Brain and Behaviour

in

Functional Retrograde Amnesia

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To Anna

Because memory and sensations are so uncertain, so biased, we always rely on a certain reality – call it *alternate* reality – to prove the reality of events. To what extent facts we recognize as such really *are* as they seem, and to what extent these are facts merely because we label them as such, is an impossible distinction to draw. Therefore, in order to pin down reality *as* reality, we need another reality to relativize the first. Yet that other reality requires a third reality to serve as its grounding. An endless chain is created within our consciousness, and it is the maintenance of this chain which produces the sensation that we are actually here, that we ourselves exist. But something can happen to sever that chain and we are at a loss. What is real? Is reality on this side of the break in the chain? Or over there, on the other side?

Haruki Murakami: *South of the Border, West of the Sun*

translated by Philip Gabriel (Vintage, London)

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Abbreviations

AA	anterograde amnesia
AC-PC	anterior commissure-posterior commissure
ACTH	adrenocorticotropic hormone
AGI	Autobiographisches Gedächtnis Inventar
BDI	Beck Depression Inventory
BOLD	blood-oxygen-level-dependent
CBF	cerebral blood flow
CT	computer assisted tomography
CVLT	California Verbal Learning Test
d2	Concentration Endurance Test d2
DES	Dissociative Experience Scale
df	degrees of freedom
DNA	deoxyribonucleic acid
EEG	electroencephalography
EPI	echo planar imaging
FAS-Test	Lexical Fluency Test (with letters F, A, S)
FBT	Fragmentierter Bildertest
FDG	^{18}F-fluoro-2-deoxy-D-glucose
Fig.	Figure
fMRI	functional magnetic resonance imaging
FN	Fictitious New
FO	Fictitious Old
FOV	field of view
FPI-R	Freiburger Persönlichkeitsinventar – revidierte Fassung
FWIT	Farbe-Wort-Interferenztest
GSI	global severity index
$H_2{}^{15}O$	radioactive water isotope
HAWIE-R	Hamburg Wechsler Intelligenztest für Erwachsene – revidierte Fassung
HERA	hemispheric encoding retrieval asymmetry
HR	high resolution
IQ	intelligence quotient
ISI	interstimulus interval
LPS	Leistungsprüfsystem
LTD	long-term depression
LTP	long-term potentiation
MBq	microbecquerel
mCi	milliCurie
MCST	Modified Card Sorting Test
MP-RAGE	magnetisation-prepared rapid acquisition gradient echo

MRI	magnetic resonance imaging
n.a.	not administered
NART	National Adult Reading Test
PET	positron emission tomography
PTSD	Post-Traumatic Stress Disorder
RA	retrograde amnesia
rCBF	regional cerebral blood flow
Rey Osterrieth CFT	Rey Osterrieth Complex Figure Test
SCL-90-R	Symptom-Checklist-90-revised
SCR	skin conductance response
SD	standard deviation
SOT	stimulus onset time
SPECT	single photon emission computed tomography
SPI	(s)erial, (p)arallel (i)ndependent
SPM	Statistical Parametric Mapping
STAI	State-Trait-Anxiety Inventory
Tab.	Table
TE	time of echo (echo time)
TEA	Transient Epileptic Amnesia
TGA	Transient Global Amnesia
TI	time of inversion (inversion time)
TMT-A	Trail Making Test – Part A
TMT-B	Trail-Making Test – Part B
TN	True New
TO	True Old
ToM	Theory of Mind
TR	time of repetition (repetition time)
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WMS-R	Wechsler Memory Scale – Revised

Preface

In humans, the ability to remember autobiography and culture essentially determines subjective reality. Without a past, the present self is uncoupled from its development through previous faults and successes, feelings and thoughts, decisions and goals. Likewise, it cannot rely on former relationships with family and friends to guide current behaviour and be a mirror of oneself. Consider the case if the personal past is burdened by conflicts and problems. If a stressful life is suddenly erased in memory – does it not give an opportunity to start anew, to be someone else?

In this study, the syndrome of functional retrograde amnesia is comprehensively investigated across five patients. In this disease loss of remote memories is not accompanied by brain damage and therefore, the conscious or unconscious motivation to forget has to be considered as well. However, as all behaviour has a brain correlate, in these patients, functional metabolic disturbances can underlie the memory deficit. Investigation of the patients' previous life and circumstances under which the amnesia started was conducted. Extensive neuropsychological and psychological-psychiatric evaluation was carried out to enable comparisons across patients. Functional neuroimaging experiments were conducted to compare brain correlates within and across patients while they attempted to retrieve forgotten or accessible autobiographical events. To complement the imaging results, behavioural data for the presented stimuli were acquired following the brain scans.

The first section of the Theoretical Background gives an overview of content-based classifications of human memory. Brain structures associated with differentiable memory systems and memory processes are illustrated focussing on episodic memory. In functional retrograde amnesia emotional factors can underlie the memory deficit, and therefore biological and behavioural relationships between emotion and memory are elucidated. These relations and their possible pathology are illustrated with the examples of Major Depression and Post-Traumatic Stress Disorder. As in functional retrograde amnesia a decoupling of previous and current conscious and unconscious access to autobiographical and self-related information is observed, neuroscientific models focussing on interrelations among autobiographical memory, self and levels of consciousness are outlined. Furthermore, brain correlates of autobiographical memory retrieval in healthy subjects as well as methodological commonalties and differences across previous studies are reviewed. In the second section of the Theoretical Background, disproportionate forms of retrograde amnesia are illustrated by previous single cases. Following an overview of organic focal retrograde amnesia, memory disturbances in psychiatric disorders of dissociative nature are described. The Theoretical Background closes with a review of previous single cases of functional retrograde amnesia summarising behavioural and functional brain correlates underlying the remote memory deficit.

