Various research groups assume that the medial temporal lobe system sometimes does not contain all of these structures. In the context of memory it is often equated with the term *hippocampal region* (see Figure 2 on the next page).

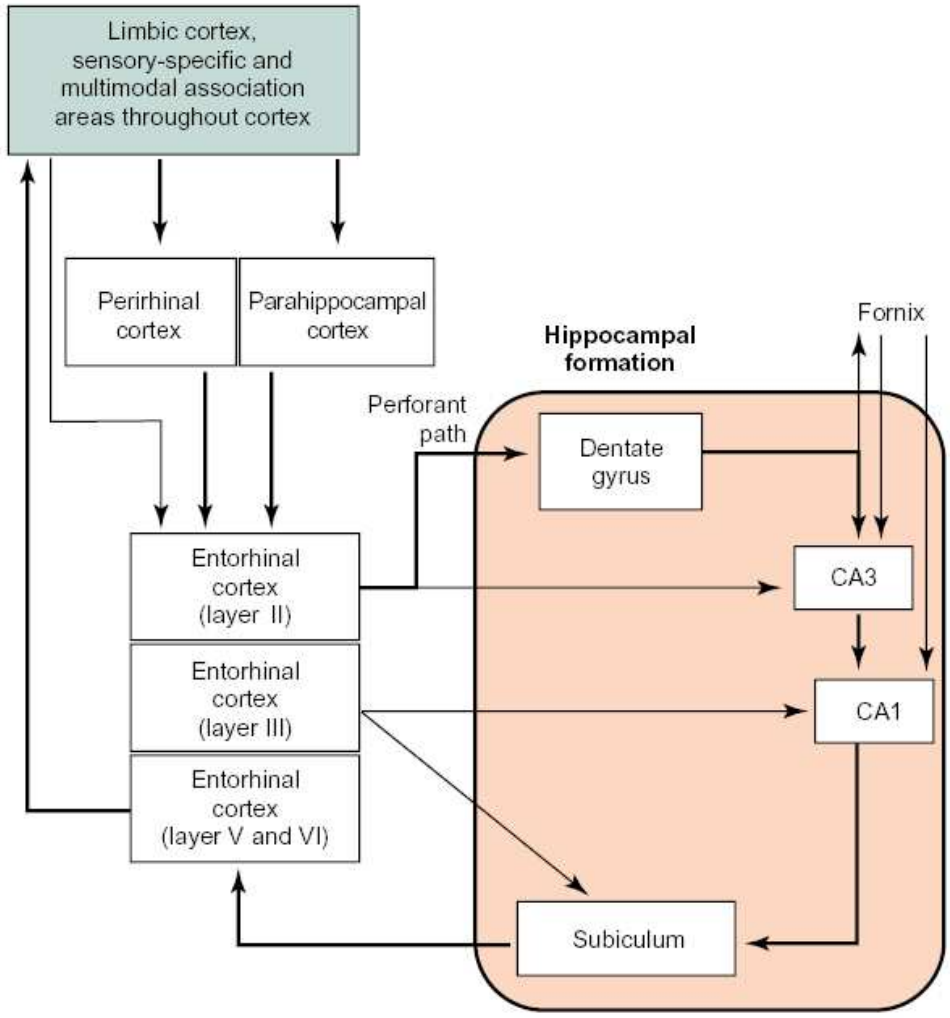
The medial temporal lobe became the focus of memory research during the 1950s. After surgical removals in this region, patients showed a severe and selective memory impairment (Alvarez and Squire [1994]). Memory dysfunction in diseases like semantic dementia and amnesia have been widely associated with non-functional medial temporal lobe structures. Over 50 years of research in this area have revealed that the medial temporal lobe memory system is intricately connected to various other brain structures which influence, mediate or contribute to the processes of encoding, storage and retrieval.

The brain regions and substructures of the medial temporal lobe involved in memory processing work in concert in order to make normal memory performance possible. If a system or connections between systems are damaged, this damage affects overall memory performance, according to the site of the lesion and the functions attributed to that region (Simons and Spiers [2003], Gluck and Myers [1997]).

The extended system of medial temporal lobe and diencephalic structures appears to play a role in the conscious recollection of events and facts, but does not play a role in non-conscious forms of memory, and is strongly linked to neo-cortical areas (Alvarez and Squire [1994], Squire and Knowlton [1995]). The right hippocampus and the parahippocampal gyrus have both been found to be involved in face recognition (Simons et al. [2001]). It has been hypothesized that perirhinal cortex atrophy impairs both recall and recognition, whereas hippocampal damage impairs only recall memory (Kopelman [2002]). In a different approach, recognition of familiar items is supported by the perirhinal cortex, whereas associative recollective recognition is attributed to the hippocampus. Both regions are anatomically linked to each other but have independent connections to other cortical association areas (Aggleton and Brown [1999]). Additionally, the perirhinal cortex has been made responsible for the quality of visual stimuli (Mikkonen [1999]), which might be important in the recognition of visual aspects of stimuli as this is often part of an episodic memory.

Relevant to semantic dementia, it has been found that during a semantic decision task several cortical areas are active. Confusingly, patients with seman-

Figure 2: Schematic overview of the connections between different subregions of the medial temporal lobe and their hierarchical organization. Arrows symbolize major pathways. The hippocampal formation represents the area known as hippocampus proper (CA1 to CA3) and closely-related structures; it must not be confused with the terms hippocampal region or medial temporal lobe, which are terms for the compound of all the areas shown below (Gluck et al. [2003]).



tic dementia and healthy subjects both showed activation in the inferior frontal gyrus (BA 44,45,47), the left middle temporal gyrus (BA 21/37), the left temporal-occipital-parietal (T-O-P) junction (BA 19/39), the left superior occipital gyrus (BA 19), the anterior cingulate cortex and the right cerebellum. Nevertheless, this finding highlights these regions as being somehow involved in semantic processing during a semantic decision task (Mummery et al. [1999]). Lambon Ralph et al. suggested that the connections between the semantic system and phonological representations should not be underestimated and that phonological representations provide not just the basis for speech production but may also be cues for naming objects and concepts, which is a prominent deficit in patients with semantic dementia (progressive fluent *aphasia*) (Lambon Ralph et al. [2001]).

Long-term episodic and semantic memory seems to be highly dependent on functionalities in the medial temporal lobe (Mikkonen [1999]). Different features of a representation are thought to be bound together here to build up a complete memory during episodic encoding (Simons and Spiers [2003]). Neuro-imaging and lesion studies revealed close interaction and some functional overlap of memory functions between the medial temporal lobe and frontal lobe regions. In experiments with healthy subjects, activation of the right frontal and temporal lobes and left medial temporal regions were measured when the patients remembered events from their remote past. Remembrance of time-specific autobiographical events caused activation in the left hippocampus and temporal pole, and in the medial prefrontal cortex. Remembrance of time-unspecific autobiographical events caused activation in the bilateral temporo-parietal areas (Kopelman [2002]). The medial temporal lobes receive highly-processed information from the cortical regions and project back to them (Squire and Knowlton [1995]). The connections between the neocortex and the medial temporal lobe are not neuro-anatomically and topographically organized. However, Squire and Alvarez have shown that for these areas to function as memory stores there is no necessity for specific a priori connections between them. In their simple network model they simulated that connectional specificity occurs during initial learning (Alvarez and Squire [1994]).

The distinguishable activation of different temporal and cortical regions, depending on the time-specificity of a memory, the connectivity between the brain areas, and their interaction during memory processing, led researchers to the idea that these regions may have different roles in long-term memory storage and retrieval. It was suggested that the hippocampal complex may be involved in the retrieval of recent experiences, but that older memories are independent of this structure. The long-term memory stores are regions of the neo-cortex (Meeter and Murre [2002]), therefore the role of the medial temporal lobe is only temporary in long-term storage. It must have the capability to transfer memories to the neocortex (Alvarez and Squire [1994]).

This short overview illustrates the complexity of the connections between and contributions of various brain sites in processes concerning memory. The following sections highlight the interaction between and the functions in the medial tem-

poral lobe and its main interaction sites.