The Empirical Part is introduced by questions and assumptions concerning behavioural and brain correlates of patients with functional retrograde amnesia. These consider the aetiology of the memory deficit and how the disease may be related to differential functional brain correlates during retrieval attempts of accessible and inaccessible information and time periods. Following detailed case histories of the patients, the applied neuropsychological methods and tests are described. This is concluded with an explanation of the functional magnetic resonance imaging (fMRI) study conducted with three of the patients and the positron emission tomography (PET) experiment in which two patients were enrolled. The Empirical Part closes with presentation of the results along three major areas: behaviour, neuropsychology and neuroimaging.

Data from the individual patients' behavioural, neuropsychological and psychological-psychiatric investigation are discussed in light of potential organic, psychogenic and malingering-related co-contribution to onset and maintenance of their amnesia. Subsequently, findings of the neuroimaging experiments and how they relate to the patients' behaviour and to previous findings in healthy subjects are discussed. Finally, a classification of the patients is given and possible future research on the behavioural and functional brain correlates of functional retrograde amnesia is suggested.

Examples of the applied neuropsychological tests of remote memory, stimulus sentences used in the neuroimaging experiments and questionnaires to control behaviour in the neuroimaging experiments are given in the Appendices.

I. Theoretical Background

1. Memory

The first section of the Theoretical Background gives an overview of contemporary classifications of memory centring on the memory systems approach of Endel Tulving. Mechanisms of emotional modulation of memory are outlined and elucidated by the examples of Depression and Post-Traumatic Stress Disorder. Then, theories of autobiographical memory and previous neuroimaging studies of autobiographical memory retrieval are reviewed. The syndrome of functional retrograde amnesia will be the focus of the second part of this chapter.

1.1 Classifications of memory

Memory must not be understood as a unitary function or system. Rather it can be categorised according to temporal characteristics, according to its contents and processes.

1.1.1. Time-based classifications of memory

A classical approach to memory divisions distinguishes memory stores according to their temporal duration. Herein ultra-short-term, short-term, and long-term memory are separated. Ultra-short-term memory (also labelled iconic or echoic store) briefly keeps sensory information and decays after milliseconds (e.g. Crowder, 1982; Loftus, Duncan, & Gehrig, 1992). Short-term memory lasts for seconds up to minutes (Waugh & Norman, 1965). In another view, it can maximally process seven plus/minus two chunks of information (Miller, 1956; Yoshino, 1993), or, according to other researchers, its maximum capacity may be restricted to only four chunks (Cowan, 2001). A specific form of short-term memory is labelled 'working memory'. Contents within working memory can actively be held and manipulated over a limited period of time (Baddeley, 1986, 2000b; Baddeley, Chincotta, & Adlam, 2001). Following Baddeley's model (Baddeley, 1986; 2001), working memory can be subdivided by two main components. The 'phonological loop' processes, holds and manipulates language-based information, whereas the 'visuo-spatial sketch-pad' handles visual and spatial information. Working memory information is constantly compared with the contents of long-term memory. In Baddeley's newer accounts of working memory (Baddeley, 2000a), a third subcategory, the 'episodic buffer', temporarily accomplishes this comparison. It relates features of the current information to long-term memory contents in order to provide and establish a coherent but transient episode. Finally, a 'central executive' as the fourth component coordinates and controls the subsystems and allocates attention. It is controversial whether working memory constitutes a type of memory or an executive function. At least, working memory substantially contributes to all other executive functions (cf. D'Esposito et al., 1995). Information that exceeds the duration or extent of short-term and working memory, can be ascribed to long-term memory which has no temporal limitations and, in principle, an unrestricted capacity.

A further time-related memory classification refers to the time the information was initially acquired. One distinguishes old or remote and new memories. Remote memory refers to information acquired prior to a certain moment in time. In contrast, new memories are acquired or learned after this moment in time. In amnesic patients, this specific moment is determined by a critical incident such as organic or psychic trauma. The inability to access information that happened before this incident is referred to as retrograde amnesia and the incapacity to acquire new information after the incident is labelled anterograde amnesia (see Fig. 1).