4.1 Hippocampus

The involvement of the hippocampus in certain cognitive processes, especially memory processes, has become clear, not just since the famous patient H.M. The hippocampi are associated with the retrieval of recent overall memories, the rapid storage and retrieval of episodic memories and with the transfer of memories to long-term memory stores in the neo-cortex (consolidation). Furthermore, the hippocampi have been associated with spatial memory, navigation tasks, incremental learning, stimuli representation, associative learning and classical conditioning. These processes need the hippocampus to be able to develop novel and flexible representations and also to be sensitive to regularities in stimulus pairs (Gluck and Myers [1997], Alvarez and Squire [1994], Nestor et al. [2002], Murre et al. [2001], Simons et al. [2002], Gluck et al. [2003]).

In the human brain, the hippocampus is closely linked to the anterior thalamic nuclei and has reciprocal connections with the entorhinal, perirhinal and parahippocampal cortices. Major inputs to the hippocampus arrive through the perirhinal, entorhinal and parahippocampal cortices (Aggleton and Brown [1999]). A main input plus output pathway is the fornix, which connects the hippocampus with subcortical structures (which in turn may provide neuro-modulation to the hippocampus), and the prefrontal cortex (see Figure 2 on page 23). Field CA3 of the hippocampus contains a large number of pyramidal cells with a very high degree of internal recurrency, hinting at possible auto-associative neuronal processes which might take place here. The pyramidal cells of region CA3 are innervated by mossy fibers of the dentate gyrus, which relays entorhinal information. These connections of the dentate gyrus to the hippocampus are often characterized as sparse connections, which would allow a pattern separation process to take place. The overlap between memory patterns is minimized and thereupon catastrophic interference phenomena are avoided and capacity is increased. Region CA3 also has sparse afferents connecting it directly to the entorhinal cortex (Gluck and Myers [1997]). It has been suggested that the spatial and temporal context associations in memory processes which support memory recollection take place in a system of the hippocampus, the mammillary bodies and the retrosplenial cortex (Simons and Spiers [2003]).

The hippocampus and especially its fields CA1 and CA3 are the natural substrates which are modeled in auto-associator models, and auto-associative functions of hippocampal neurons can be seen as one physiological basis for learning and memory. Marr proposed that field CA3 is the location of auto-associative memory in the brain. (Gluck and Myers [1997], Hasselmo et al. [1996]). Auto-associative memory has three requirements. Firstly, the principal cells have to have highly recurrent connections. Secondly, strong but sparse synapses must force input to the memory system. Thirdly, a high level of synaptic plasticity must ex-

ist between co-active cells. The hippocampus fulfills all three requirements: high internal pyramidal recurrency in CA3, sparse connections from dentate gyrus to hippocampus and high synaptic plasticity as well. This led Marr to draw the analogy between hippocampus and auto-associator. He perceived the hippocampus as a separate or intermediate processor that is able to rapidly store event memories which will then be gradually transferred to the neo-cortex, because the hippocampus cannot organize and classify information and integrate it into an existing network of knowledge and memories. The hippocampus acts as a temporary memory store of rapidly-acquired patterns in an auto-associative manner (Gluck and Myers [1997]).

Semantic dementia has typically spared the hippocampi of patients as long as the disease has not reached a very progressed stage. Contrarily, patients with more accented episodic memory deficits, such as amnesics, have damage to one or both hippocampi. A selective damage to the hippocampus proper mainly results in a temporally graded retrograde amnesia. Studies of children with perinatal damage to the hippocampus revealed impairments in episodic memory as well (Hasselmo and McClelland [1999]). The preservation of the hippocampal complex in individuals with semantic dementia allows these patients to encode and maintain some new episodic memories for some time. But this is limited in extent due to the small hippocampal size and capacity. This limited capacity also induces catastrophic inference and memory overwriting. Amnesics cannot acquire new episodic information because of their atrophied hippocampal regions (Murre et al. [2001]).

Simons et al., 2002, report an experiment where no significant correlation between atrophy of the hippocampus and performance in a recognition test was found. Accordingly, the hippocampi seem to be not at all or only very minimally involved in recognition memory processes.

4.2 Parahippocampal Gyrus

Simons et al. refer to the parahippocampal gyrus as including both the entorhinal and perirhinal cortices (Simons et al. [2002, 2001]). Atrophy of the right parahippocampal gyrus has been found to correlate significantly with impairments in recognition memory (Simons et al. [2002]). Refining these results, it was found that atrophy of both the right hippocampus and the right parahippocampal gyrus negatively affect performance on the recognition memory test for faces, but the correlation was significantly higher for parahippocampal damages (Simons et al. [2001]). Despite the fact that damage to the parahippocampal gyrus mostly predicts recognition memory deficit, damage to this region is not associated with retrograde amnesia (Aggleton and Brown [1999]).

4.2.1 Perirhinal Cortex

The location of the perirhinal cortex is circumscribed as being part of the parahippocampal gyrus (Simons et al. [2001]). Other authors describe it more precisely as

rostrally occupying the banks of the collateral sulcus and stretching onto the medial surface of the temporal pole at its caudal end (Murre et al. [2001], Simons and Graham [2000]). The perirhinal cortex is connected with the medial dorsal thalamic nucleus and has numerous connections to the hippocampus (Aggleton and Brown [1999]). The perirhinal cortex has been associated with context-independent (semantic) learning (Murre et al. [2001]), familiarity-based and general recognition processes (Simons et al. [2002], Simons and Spiers [2003], Simons et al. [2001]) and independent perceptual mnemonic processes (Simons and Spiers [2003], Aggleton and Brown [1999], Simons et al. [1999], Murre et al. [2001], Simons et al. [2002, 2001]).

As mentioned above, an atrophy affecting the parahippocampal gyrus leads to recognition memory deficits. More specifically, damage to the perirhinal cortex alone can produce the same or almost an identical pattern of recognition memory deficits. At the very late stages of semantic dementia, the progression of damage to cortical tissue, including the parahippocampal gyrus, leads to these recognition deficits.

In general, the perirhinal cortex is less affected in semantic dementia. At least the caudal portion is widely intact in semantically-demented persons. This could explain why patients with this disease still have a relatively preserved recognition memory; or at least preserve some aspects of recognition memory (Simons et al. [2002, 1999]).

The contribution of the perirhinal cortex to recognition processes may differ form that of the hippocampus. The hippocampus is often seen as being more important in associative recollection (endowed by the intra-hippocampal recurrency; auto-associator), whereas the perirhinal cortex rather supports recognition processes for item familiarity (Aggleton and Brown [1999]). Even though atrophies of both regions, perirhinal cortex and hippocampus, have been associated with recognition memory deficits (perhaps due to their high inter-connectivity), a damaged perirhinal cortex correlates more significantly with recognition deficits than an atrophied hippocampus (Simons and Spiers [2003]). Experiments in amnesic patients confirmed this pattern of distributed and differentiated recognition processing in the perirhinal cortex and hippocampus (Simons et al. [1999]).

The exact involvement of the perirhinal cortex in memory processes such as recognition and semantic knowledge still remains quite unclear, and experimental results are often too diffuse to allocate these specific functions to the perirhinal cortex. (Simons et al. [1999]).

4.2.2 Entorhinal Cortex

The entorhinal cortex (BA28) is included in the parahippocampal gyrus next to the perirhinal cortex and is part of the hippocampal formation. It is located in the six-layered ventro-medial surface of the temporal lobe, beneath the amygdaloid complex and the hippocampus. Rostral-medially and caudally it is attached to the

peri-amygdaloid cortex and subiculum respectively. It is approximately 2.5 to 3 cm long (measured from rostral tip to caudal end) (Simons et al. [2001], Mikkonen [1999], Aggleton and Brown [1999]).