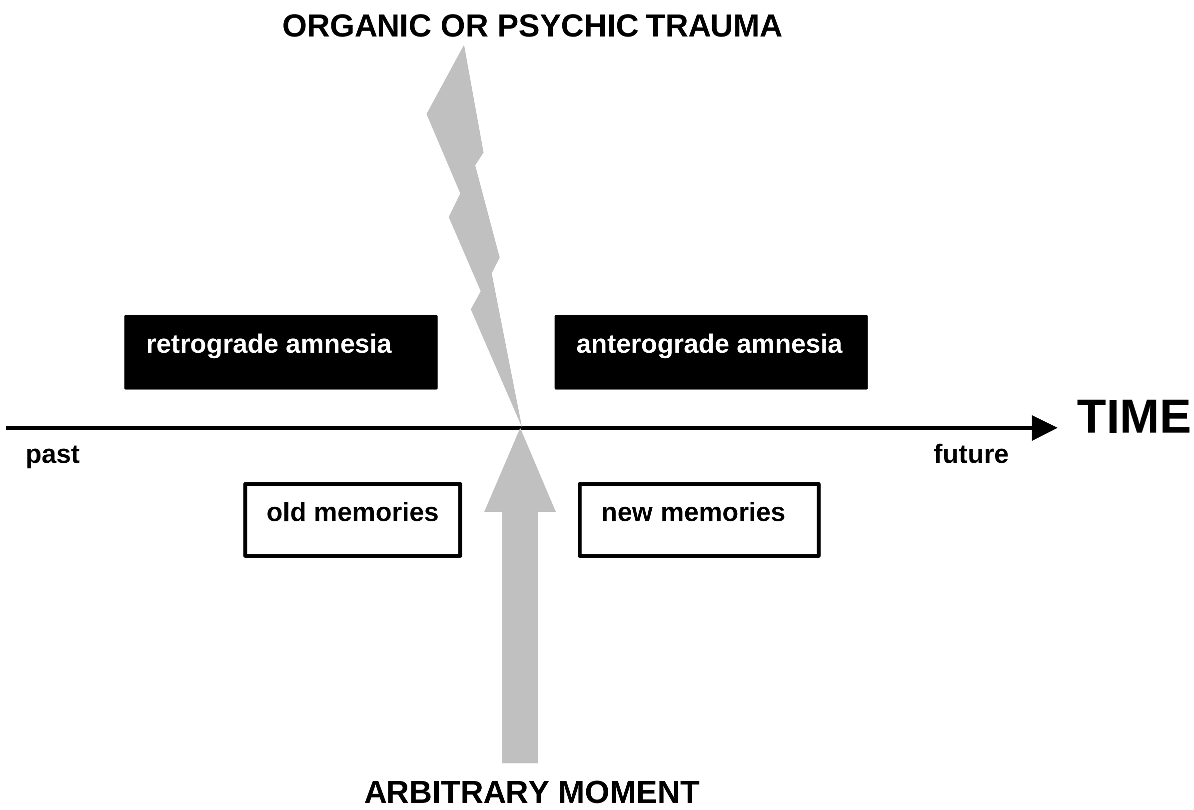

Figure 1: Old and new memories relative to an arbitrary moment in time; corresponding classification between retrograde amnesia and anterograde amnesia in patients suffering an organic or psychic trauma (modified from Brand & Markowitsch, 2003).

1.1.2 Memory processes

Multiple steps of information processing are traversed in long-term memory formation. Prior to permanent storage, information first has to be registered at the sensory organs *(registration)* and initially pre-processed *(encoding)*. Then, pre-processed information is embedded into already existing information networks and associated with previous contents *(consolidation)*. Once information is successfully consolidated, memory engrams are stored permanently *(storage)* and can, in principle, be accessed later on *(retrieval)*. The type and amount of triggers required for successful retrieval depends highly on the complexity, recency, and frequency of former usage of to-be-remembered information (MacKay & James, 2002). Finally, every time stored information is retrieved, it will be re-encoded *(re-encoding)*. Thus, the initial memory trace undergoes considerable change (Tulving, 2001). The steps of information processing are illustrated in Figure 2.

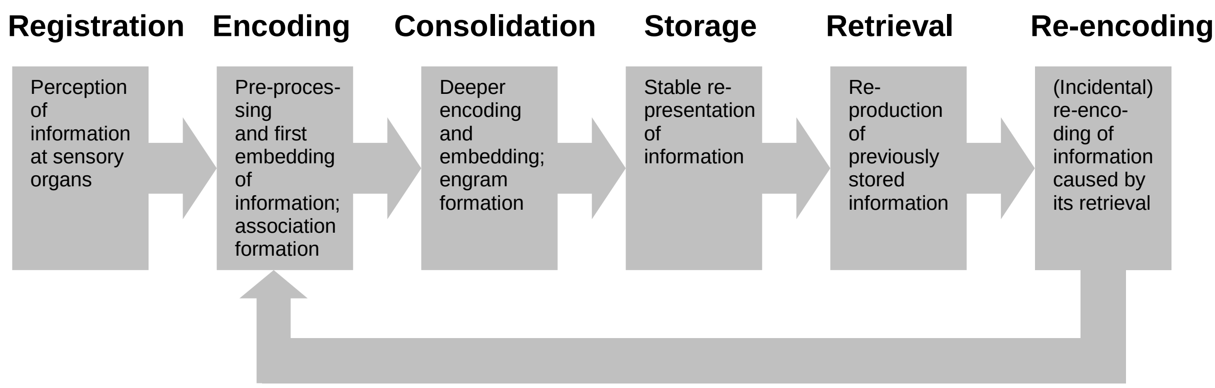

Figure 2: Steps of information processing in memory formation and memory retrieval (adapted from Markowitsch, 1999b).

Anatomical bases and neurochemical changes associated with the steps of information processing will be described in **section I-1.2.**

1.1.3 Content-based classifications of memory

Beyond time-based categorisations, memory can be subdivided according to its contents. The two most influential content-based theories of memory were introduced by Larry R. Squire and Endel Tulving.

1.1.3.1 Larry R. Squire: Declarative and non-declarative memory

Squire (1987) separates declarative and non-declarative memory contents. Declarative memories are conscious, explicitly reproducible and they can be verbally formulated *(declared)*. In contrast, non-declarative memories are unconscious, implicit and normally cannot be verbalised (Squire, 1994; Squire & Knowlton, 1995; Squire & Zola, 2000; Squire & Zola-Morgan, 1991). It is controversial whether retrieval of all declarative information requires conscious processing (cf.

Markowitsch, 1996; Tulving, 1995, 2002)[1]. Declarative memory comprises factual knowledge or semantic memory as well as knowledge of experiences and events or episodic memory. Non-declarative memory refers to learning that implicitly guides behaviour. It comprises procedural learning (e.g. motor skills), conditioning, non-associative learning (e.g. habituation), and priming. Priming refers to a higher probability of recognising (partly) presented information that was non-consciously processed before without intentionally attending to its encoding (e.g. the faster and easier recognition of tones belonging to a certain melody if it has – accidentally – been heard before). Figure 3 summarises the content-based memory classification according to Squire.