The entorhinal cortex has afferents from the perirhinal and parahippocampal cortices, which relay neo-cortical information and provide in total two thirds of all entorhinal input. Most of the connections of the entorhinal cortex are reciprocal, so that it projects back to perirhinal and parahippocampal cortices and also has reciprocal connections to the hippocampus (Simons et al. [2001], Mikkonen [1999], Aggleton and Brown [1999]). Other projections into various layers and subfields of the entorhinal cortex start in the cingulate cortex, the basal forebrain providing cholinergic modulation, the amygdala, and some thalamic and brain-stem nuclei. A main pathway is the *perforant pathway* which connects layer II of the entorhinal cortex to the molecular layer of the dentate gyrus and region CA1 of the hippocampus (Hasselmo et al. [1996], Mikkonen [1999]).

The perforant pathway is considered to be a major pathway for interaction between the neo-cortex and hippocampus; this emphasizes the important role of the entorhinal cortex as a relay station and the effects of its high cortical and sub-cortical connectivity.

The entorhinal cortex is a gateway and an integral component of the hierarchical organization of the medial temporal lobe memory system. It receives sensory information via the perirhinal and parahippocampal cortices, forwards this information to the hippocampus via the perforant pathway and then re-receives hippocampally-processed information (Mikkonen [1999]).

4.3 Frontal Lobes and Prefrontal Cortex

About one third of the human cerebral cortex is occupied by the frontal lobes. Each of the frontal lobes consists of three main sub-areas: the primary motor cortex (superior frontal lobe), the pre-motor cortex, and the prefrontal cortex (anterior frontal lobe). The prefrontal cortex covers the largest surface of the frontal lobes and is subdivided into a medial and lateral surface. The lateral surface of the prefrontal cortex is split again into ventro-lateral and dorso-lateral. The anterior prefrontal regions and the most anterior tip of the frontal lobe are denoted as the orbital frontal region (or orbito-frontal cortex).

The prefrontal cortex is connected reciprocally to medial temporal lobe regions via the sub-cortical medial dorsal nucleus of the thalamus. Other complex connections exist between some regions of the prefrontal cortex and sensory and association areas in posterior cortical regions, and to some limbic structures (Shimamura [1995], Simons and Spiers [2003]). The orbito-frontal cortex projects directly to the entorhinal cortex and has connections to the insular cortex, which in turn is connected to the perirhinal and entorhinal cortices (Mikkonen [1999]).

Frontal lobes in general are thought to be responsible for cognitive executive functions, such as planning, problem solving, working memory, temporal memory,

information organization and inhibitory control responses. The orbital prefrontal cortex is associated with personality. Broca's area in the prefrontal cortex is well-known for language production. In patients with frontal lesions, all these functions are in some way disturbed, depending on the exact location of their frontal atrophy.

In functional imaging studies during memory tasks, co-activation of medial temporal lobe regions and the prefrontal cortex have been demonstrated. The prefrontal cortex also shows activation when novel stimuli occur. This has led researchers to the conclusion that interactions between the prefrontal cortex and the medial temporal lobe are crucial elements of the network of systems and memory processes (Simons and Spiers [2003], Golby et al. [2001]).

The planning and monitoring of memory retrieval processes may require frontal resources in a reconstruction process, and frontal lesions can therefore lead to memory malfunctions in semantic and episodic retrieval. The inhibition capability of the frontal lobes may function as a dynamic filtering or gating mechanism in memory retrieval. Damage here may result in impaired retrieval of the contextual information of an experience, due to the absence of the filtering or gating which controls the mutual activation of memory patterns, making relevant information more salient than associations not belonging to the specific memory. This concept would suggest various other behavioural and processing deficits which result from frontal lobe damage. All the brain processes that need frontal inhibitory control would not output adequately (Kopelman [2002], Nestor et al. [2002], Shimamura [1995]).

It was also proposed that frontal lobe lesions impair the process of encoding and registering semantic information. Simons and Spiers made a concrete proposal on the interaction between medial temporal lobe and prefrontal cortex during encoding. After uni- and poly-modally processed information arrives in the medial temporal lobe with the goal of becoming a long-term representation, this information has to be transformed, associated and integrated with all its different characteristics to make up a bound higher-level representation. To facilitate these processes, the prefrontal cortex provides variable top-down control to the medial temporal lobe encoding process. The prefrontal innervation effectuates the modification of the representations and forces them to be as non-overlapping as possible, in order to make them more invulnerable during long-term transfer and in their long-term storage sites (Simons and Spiers [2003]).

Various characteristics of stimuli (type of material, for example, lexical versus non-lexical input) as well as different information-processing goals (encoding versus retrieval) can influence the activation of different prefrontal regions during their interaction with the medial temporal lobe memory system. For example, the anterior left inferior prefrontal cortex and anterior ventrolateral prefrontal regions are active during tasks that require controlled semantic processing and are thought to hold strategies for encoding processes on verbal and other strategically applicable stimuli. The posterior ventrolateral prefrontal cortex is active during phonological processing (Golby et al. [2001], Simons and Spiers [2003]).

4.4 Perceptual Systems Contributing to Episodic Memory

Patients with semantic dementia show their ability to acquire new episodic information through their relatively good performance in recognition memory tests, especially for perceptual identical (PI) items. In Graham et al. [2000] the authors investigated in more detail semantic and sensory/perceptual contributions to the formation of new episodic memories. Their test patients with semantic dementia (including J.H.) had impaired semantic knowledge, but relatively preserved episodic knowledge (contradicting the predictions of Tulving's SPI model). They were presented pictures of objects still semantically known or semantically unknown to them. In the testing session, pictures with the same objects were shown, but some of the objects were depicted from another perspective.

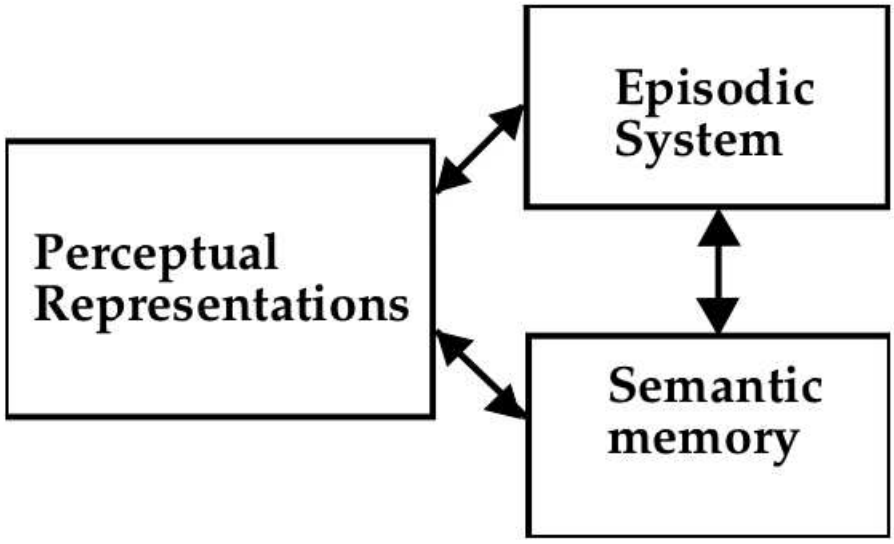
The only test constellation where the subjects showed impaired episodic memory was when a perceptually different (PD) object about which they had no semantic knowledge was presented. In another experiment with the patients D.M. and S.L., the same procedure was used but with faces instead of objects on the pictures. The effects on recognition memory were the same as with general objects. A significant difference was found between PI/known and PD/known faces, with the patients recognizing PI/known faces better. There were also differences in both patients' performance on PI/unknown and PD/unknown photographs and between the PD/known and PD/unknown pictures, with the patients recognizing better PI/unknown than on PD/unknown items, and PD/known than PD/unknown pictures respectively.

In general, patients with a disturbed semantic memory system have better recognition for objects and faces which they know and which are presented from a perceptually identical perspective. Unknown objects shown from a different perspective than in the learning session are recognized the worst (Simons et al. [2001]).