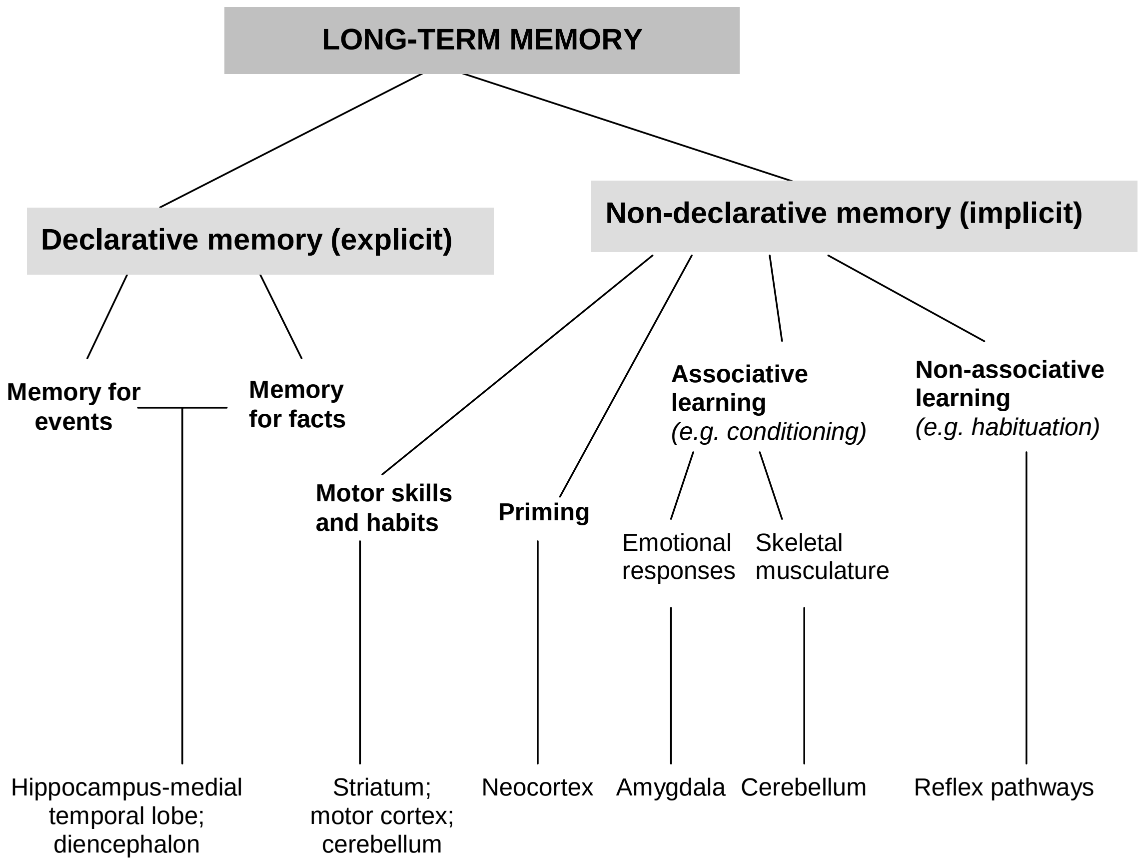

Figure 3: Content-based classification of memory after Squire (modified from Squire & Zola-Morgan, 1991).

Acquisition of declarative memory occurs quickly, and a single exposition may be sufficient for the storage of such information in declarative memory (e.g. Squire, Knowlton, & Musen, 1993). Furthermore, declarative information is flexibly transferable to new situations, independent of initial learning contexts (e.g. Reber, Knowlton, & Squire, 1996). However, declarative memory is unreliable since it can be affected by retrieval errors and forgetting (e.g. Squire et al., 1993). In

[1] According to Squire (1987), semantic memories – as they belong to declarative memory – are retrieved consciously, whereas Tulving (e.g. Tulving, 1995) proposes that their retrieval can be implicit.

contrast, non-declarative memories are only acquired by repeated exposition and exercise of specific procedures. Priming may be the exception, in that a single previous exposition to information can prime or prepare someone to faster or easier access this information later on. Therefore, retrieval of non-declarative memory is reliable but inflexible for transfer to different contexts. This assumption implies that non-declarative memories exert their effect on behaviour only if the context of their initial acquisition is present (Squire et al., 1993).

As can be derived from Figure 3, according to Squire, declarative and non-declarative memory can be assigned to different neuroanatomical structures. The further subdivision of semantic and episodic memory within declarative memory is not supported. In fact, Squire proposes that both declarative systems depend on functionally connected regions of the medial temporal lobes (hippocampal region, entorhinal cortex, perihippocampal and perirhinal cortex) and suggests that lesions to these regions evenly affect episodic and semantic memory contents (e.g. Squire & Knowlton, 1995; Zola & Squire, 2000). Furthermore, a linear relationship between size of a brain lesion in medial temporal lobe/hippocampal formation and resulting memory dysfunction is suggested (e.g. Eichenbaum, 2001a; Squire & Zola-Morgan, 1991; Zola-Morgan, Squire, & Amaral, 1986; cf. Zola & Squire, 2001). In summary, Squire emphasises similarities between episodic and semantic memory and gives evidence that both crucially rely on the hippocampal formation, probably in a time limited way (Bayley, Hopkins, & Squire, 2003). The origin of his memory classification from animal research may in part explain this observation, though there is evidence for his theory from human studies as well (e.g. Manns, Hopkins, & Squire, 2003). Directly investigating similarities or differences between episodic and semantic memory, some recent neuroimaging studies found common brain activations (e.g. Menon, Boyett-Anderson, Schatzberg, & Reiss, 2002; Poldrack et al., 2001), whereas others emphasised the differences (e.g. Nyberg, Forkstam, Petersson, Cabeza, & Ingvar, 2002). Generally, Squire's memory model and assumptions may only be partly transferable to human memory and particularly to human amnesia (cf. Tulving & Markowitsch, 1994, 1998).