It became clear that new episodic learning draws on information from both perceptual and semantic systems (Multiple Input hypothesis) and that patients with semantic dementia can still rely on well-processed perceptual information to develop new episodic memories. For these reasons, the episodic and semantic memory systems seem to be dissociable (see Figure 3 on the next page). The impairments to the semantic system can be partially reduced by perceptual contributions to the episodic memory system. Perceptual representations might provide enough information to reactivate a corresponding episodic memory without any additional semantically-processed input to the episodic memory.

Patients with semantic dementia were tested to have intact perceptual processing. Even at the late stages of the disease, when their recognition performance declines, this drop is not due to any perceptual limitations and has to have other pathological causes, such as the involvement of other and more medial temporal lobe areas (Simons et al. [2001, 2002], Graham et al. [2000]). The reason why patients with semantic dementia do not learn words as fast as, for example, spatial objects may be that letters do not provide rich visual information (spatially-

Figure 3: Graham et al. revised the SPI model of Tulving. Both semantic and episodic learning can draw on input from perceptual systems to form new memories. Both memory systems are dissociable. They are interactive, but are not strictly dependent on each other as in Tulving's SPI model (Graham et al. [2000]).



arranged bars, and (semi-) circles), so that the contributions of the perceptual systems to episodic memory are not that valuable (Simons and Graham [2000]). The Multiple Input hypothesis also explains why normal subjects can remember information about which they have no semantic information (Graham et al. [2000]).

4.5 Other Cortical and Subcortical Structures

Various other cortical and sub-cortical areas of the human brain also contribute to memory processes, reflecting the "overall nature" of memories.

During the recollection of autobiographical memories, visual imagery and auditory representations may play critical roles. If the visual or auditory cortices are atrophied, some memory representations lose their visual and auditory associative connections, and critical memory components cannot be retrieved, finally resulting in the inability to reactivate other aspects or the complete pattern of the representation. That is why patients with atrophied visual areas show a severe retrograde amnesia with no temporal gradient, but no anterograde amnesia (Nestor et al. [2002]). Visual representations linked to old memory traces are destroyed, but new visual associative connections can appear as long as the large visual cortex is not completely destroyed.

Procedural learning and skill memory are affected if the basal ganglia are atrophied. But patients with such damage do not show any impairments in episodic or semantic memory. Additionally, the cortico-striatal system and the cerebellum are involved in the acquisition of motor skills and procedural memory respectively.

Amygdaloid contributions to memory representations ensure emotional col-

orization of experiences (Markowitsch [1995]).

As formulated above, the hippocampus has connections through the fornix to the mammillary bodies and anterior thalamic nuclei. Aggleton and Brown (Aggleton and Brown [1999]) see this link of the medial temporal lobe memory system to the two diencephalic structures as functional extensions of the hippocampal system and important for normal hippocampal activity and episodic memory. Damage to the mammillo-thalamic tract is a proven cause of amnesia. They proposed a model of a medial-temporal diencephalic memory system. The model emphasizes the connections between the regions CA1-CA4, the dentate gyrus and the subiculum to the mammillary bodies and the medial thalamus. In turn, the mammillary bodies and the medial thalamus both have connections into the anterior thalamic nuclei. This neuronal route allows diencephalic modulation on temporal lobe memory processing. To substantiate their model, the authors report on some patients with damage to the fornix, which is the main connector between the hippocampus and the diencephalic structures. The patients all displayed a loss of recent verbal and non-verbal memory, ascribed to the fornix damage. Their poor performance on tests of verbal memory indicates how well-balanced tests of memory have to be in order to reveal the subtle memory performance differences resulting from the dispersed loci of atrophied brain tissue.

In summary, Aggleton and Brown highlight the fact that the *hippocampus-anterior thalamic axis* is an extension of the medial temporal lobe system and therefore indispensable to the creation of associative episodic scenes and to the facilitation of discrimination processes and memory retrieval (multiple process model of recognition) (Aggleton and Brown [1999]).

4.6 Laterality

Asymmetrical pathological patterns, often evident in patients with semantic dementia, have been included in discussion of the coherence of episodic and semantic memory and their specific brain sites. The most prominent lateralized effects (spatial processing is right-hemispheric and verbal processing is left-hemispheric) have been extended into the memory domain.

Like visual imagery, which is strongly associated with the right hemisphere, the retrieval of episodic memories in a reconstructive process reinforced by visual imagery depends more heavily on the right temporal lobe. The left temporal lobe is proposed to be more responsible for the storage and access of semantic and lexical information (Kopelman [2002]).

Asymmetrical activation patterns also occur in the medial temporal lobe and frontal regions, depending on the type of material to be encoded. Word-encoding activated more left-side prefrontal regions and pattern-encoding activated more right prefrontal regions, with the activation being not unilateral but asymmetrical. Hence, memory for verbal material is more likely to be impaired after left-hemispheric lesions, while a right-hemispheric lesion is followed by poorer mem-

ory for non-verbal material.

Further lateralized activation was revealed through functional imaging studies which examined the influence of the processes involved in memory acts. Independent of the type of material, encoding material into memories typically produced left-lateralized medial temporal lobe and frontal activation, whereas retrieval processes were more right-hemispheric (Golby et al. [2001]).

As noted above, portions of the parahippocampal gyrus (and maybe hippocampus) support face recognition. Laterality studies demonstrated that only right atrophy affected the performance of patients with semantic dementia on the recognition memory test for faces, and that damage to only the left medial temporal lobe seems to have no impact on the recognition of faces (the patients performed in the range of healthy control participants). A bilaterally damaged individual's performance was hardly better than that of the right-atrophied group. This means that right-sided parahippocampal regions are critical for face recognition (Simons and Graham [2000], Simons et al. [2001], Murre et al. [2001]).

In patients with semantic dementia, both anomia and comprehension deficits are mostly linked, but at an early stage of the disease some patients have more naming problems than comprehension deficits, and others behave vice versa. Lambon Ralph et al. found this to be due to asymmetrical atrophied regions of the temporal lobe. Patients with a left-sided temporal lesion suffer a serious anomia. Bilateral lesions produce comprehension impairment. But, as the disease progresses and the pathology becomes more bilateral, comprehension and naming equalize and are reduced to the same lower level. This offers conclusions concerning the source of the anomia in patients with semantic dementia. Comprehension problems point to a pure semantic source of the naming deficits, whereas patients who still comprehend but cannot name things may have post-semantic processing deficits (Lambon Ralph et al. [2001]).

4.7 Summary

Medial temporal lobe structures (for example the hippocampus, and the entorhinal and perirhinal cortices) have been widely associated with memory function. The different substructures of the medial temporal lobe work in concert with multiple other cortical and sub-cortical brain areas in order to make normal memory performance possible. The hippocampi have been associated with the rapid storage and retrieval of memories and with consolidation. Damage to the perirhinal cortex usually predicts recognition memory deficit. The entorhinal cortex functions as a gateway or relay-station between the medial temporal lobe memory system and the neo-cortical memory regions. The distinguishable activation of different temporal and frontal cortical regions suggest different but related roles of both regions in long-term memory storage and retrieval. The importance of the contribution of perceptual systems to episodic memory as well as the involvement of various other cortical and sub-cortical areas of the human brain in memory processes re-

flect the "overall nature" of memories. Asymmetries in pathological patterns or in neuronal activation during memory processing further determine the special roles of specific brain regions.

The exact contributions of each of the neural systems involved in memory processes and in consolidation have not yet been identified in full detail. Theories of consolidation often only name the gross location of memory-supporting brain areas, like the medial temporal lobe or neo-cortex. Nevertheless, current theories on consolidation offer clearer views on how and when the consolidation process may take place. Some of them are presented in the next chapter.

5 Consolidation

Consolidation refers to the neuro-biological process of fixing memories over time in order to make them more resistant to forgetting. The term "consolidation" was introduced by Georg Elias Müller and Alfons Pilzecker in 1900 as a result of various memory experiments which they conducted. They discovered that permanent memories are not acquired instantaneously, but rather need some time to become fixed by internal psychological processes. The intermediate unconsolidated memories are meanwhile more vulnerable to decay.