1.1.3.2 Endel Tulving: Hierarchical organisation of memory systems

In contrast to Squire, Tulving does not suggest the two distinct systems of declarative and non-declarative memory, but claims that these systems are different expressions of memory (Tulving, 1972, 1983, 1995; Tulving & Markowitsch, 1998).

Thus, according to Tulving, long-term memory can be divided into separate subdivisions but these are supposed to be interdependent and hierarchically organised. In contrast to the long-term memory systems, the so-called primary memory contains short-term and working memory (e.g. Tulving, 1995). Tulving proposes the long-term memory systems episodic memory, semantic memory, priming, and procedural memory. Recently, a further memory system, perceptual memory, residing between priming and semantic memory, has been proposed (Tulving & Markowitsch, in prep.; see. Fig. 4).

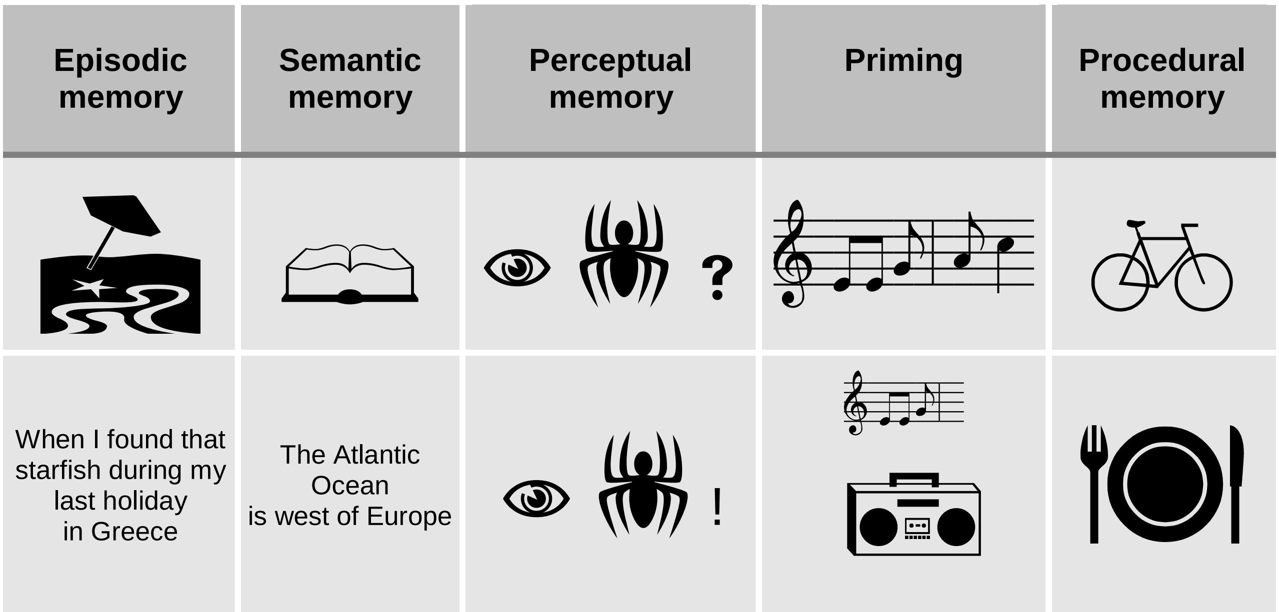

Figure 4: The five long term memory systems (Tulving & Markowitsch, in prep.).

Procedural memory differs from all other systems in that its mechanisms and contents are usually observable in overt behaviour (such as riding a bike or using knife and fork), whereas all other memory systems comprise symbolic forms of learning as well. Therefore, procedural memory is also known as the *behavioural system* while all other systems are termed *cognitive systems*.

Identical with Squire's definition (see above), priming is understood as the higher probability of recognising (partly) presented information that was perceived before (cf. example in Fig. 4). Perceptual memory refers to the feeling of knowing an object or situation solely on the basis of its sensory features. It is supposed to be pre-semantic. For processing in perceptual memory, it is not required to know the meaning, function, or conceptual category of an object or situation to be able to recognise them as familiar[2]. The knowledge system or semantic memory refers to context-free facts of a broader range. It comprises general knowledge such as names of cities and countries or arithmetic rules. Finally, episodic memory – to follow Tulving – contains

2 Mostly resulting from memory profiles of semantic dementia patients, there is a controversy concerning the independence of perceptual from semantic memory. Though these patients showed preserved perceptual memory skills in the absence of semantic knowledge, however, former experiences and knowledge of the to-be-perceived objects increased their perceptual memory performance (e.g. Hovius, Kellenbach, Graham, Hodges, & Patterson, 2003; Simons, Graham, Galton, Patterson, & Hodges, 2001). This raises the question whether semantic memory is dependent on perceptual memory or vice versa.

context-embedded, specific and distinctive events and allows a 'mental time travel' to the past (Tulving, 2002).

The terms 'episodic memory' and 'autobiographical memory' are often used interchangeably. This may partly result from the fact that Tulving himself never draw a definite distinction between episodic autobiographical memory and episodic recall and recognition of items such as words or pictures to be remembered in experimental settings (cf. Tulving, 2001). However, both forms of episodic memories are clearly differentiable in several aspects (e.g. emotional connotation, personal significance, complexity of the information, temporal distance of the 'time travel'). Though Tulving eventually referred to episodic memories for single items from experimental settings as 'mini-events' (e.g. Tulving, 1983), their contents is unlikely to match episodes from one's own autobiography. However, rather than referring to the different contents of autobiographical episodic memories versus non-autobiographical episodic memories, that is undoubtedly different, Tulving emphasised the similarities of retrieval consciousness associated with both types of episodic memories. In this vein, Tulving (2001) claims that the contents of all memory systems is associated with different levels of awareness. Episodic information is thought to be *autonoëtic* in that it requires an awareness of one's own self (Markowitsch, 2003). This is even then the case, if episodic memory contents only comprises single items from experimental settings, since one has to mentally go back to the learning episode ('mini-event') when the item was encountered. Reconsidering the difference between autobiographical and non-autobiographical episodic memory, it may be obvious that retrieval of both requires autonoëtic consciousness and that this holds even if their contents undoubtedly differ. Thus, one has to be aware that a certain event has happened with regard to its temporal-spatial context and to oneself experiencing it in the past, regardless whether its contents are autobiographically relevant or not. The contents of semantic memory system are thought to be *noëtic*. This includes the possibility to consciously retrieve semantic information but excludes the obligatory involvement of the self. A similar relationship holds for perceptual memory. Though instant perceptual identification of objects is not under deliberate control and occurs unconsciously, the recognition of something as familiar can be an aware process. Therefore, perceptual memory is thought to be *noëtic*. In contrast to this, priming and procedural memory are processed on an *anoëtic* level since their contents can hardly be made conscious and verbalisation of these kinds of information is strikingly difficult. One may not even notice retrieval of priming and procedural memory contents.

A further assumption resulting from the hierarchical organisation of the memory systems refers to their interdependence. For a transfer into higher (or later) hierarchical levels, encoding of any information has to be successful on lower (or earlier) levels. A specification of this relationship is given in the SPI model, describing serial ('S'), parallel ('P') and independent ('I') mechanisms in memory information processing (Tulving, 2002). According to the SPI model, encoding of information occurs serially through the systems, they are then stored in parallel and memory retrieval can finally be independent of initial encoding and storage (see Fig. 5).

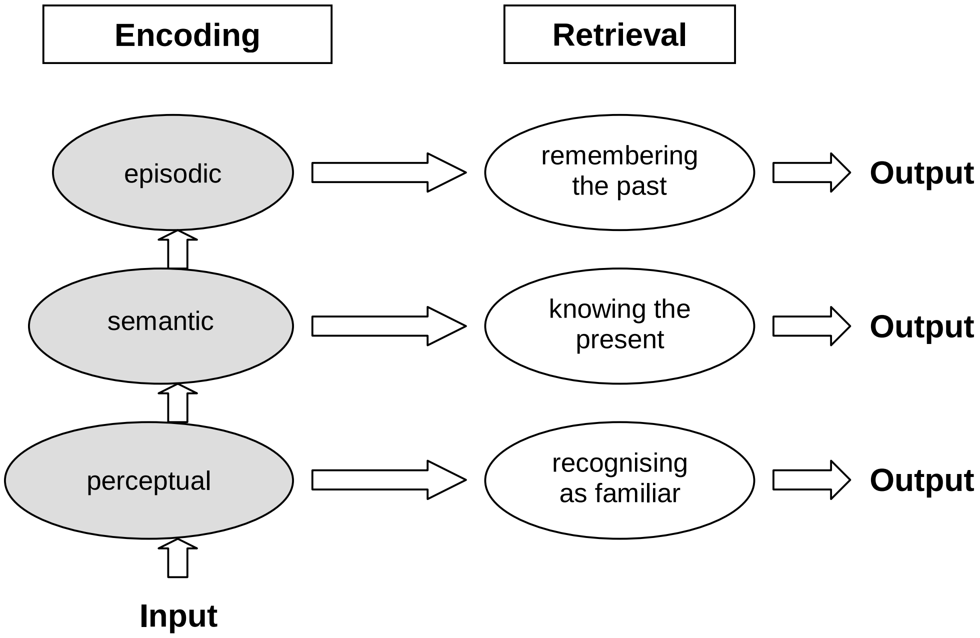

Figure 5: SPI model: Information has to pass through perceptual and semantic memory to be encoded in episodic memory. Perceptual, semantic and episodic features of episodic memories are stored in parallel. Independent of the nature of the information, it can be accessed by retrieval of its perceptual, semantic and episodic features triggered by cues (modified from Tulving, 2001).

'Parallel' indicates that information can be simultaneously stored in all systems that were traversed during encoding. Finally, stored information can be retrieved 'independently' from the different systems mostly resulting from trigger cues. The following example may elucidate these relations:

A person celebrates her birthday. Given that she has intact perceptual memory, she will be able to encode and recognise all sensory features of the event as familiar such as the faces of her friends, the sound of a birthday song, the smell of the birthday cake and so on. Then, she will encode semantic aspects of the event such as the age she reaches. Finally she will encode episodic features such as the feelings she had on this specific event, what a certain friend gave her as a present, or how the weather was like on that day. All these types of information are stored in parallel. On another occasion she might remember the entire episode from a visual cue in the environment (such as sensing the odour of a cake or hearing a birthday song), from a semantic fact (such as knowing that her next birthday will be soon) or from episodic retrieval cues (such as meeting one of the birthday guests). Thus, information is encoded serially but stored in several systems in parallel and retrieval can later occur independently from its initial encoding and storage.