In 1949 Hebb postulated the dual trace theory of memory formation: Structural and functional changes at the molecular level of nerve cells, their dendrites and especially their synapses induced by neuro-chemical mechanisms were found to be the underlying biological principle of memory. These underlying molecular mechanisms appear to be long-term potentiation (LTP) and long-term depression (LTD). The hippocampus has proven to be a brain region of high plasticity, with LTP as the basic mechanism at the neural level, and is therefore a likely candidate for the speedy encoding of episodic memories. Hippocampal synapses are capable of changing quickly, thus enhancing fast learning, but also fast forgetting. Neocortical synapses have a much lower plasticity and only change slowly (Lechner et al. [1999], Alvarez and Squire [1994]).

Later, Alvarez and Squire proposed that the neural substrate of consolidation is a process of *"gradual binding together [...] geographically separated areas that together store the representation of the whole event "* (Alvarez and Squire [1994]). The medial temporal lobe and the neo-cortex are the brain regions where the consolidation processes are thought to take place. The functions attributed to these structures vary somewhat, for example, according to their temporal involvement in consolidation and retrieval processes. The neo-cortex has been identified as the permanent storage-site for long-term memories. The hippocampal complex in general has been associated with the acquisition and initial retrieval of episodic and semantic memories and the transfer of these memories into long-term stores (Nestor et al. [2002], Markowitsch [1995]). It was suggested by Marr that the hippocampus provides some form of "simple memory" and temporary store, and that it is able to store new data instantly (auto-associator). Other researchers do not think

that the hippocampus acts as a store but is rather an "orienting system", signaling to the neo-cortex the need to form a new memory representation. A further concept of the hippocampus, as an indexer connected to event-induced neo-cortical representations, emphasizes the role of hippocampal links as retrieval cues for the original patterns in the neo-cortex (Alvarez and Squire [1994]). Although there are suggestions that consolidation may be intrinsic to neo-cortical structures, the gradual modification, reorganization and stabilization of neo-cortical representations is generally thought to be managed by the medial temporal lobe (Lechner et al. [1999], Hasselmo and McClelland [1999]).

The standard model of memory consolidation is a widely-accepted view of how the hippocampal complex and neocortex might interact during consolidation. Both fulfill complementary but differing roles in long-term memory acquisition and maintenance. Components of an experience activate corresponding neocortical representations, which are then bound together through the hippocampus. In this recent form, memories of an experience can only be retrieved with involvement of the hippocampi. Then, repeated re-activation of hippocampal cells bound to the neo-cortical representations (hippocampal-neo-cortical ensembles) enables connections to be formed between these representations, which are subsequently strengthened. After the cortical ensemble of neurons is strongly connected, the retrieval can be done without the mediating support of the hippocampal complex. The memory becomes hippocampally independent and is now maintained by neo-cortical long-term storage sites. At least early in the disease, patients with semantic dementia have an advancing pathology in the temporal neo-cortex and spared medial temporal lobe regions. According to the standard model of memory consolidation, this would result in loss of solely cortically represented (long-term) knowledge and unimpaired encoding and retrieval of recent memories, which are still hippocampally dependent. This is actually true for semantic dementia.

According to the standard model of memory consolidation the impairment of long-term memory in patients with semantic dementia is influenced by two factors. 1. When neo-cortical sites are destroyed, no (or only limited) formation or strengthening of connections between neo-cortical neuronal ensembles can take place. 2. The limited capacity of the hippocampus is not sufficient to emulate neo-cortical storage capacities. This results in the relatively fast re-assignment of hippocampal representation units to newly to-be-encoded material and the forgetting of older recent information (Nestor et al. [2002], Murre et al. [2001]).

Until it is clear exactly how the hippocampus is pathological in semantic dementia, another theory of memory consolidation may give valid explanations for episodic memory impairments. The multiple trace theory of memory consolidation was introduced by Nadel and Moscovitch and is a reformulation of the standard model. They excluded semantic long-term memory encoding and consolidation processes from their theory, because they thought that these take place without medial temporal lobe involvement. The multiple trace theory is therefore only valid for the domain of episodic, autobiographical memories. It claims

that consolidation is the strengthening of intra-hippocampal connections between hippocampal memory representations.

The initial stages of memory acquisition are similar to those in the standard model of memory consolidation. Activation in the neo-cortex and other geographically distant areas representing different aspects of an experience are bound together by the hippocampal complex to form a cohesive memory trace. The medial temporal lobe component of that trace now functions as a pointer to or index of the different neo-cortical representations and is the access gate to retrieve all the details of the memory trace. If that memory trace is retrieved repeatedly over time, re-coded traces of the corresponding experience are created within the hippocampal complex. The different sub-regions of the hippocampal complex may have distinct functionalities according to different aspects of stimuli. They may therefore store the traces for these different aspects. The additional multiple traces are highly related to each other and are widely distributed in the medial temporal lobe regions. This implies that older memories, which have been remembered more often, have more corresponding and multiply-coded memory traces, and are more widely distributed than younger memories. The higher number and wider dispersion of traces for old memories reduces the vulnerability of a specific memory to selective hippocampal lesions.

Contrary to the standard model, in the multiple trace theory the medial temporal lobe structures are necessary for the retrieval of memories from the whole lifetime. Hence these are needed as long as the memory of that experience is needed. Lesions affecting the whole hippocampal region would result in complete amnesia: the loss of all region-dependent memories and the inability to bind together new cortical representation and to form new memories. Incomplete lesions would entail a temporally-graded amnesia. Older memories may stay better-preserved than younger memories, due to their multiple traces in widely distributed regions. The wider a lesion is, the more the retrieval of memories from distant time periods is affected. The multiple trace theory therefore cannot explain the temporal-gradients in memory retrieval seen in semantic dementia with the extent of lesions to the hippocampal complex[6]. Nadel and Moscovitch proposed that semantic systems connected to the episodic memory systems may provide additional cues for memory retrieval, especially for memories with a significant semantic component. Damage to semantic structures supporting such memories therefore results in impaired episodic memory retrieval (Murre et al. [2001], Nestor et al. [2002], Moscovitch and Nadel [1999], Graham [1999]).

To summarize: consolidation is dependent on the following premises. The hippocampal region is capable of fast and one-trial learning, so it learns quickly, but has only limited capacity (Alvarez and Squire [1994]). The rapid hippocampal

[6]Nevertheless the multiple trace theory can explain temporal gradients seen in retrograde amnesia caused by medial temporal lobe lesions. Patients with medial temporal lobe amnesia show retrieval deficits for events extending back 25 to 40 years. This was what led researchers to the assumption that the hippocampal complex might be important for the retrieval of memories from all times (Murre et al. [2001], Nestor et al. [2002]).

plasticity is possibly due to changes of synaptic strength according to simple hebbian learning rules (Alvarez and Squire [1994]). On the other hand, the neo-cortex supports slow and gradual learning and has a huge capacity (Alvarez and Squire [1994]). In neuro-anatomical investigations it was found that hippocampal lesions do not correlate with long-term memory loss, but with a temporally-graded retrograde amnesia in episodic memory (Hasselmo and McClelland [1999]). After that, the neo-cortex is the seat of long-term permanent semantic and episodic memories independent of the medial temporal lobe, whereas the hippocampal complex is only temporarily involved in episodic memory. Temporary memories have to be carefully and gradually integrated into the existing network of knowledge and experience (interleaved learning), to avoid interference effects with older memories (Hasselmo and McClelland [1999], Alvarez and Squire [1994]).

One question which remains open is when consolidation occurs. It is not clear whether it is a continuously-occurring process or whether there is a special brain state during which consolidation might occur. If consolidation is a continuous process, questions arise as to how consciousness may or may not be involved in this process. If consolidation occurs during a special state of brain activity, this state and its characteristics have to be identified (Alvarez and Squire [1994]).

Two proposals have been made for such states. There are indications that consolidation might occur during the REM phase of sleep or during slow-wave sleep and quiet alertness. Slow-wave sleep is characterized by sharp electrical waves in the hippocampal region (Alvarez and Squire [1994], Meeter and Murre [2002], Murre et al. [2001], Gluck and Myers [1997]). During active waking, when animals explore their environment and encode new information, a theta rhythm is present in the hippocampus (Hasselmo [1999]).