The hierarchical organisation of the memory systems may result from their phylogenetic and ontogenetic development, whereby episodic memory evolves latest (Tulving, 2002). According to some authors, episodic memory is largely restricted to humans (McCormack & Hoerl, 2001; Mcphail, 1998; Suddendorf & Busby, 2003; Tulving, 2001), whereas others suggest that some animals exhibit 'episodic-like memory' as well (Clayton, Griffiths, Emery, & Dickinson, 2001; Griffin, 2000; Morris, 2001; Weiskrantz, 2001). Lower memory systems can operate without higher systems. This hypothesis is confirmed in species exhibiting only lower memory systems (but see above) such as perceptual memory testable by visual or auditory recognition paradigms (e.g. Aggleton & Pearce, 2001). Another verification of the described hierarchy relates to human ontogenesis. Children by the age of about four years or less are capable to acquire semantic knowledge about the world without, however, displaying episodic memory abilities. They are not yet able to retrieve temporally and contextually specific events from their personal past (e.g. Newcombe, Drummey, Fox, Lie, & Ottinger-Alberts, 2000; Perner & Ruffman, 1995; Reese, 2002; Uehara, 2000; Wheeler, Stuss, & Tulving, 1997). Moreover, loss of episodic memory with spared semantic knowledge and perceptual memory is usually seen in patients with acquired brain lesions or neurodegenerative diseases (e.g. Tulving, 2001; Hamann & Squire, 1995; Vargha-Khadem, Gadian, & Mishkin, 2001; Vargha-Khadem et al., 1997).

Table 1 summarises Tulving's assumptions concerning contents, mode of retrieval and associated levels of consciousness of his memory systems.

Table 1: Memory systems (modified from Tulving, 1995)

System	Different notation	Description and subsystems	Retrieval mode and associated consciousness
Procedural memory	Non-declarative memory	Motor and simple cognitive skills; basic conditioning; simple associative learning	implicit; *anoëtic*
Perceptual representation system	Priming	Description of structures, higher probability of recognition of stimuli which were (partly) presented before	implicit; *anoëtic*
Perceptual memory		Recognition of stimuli on the basis of familiarity; recognition based on their sensory features	implicit; *noëtic*
Semantic memory	Generic memory, knowledge of facts	Spatial memory, relational memory	implicit; *noëtic*
Primary memory	Short-term memory; working memory	visual, auditory	explicit; *noëtic*
Episodic memory	Personal memory, event memory, autobiographical memory		explicit, *autonoëtic*

In the following sections a brief overview of neuroanatomical bases of memory systems and processes will be given.

1.2 Memory and the brain

Amnesic patients normally show impairment in conscious forms of memory whereas unconscious systems are mostly preserved. This dissociation can usually be seen in patients with organic amnesias, as for example resulting from bilateral medial temporal lobe lesions (e.g. Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997; Scoville & Milner, 1957) or medial diencephalic pathology (e.g. in alcoholic Korsakoff-syndrome: Kopelman, 1995; Phaf, Geurts, & Eling, 2000). Similar dissociations are apparent in psychiatric patients (Ellwart, Rinck, & Becker, 2003; Kazes et al., 1999). Comparably, in functional neuroimaging studies with healthy subjects, memory systems and processes have been associated with clearly differentiable brain regions (cf. Neuropsychologia (2003), 41(3); Special Issue on Functional Neuroimaging of Memory).

1.2.1 Encoding and consolidation

Whereas encoding and consolidation of procedural memory require structures of the basal ganglia and cerebellum (e.g. Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; Mandolesi, Leggio, Graziano, Neri, & Petrosini, 2001; Ghilardi et al., 2000), acquisition of priming and perceptual memory are organised in uni- and polymodal cortical areas (cf. Buckner & Koutstaal, 1998; Paller, 2000). The medial temporal lobe, medial diencephalon, and – more loosely – the basal forebrain act as so-called bottleneck structures for the episodic and semantic memory systems (cf. Markowitsch, 2000c). Even small lesions to these structures can lead to massive impairment in the storage of new materials (Benabarre et al., 2001; Gaffan, Gaffan, & Hodges, 1991; Kesler, Hopkins, Blatter, Edge-Booth, & Bigler, 2001; Markowitsch, von Cramon, & Schuri, 1993; von Cramon, Markowitsch, & Schuri, 1993).

Markowitsch (2000a) proposed that episodic and semantic encoding and consolidation depend on two separable but interrelated circuits within the limbic system: the Papez circuit and the amygdaloid circuit. The Papez circuit comprises hippocampal formation → Fornix (→ Septum) → mammillary bodies → mammillothalamic tract → anterior thalamic nuclei → thalamo-cortical pedunculi (→ cingulate cortex → cingulum) → subiculum of the hippocampal formation. While Papez himself considered this circuit to be specifically involved in processing of emotional material (Papez, 1937) it is now thought to be responsible for transfer of all types of information into long-term stores (Markowitsch, 2000a). Instead, the amygdaloid circuit – comprising amygdala → ventral amygdalofugal projection → mediodorsal thalamic nucleus → anterior thalamic pedunculi → area subcallosa of the basal forebrain → bandeletta diagonalis → amygdala – is considered responsible for encoding and consolidation of emotional memories (Markowitsch, 1998, 2000a). In summary, it can be concluded that medial temporal brain regions and parts of the diencephalon crucially influence the formation of new memories contingent on neural transmission within the limbic circuits. Activity within these circuits may be crucial for the transfer of short-term memory contents into long-term memory in that, probably, new information is embedded into existing information networks (Eichenbaum, 2001a, 2001b; Wallenstein, Eichenbaum, & Hasselmo, 1998).