Hippocampal electrical activity during the slow-wave sleep phase is markedly different from that in the encoding phase of active waking. Animal studies revealed that the hippocampal region echoed activities from the active waking environment-exploring phase during slow-wave sleep. This was interpreted in that the hippocampus reinstated patterns encoded during active waking and presented them to the neo-cortex during slow-wave sleep for the purpose of consolidation (Gluck and Myers [1997], Hasselmo [1999]).

This evidence suggests that the hippocampal region might operate in two different modi: one for fast encoding and storage of information, and another in which the consolidation process is promoted (two-stage model of memory consolidation; Gluck and Myers [1997], Hasselmo [1999]). The different modes correlate with specific EEG phenomena in the behavioural states of initial acquisition and subsequent consolidation of long-term memories. The sharp electrical waves seen in the hippocampus during slow-wave sleep correlate with EEG phenomena in cortical areas like the prefrontal cortex – another hint to the interaction of the medial temporal lobe regions and the neo-cortex in consolidation processes. This could be the phase in models of consolidation, when the repeated reactivation of medial-temporal neo-cortical neural ensembles strengthens the connections

between the memory-representing cell units.

Recent research indicates that the two modi could be set by the modulating influence of the neuro-transmitter acetylcholine. The levels of acetylcholine fluctuate parallel to active waking and slow-wave sleep, with high acetylcholine levels in the former case and lower levels in the latter case (Hasselmo [1999]).

5.1 Modeling Consolidation and Semantic Dementia

Computational models are important tools for extending our knowledge about memory and learning mechanisms. They are mostly based upon psychological theories and neuroanatomical findings (Gluck et al. [2003], Murre et al. [2001]). Substantiated by these theories and constraints, Felleman and van Essen, 1991, and Zola-Morgan and Squire, 1991, worked out a neuro-anatomically based framework for computational connectionist models. According to this framework, the hierarchy of interconnected brain areas involved in memory processes, the importance of medial temporal lobe areas (for example, the entorhinal and perirhinal cortices, the parahippocampal gyrus) and the hippocampus in long-term memory consolidation, as well as the high and bi-directional connections between the neocortex and the hippocampal region, are biological facts that should be embedded into models.

The TraceLink model of Murre et al., as well as the models of Alvarez and McClelland, all assume this framework and additionally the precept that the neocortex and hippocampus are distinct but complementary portions of long-term memory during the consolidation process (Murre et al. [2001]). In section 3.1 in Murre et al. [2001] there are some notes as to why two complementary memory systems have evolved, one for rapid and one for slow learning. A more general assumption made by modelers of long-term memory, especially in the domains of episodic memory and consolidation, is that the hippocampus, as a relatively small and *temporary* store of memories, interacts with a large *permanent* repository memory system in the neocortex (Gluck and Myers [1997]). This implies that there are two different time courses for memory formation which take place in two different structures (hippocampus and neocortex, respectively) (Hasselmo and McClelland [1999]).

Computational models of consolidation often take the standard model of consolidation as a basis. Stimuli activating the neocortex through sensory systems subsequently activate hippocampal cells, which in turn feed back to the neocortex, (re-)activating patterns or new cell populations. New associations between neo-cortical active cells are formed and the memory representation is enhanced (connections are strengthened). The hippocampus-mediated consolidation process may take repeated presentation of recently-acquired and temporary hippocampally stored memories to the neocortex (but no additional input from the external world), to ensure the integration of the new information into the existing net of knowledge and to prevent interference effects (Gluck and Myers [1997]). This two-

stage consolidation process assumes high synaptical plasticity in the hippocampus, enabling the rapid storage of a representation after a single exposure to the initiating stimulus, and a lower synaptic modification mechanism in neo-cortical structures, possibly reflecting an elaborated knowledge integration process (Hasselmo and McClelland [1999]).

There are different possibilities for representing memories in connectionist models. The most prominent of these is the representation through a spatial pattern distributed across a population of neurons. A specific memory is therefore a cluster of activated, but distributed, neurons in an attractor state. These fixed-point attractor systems are usually networks with extensive excitatory feedback connections. Another way of representing memories is as a sequence of activity patterns in a neural network. Chains of specific subsequent patterns are the memory traces; they are the means of representing inter-item associations or pathways through the environment (Hasselmo and McClelland [1999]). This latter kind of representation is more often used in computational models of the hippocampus simulating incremental learning, which is another function the hippocampus is thought to be responsible for[7](Gluck et al. [2003], Gluck and Myers [1997]).

Semantic dementia and amnesia both offer insights into the organization of long-term memory, and computational models should be able to simulate the memory phenomena seen in both diseases, as well as normal memory functions in healthy subjects (Meeter and Murre [2002], Murre et al. [2001]).

5.1.1 TraceLink

TraceLink is a model of long-term memory which makes specific reference to semantic dementia. It will therefore serve here as an example of how our knowledge of semantic dementia and the implications for organization of long-term memory constrain and help to develop models of consolidation.

The TraceLink model consists of three connected systems: the trace system, the link system and a modulatory system.

The trace system roughly represents the neo-cortex in this model. It functions as the permanent store of memory traces, where a trace is a distributed pattern of activated trace nodes. Trace nodes are high in number, reflecting the high capacity of human long-term memory. If they belong to the same memory they are connected to each other in variable strength (cortico-cortical connections). Input to the trace system comes from perceptual and sensory areas and it outputs to, for example, motor areas or temporal neo-cortical association areas. These systems are not explicitly included in the model but are assumed.

The link system is the module representing the hippocampus and other medial temporal lobe structures responsible for temporary storage of long-term memo-

[7]Learning mechanisms such as sequential learning and spatial navigation may take place in the input regions of the hippocampus, whereas declarative memory functions such as storage and recall of episodic memories may be localized in the hippocampal regions CA1 and CA3 (Gluck and Myers [1997]).

ries. It contains a much smaller number of node elements than the trace system. The link nodes are connected to each other in random fashion and also make links to trace nodes. The higher plasticity of connections involving link elements is ensured through modulation of the modulatory system, which is closely connected to the link system in the TraceLink model. The link system also makes connections from link nodes to trace nodes, to strengthen their cortico-cortical connections or to make new connections between trace elements. The smaller capacity of the link system corresponds to the known limitations of temporary long-term stores and results in interference during new learning, as nodes of old representations are very likely to be reassigned to form new memories.

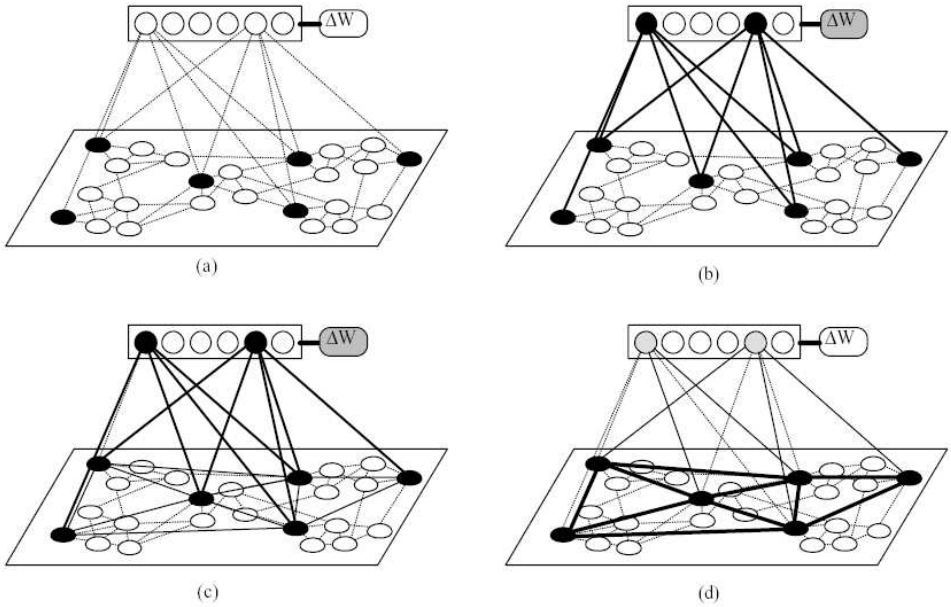
As mentioned above, the modulatory system's activation causes increased plasticity in the link system. It is not yet clear which neuro-chemical and physiological mechanisms are crucially involved in this modification, and therefore the modulatory system is not implemented in much detail in TraceLink. Candidates for the modulations to take effect are cholinergic innervation from the basal forebrain or perhaps norepinephrine release arising from the amygdaloid system. Activation of the modulatory system may occur through stimulus properties such as intensity or novelty, or through central states such as arousal and attention (Murre et al. [2001]).

The formation of a long-term episodic memory trace in TraceLink comes in four stages (see Figure 4 on the following page). The activation of sensory and motor channels in turn activates a set of nodes in the trace system. These elements initially have no direct cortico-cortical connections, but are connected to some nodes in the link system and represent the episode to be remembered (Stage 1). Then, after the trace nodes have activated some link nodes, the modulatory system becomes active and modulates the learning rate of link nodes to facilitate the formation and strengthening of trace-to-link connections. This period of increased plasticity takes seconds or minutes (Stage 2). Now the link system repeatedly activates the trace nodes of the memory trace, which enables the formation and gradual strengthening of connections between these associated trace nodes (consolidation). Synapses along long distances can arise or chains of connected neurons are formed to connect distant cortical areas (Stage 3). Finally, the trace-to-trace connections become very strong and the link-to-trace connections have decayed or already been reassigned to new memory traces. The cortical representation of the memory trace becomes independent of innervation of the link system and is a fully-qualified long-term memory (stage 4) (Murre et al. [2001]).

5.1.2 Simulations of Semantic Dementia

Recall in the model corresponds to the retrieval of a whole trace pattern as the result of cueing with a part of the trace. Stage 4 memories are speedily re-activated through the strong and direct cortico-cortical connections of the trace nodes of the

Figure 4: A schematic drawing of the TraceLink model with its three main components during the four stages of memory acquisition and consolidation (see text for explanations). The modulatory system is labeled ΔW. The link system contains nodes to a lesser extent than the trace system. Activated nodes are shown in black, an activated modulatory system is shown in grey (Meeter and Murre [2002]).



cue pattern to the rest of the full memory trace. If a cue to a stage 2 memory is offered, the activation of the full set of representing trace nodes still needs connected link system elements to be activated (Murre et al. [2001]).

To simulate semantic dementia in the model, the trace system was lesioned. The removal of trace elements as well as trace-to-trace connections simulates the atrophy of the temporal neo-cortex seen in patients with semantic dementia, at least in an early state of the disease where the medial temporal lobe structures (the link system) do not seem to be atrophied. The lesions in the trace system were set in such a way that far more cortico-cortical connections were removed than trace nodes, reflecting the possibly greater vulnerability[8] of the connections than of the trace nodes.

With these lesions, and the complete sparing of the link and modulatory systems, the model is still able to receive input into the trace system from the perceptual and sensory areas. Activated trace nodes can still activate link nodes through the random link-to-trace connections, and the well-functioning link and modulatory system transform the stage 1 activation into a stage 2 memory. Nevertheless, the formation of stage 3 memories and subsequently stage 4 memories is severely impaired in the TraceLink model with simulated semantic dementia. As the lesion has eliminated a lot of cortico-cortical connections, there are not enough contacts

[8]Cortico-cortical connections connect remote areas, and are not functionally organized as in neuronal ensembles or in hyper-columns, which have a greater redundancy, and which are therefore less vulnerable (Murre et al. [2001]).

left to support the formation of a stable new, link system independent, representation in the trace system. The consolidation process cannot occur. When the link-to-trace connections from stage 2 decay and/or become reassigned to new traces, the memory is virtually lost. (Murre et al. [2001])

The simulations of semantic dementia in TraceLink have evidently produced three of the most common deficits which are seen in real patients with semantic dementia. As the lesion affected a lot of trace-to-trace connections, the model lost a relatively large number of previously existent and well-consolidated memories. This corresponds to the extensive loss of semantic facts in patients. Patients with semantic dementia have been shown to have intact new episodic learning, and the model simulates this correctly by correctly transferring stage 1 activation to stage 2 (link system dependent) memories. These recent memories are recalled relatively well by patients and TraceLink, and this may be the reason for the temporal step-function in recall of episodic memories in patients with semantic dementia. However, as reported above, the limited capacity does not allow as many memories to be stored in the link system as would be possible in the trace system and strong interference effects occur. This leads to the faster forgetting seen in patients and in the lesioned model. With decreased connectivity in the trace system, only minimal connections between trace nodes are possible, so a permanent memory trace can hardly be established in the trace system. Regular rehearsals may prevent this loss of memories, by storing them consistently as stage 2 memories.

Variations in the size of the lesions to trace nodes compared with those to trace connections have also been simulated. The lesion described above consisted of 80% connection loss and 10% trace node loss. In the variations, lesions to the nodes were between 0% and 40% and lesions to the trace-to-trace connections varied between 0% and 100%. It was found that new learning was relatively unaffected if the connectivity of the trace system was lesioned, but was greatly impaired when trace nodes were eliminated, declining with the number of eliminated trace nodes. Increasing lesions to both nodes and connections in the trace system was shown to increase the retrograde amnesia of TraceLink. Loss of nodes causes impaired new learning.

In summary, TraceLink is able to model the pattern of intact episodic learning combined with accelerated forgetting, the loss of long-term information and the temporal gradient seen in semantic dementia (Murre et al. [2001], Meeter and Murre [2002]).

To model amnesia in TraceLink, in contrast to semantic dementia, a lesion to the link system is made. This corresponds to the damage to medial temporal lobe structures, which are mostly affected in amnesia and are thought to be part of the biological substrate of the link system (Murre et al. [2001]). The TraceLink model simulates amnesia as well as semantic dementia and no additional assumptions had to be made for one or the other disease. This speaks for TraceLink as a valid model for both diseases and consequently for the interaction of hippocampus and medial temporal lobe with the neo-cortex in normal episodic memory acquisition

and long-term storage (Murre et al. [2001]).

6 Summary and Conclusions

A specific pattern of semantic and episodic deficits and pathological changes in the temporal lobe can be extracted from the patient cases in section 3.7. Semantic memory is severely impaired, with subordinate conceptual knowledge being affected at the beginning of the disease. During the disease's progression superordinate semantic knowledge becomes affected as well, and finally semantic knowledge completely breaks down. Semantic knowledge can not be re-learned by patients with semantic dementia. Episodic memory deficits disclose a temporal step function in episodic retrieval in semantic dementia. Recent episodic memories from the last two to three years can be better remembered by patients than more distant episodic memories. New episodic learning is still possible in a limited manner.

The corresponding brain damage is mostly evident in the left temporal neocortex (temporal pole, infero-lateral temporal lobe, anterior temporal lobe). Bilateral damage is mostly asymmetrical with more left-hemispheric than right-hemispheric damage. Damage to the left parahippocampal gyrus and the hippocampus may be sometimes evident in semantic dementia, but more often, the right temporal lobe and the medial temporal lobe regions (hippocampus, parahippocampal gyrus, perirhinal and entorhinal cortices) in both hemispheres are not pathological in patients with semantic dementia.

The pathology and symptoms found in semantic dementia indicate that damage to temporal neo-cortical regions corresponds highly to the loss of previously learned semantic knowledge. This area therefore seems to be the location of semantic long-term memories or is crucially involved in semantic processing. Research from amnesia and semantic dementia revealed that regions of the medial temporal lobe are involved in the processing of episodic memories. The perirhinal cortex supports recognition memory and the hippocampi have been associated with the rapid storage and retrieval of memories and with consolidation. As patients with semantic dementia initially have relatively well-preserved medial temporal lobe structures, but exhibit a reverse Ribot effect in memory retrieval, it was concluded that the hippocampus and related medial temporal lobe structures play a time-limited role in the initial formation and maintenance of recent memories, but that these structures are not involved in the retrieval of long-term episodic memories. Therefore, medial temporal lobe structures have to be additionally responsible for consolidation – the transfer of recent memories to the neo-cortical regions, which are thought to store or index long-term episodic memories or components of them. The entorhinal cortex functions as a gateway or relay-station between the medial temporal lobe memory system and the neo-cortical memory regions.

The interaction between different sub-regions of the temporal neo-cortex, the medial temporal lobe and other cortical and sub-cortical areas which contribute to

memory are intricate. Additionally, some brain regions contribute to both episodic and semantic memory, or semantic and episodic memory processes require similar processing resources on these structures. That means, that one brain region can be involved in more than one psychological memory process, which makes it more difficult to find exact mappings between psychological dissociations of memory and their biological substrates. Some specific interaction between episodic and semantic memory, and between their biological substrates, can be concluded from the presented patient cases. If semantic contributions are a vital component of an episodic memory the patients exhibit impairments, as seen in the picture recognition experiments with perceptually identical or different stimuli about which the patients knew or did not know semantic information. This also introduced into the discussion the hypothesis that it is not the semantic system alone that feeds the episodic memory system, but that additional input into episodic memory comes from sensory/perceptual brain regions (Multiple Input hypothesis), and that patients with semantic dementia can still rely on this sufficient sensory/perceptual information to encode new episodic memories[9]. Contributions of the episodic memory system to semantic memory are also evident in patients with semantic dementia. Patients have shown to have some sort of autobiographical-cued semantic memories, that is, autobiographical experiences facilitates maintaining and remembering semantic facts, which are related to the patients' life.

The majority of theories and models of consolidation highlight the interaction between the hippocampal region and the neo-cortex to explain long-term memory storage and retrieval. They make suggestions about the possible temporal course of consolidation; neuro-anatomically based models such as TraceLink even make it possible to simulate the effects of different lesions or brain states on memory acquisition, consolidation and retrieval. The TraceLink model can simulate some deficits resulting from specific lesions, as seen in diseases like semantic dementia or amnesia, very well, and may therefore be a valid model for long-term memory and consolidation. The loss of long-term memories in semantic dementia corresponds to the loss of stage 4 memories in TraceLink. The fast forgetting is analogical to the inability to transfer stage 2 memories into stage 3 memories. The preservation of new learning and of recent episodic memories is explained with a still functional link system and the ability to acquire and to retrieve stage 2 memories.

TraceLink and the Multiple Input hypothesis explain differently why new episodic learning is possible in semantic dementia. TraceLink proposes intact abilities to acquire stage 2 memories and the multiple input hypothesis attributes new episodic learning abilities to intact perceptual processing in patients with semantic dementia. Therefore, a combined account of both approaches, including results from neuro-psychological research, may help to differentiate the contributions of different sub-structures of the medial temporal lobe, which are represented in TraceLink as a unity.

[9]It should not be forgotten that a memory consist of and includes several associative components (like olfactory, visual or auditory associations), and that the storage sites of these components are often in cortical areas corresponding to the associated perceptions.

The link system of TraceLink may be extended according to the following premises, which emerged from research on semantic dementia. The entorhinal cortex has been described as a bi-directional relay-station and interaction site of neocortical and medial temporal lobe information. The parahippocampal gyrus, and in particular the perirhinal cortex have been highly associated with recognition processes. Recognition is a kind of memory retrieval which is highly dependent on perception: recognition implies some sort of comparison of stored information with straightly perceived information. Therefore, the parahippocampal gyrus and perirhinal cortex may be part of the perceptual memory systems, which support the relatively well-preserved episodic memory retrieval, as it is documented in the patient cases of semantic dementia and was suggested by Graham et al. Additionally, the perceptual contributions to the formation of new memories have been emphasized.

Under the assumption, that the formation of episodic memories is not just the binding of cortical neuronal ensembles by the medial temporal lobe (as suggested by TraceLink and other theories of consolidation), but concurrently relies on perceptual processing (presumably in the perirhinal cortex), it is very likely that the specific sub-structures of the medial temporal lobe/link system, in particular the hippocampus, the entorhinal cortex and the perirhinal cortex fulfill different roles in the initial acquisition of episodic memories. The entorhinal cortex may relay cortical "content-nodes" (for example, conceptual knowledge or episodic information), whereas the perirhinal cortex may process and relay the perceptual information arising from, for example, visual or auditory association cortices. Finally, the hippocampus might be the region where the overall binding of memory components is accomplished, using its auto-associative capabilites. Furthermore, the entorhinal cortex is known for feeding back to neo-cortical areas. This might occur when perirhinal relayed perceptual information additionally needs content to be assigned to it, in order to form a coherent and complete memory trace.

The trace system of TraceLink may be extended by the specification of subsystems as well. Trace nodes can be assigned to belong to different classes of information and to different cortical substrates. The information the perirhinal cortex relies on in this model comes from neo-cortical association areas. Therefore, one portion of the trace system could represent such perceptual knowledge, which could be further subdivided according to the different possible perceptions. This "perceptual" area of the trace system is connected to the link system, with an emphasis on connections to the perirhinal region. Another portion of trace nodes could represent the conceptual knowledge/semantic memory ("content-nodes"), which is located in the temporal neo-cortex. Again, a further subdivision is possible according to the hierarchical organization of semantic knowledge. The conceptual area of the trace system is connected to link system as well, but the emphasis is now on connections to the entorhinal portion of the link system.

This extended model should still be able to explain what the original model was able to explain, as it still contains the regions and connections of the original

model. A little variance may occur due to additional connections from the added subsystems, but the overall behaviour should not be influenced. The additions made, can give further explanations as to why patients with semantic dementia have well-preserved recognition memory and perceptually based new learning capabilites and how the mutual contributions of episodic and semantic systems facilitate the activation of a whole memory pattern from cues from just one of the systems.

Reflecting different stages of the disease, superordinate semantic knowledge is longer preserved than subordinate semantic knowledge, as, for example, priming experiments in patient A.M. disclosed. The conceptual system of the extended model can be lesioned in a way that simulates the initial loss of subordinate semantic knowledge followed by the loss of superordinate semantic knowledge, in order to investigate the effects of this graded loss on retrieval of episodic memories, which include semantic components and, vice versa, to investigate the influence of episodic activation on semantic retrieval at different stages of the disease. Lesions to different sub-systems of the model and memory experiments using partial episodic, semantic or perceptual cues to re-activate complete memory patterns can be applied to explain as to why new perceptual based learning and perceptually based retrieval is possible and how autobiographical experiences facilitates retrieval of semantic facts relevant to the patient's life (autobiographically-cued semantic memory).

The model makes clear, that remembering a fact or an episode is not dependent on the intrinsic activation of a whole sub-systemic memory pattern, but that, if the activation, which is distributed across different supporting subsystems, is high enough and if the left trace nodes form a still relatively coherent and self-cuing network, a memory pattern can be retrieved even if one of the contributing subsystems is relatively in-functional (as the semantic system in semantic dementia is). According to different cognitive memory tasks (fast-storage, recent retrieval, consolidation, long-term retrieval, semantic retrieval, recognition, associative recall) different portions of the neo-cortex and medial temporal lobe are involved in different processing circuits (multiple levels of interaction). Knowledge about the hierarchy of psychological and biological memory systems in a single processing circuit, as well as the overall interplay between these circuits and their temporal involvement in long-term storage is essential for the understanding of human memory.

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Erklärung

(nach § 7(4) der Prüfungsordnung für Cognitive Science)

Hiermit erkläre ich, dass ich noch keine Bachelorprüfung oder Teile dieser Prüfung im Studiengang Cognitive Science an einer Universität oder gleichgestellten Hochschule nicht bestanden habe.

Potsdam, den _____

Unterschrift _____