Beyond medial temporal and medial diencephalic regions, there is growing evidence for the importance of (pre-)frontal brain areas in episodic memory formation (e.g. Bernard, Desgranges, Platel, Baron, & Eustache, 2001; Fernandez & Tendolkar, 2001; Fletcher, Shallice, & Dolan, 1998; Golby et al., 2001). Fletcher and Henson (2001) reviewed neuroimaging studies of prefrontal lobe involvement during memory processing. They consistently found activations within left dorsolateral and ventrolateral prefrontal cortex during episodic memory encoding. The authors suggest from previous results (e.g. Fletcher, Shallice, & Dolan, 2000) that left prefrontal cortex contributes to episodic memory encoding through stimulus organisation and building of meaningful associations between to-be-learned materials. At the same time it suppresses irrelevant meanings and associations. Zalla, Phipps, and Grafman (2002) supported this model. In their study, amnesic patients with limbic lesions and non-amnesic patients with frontal lobe damage were investigated while they encoded a story by using different learning strategies. Though all patient showed deficient story recall, patients with frontal lobe damage were differentially impaired at an early stage of story processing. They were unable to use inferential knowledge to comprehend the stories and this caused a subsequent retrieval deficit. Therefore, the authors concluded that (pre-)frontal cortex is particularly implicated in the choice of appropriate encoding strategies and thus for the formation of new episodic memories.

A neural basis for encoding and consolidation may be seen in processes of long-term potentiation (LTP; Bliss & Lomo, 1973) and long-term depression (LTD; Eccles, Llinas, & Sasaki, 1966; Ito & Kano, 1982). Both concern electrical features of synapses and their temporary changes after learning experiences that may form the bases of long-term structural and functional synaptic changes. Given Hebb's assumption that synaptic associativity is strengthened with use (Hebb, 1949), the laboratory observation of learning-dependent temporary increases of synaptic strength (LTP), or weakening of potentially irrelevant synapses (LTD), may provide a basis for consolidation and plasticity in the brain. However, conclusions have to be drawn cautiously and it is likely that LTP and LTD do not entirely equal learning and consolidation (cf. Stevens, 1998). Reviewing previous studies on synaptic plasticity, Martin, Grimwood, and Morris (2000) conclude that learning-induced changes in synaptic strength are necessary but not sufficient to fully explain mechanisms of memory formation. The authors argue that to approve synaptic plasticity as sufficient for learning, one may have to artificially implement synaptic changes for a learning experience that in fact did not occur. Nevertheless, LTP saturation experiments in animals indirectly support the importance of synaptic plasticity during learning (Richter-Levin, Canevari, & Bliss, 1998). In these experiments, neural tissue, for example, in the hippocampus, is pre-stimulated by tetanisation leading to cumulative potentiation and therefore natural, learning-induced LTP can no longer occur. Experimental animals that were treated in this way show impairment in acquisition of new information such as spatial relations (Moser, Krobert, Moser, & Morris, 1998). Furthermore, LTP saturation and subsequent memory impairment can be prevented by prior learning experiences (Otnaess, Brun, Moser, & Moser, 1999). Taken together, a large body of evidence strongly suggests synaptic plasticity to be of crucial importance for acquisition and consolidation of new information (cf. Morris et al., 2003).

1.2.2 Storage

After successful encoding and consolidation, engrams of episodic and semantic information are probably stored in cortical association areas (e.g. Eichenbaum, 1997; Scoville & Milner, 1957). This may be testable in neuroimaging studies investigating activity during category processing and therefore information that is considered to be already fully encoded and stored. In this regard, visual perception of categories such as faces, tools, or animals usually involves activation of temporo-occipital association cortices (e.g. Ishai, Ungerleider, Martin, & Haxby, 2000) with anatomically discrete but interactive regions for different modalities (Thompson-Schill, Aguirre, D'Esposito, & Farah, 1999). Contents of lower memory systems, such as procedural memory, seem to be stored near the location where they were initially encoded and consolidated. For instance, in a study by Bao, Chen, Kim, and Thompson (2002), application of certain receptor antagonists in the cerebellum prevented rats from learning a motor conditioning task which the authors interpreted as a failure in permanent storage of memory engrams (see also Thompson & Kim, 1996). The actual engram formation likely results from structural changes at synapses (cf. Kandel, 2001). Comparable to processes in the immune system, formation of engrams may lead to permanent recoding of molecular DNA for protein synthesis (Pena De Ortiz & Arshavsky, 2001; cf. Dietrich & Been, 2001). Those newly formed proteins lead to permanent chemical changes that affect neural activity within the central nervous system. Therefore, on a structural as well as on a chemical level, engram formation is associated with permanent alterations. These two assumptions are not conflicting. For instance, it was shown that local changes in protein synthesis are associated with structural changes of specific, but not <u>all</u> synapses (Martin, Barad, & Kandel, 2000; Martin, Grimwood et al., 2000; overview in Wells & Fallon, 2000). This suggests that changes in neurochemical properties of neurons can finally lead to structural modifications at synapses.

Beyond the importance of association cortex for storage of engrams, the limbic system and especially the hippocampal formation is a crucial site for the build up of associations and establishes relations between single features of a memory trace (e.g. Markowitsch, 1999c). Lesions to association cortex can lead to irreversible loss of formerly stored memory contents as is seen in patients suffering from dementia (e.g. Desgranges et al., 2002; Meguro et al., 2001) or hypoxia (cf. Caine & Watson, 2000). Dependent on the lesion size, these patients usually show loss of remote memories besides their anterograde learning deficits. In this case, the amnesia must be understood as resulting from permanent loss of the original memory engrams.

1.2.3 Retrieval

Following successful encoding, consolidation and storage of information, memories can usually be later on retrieved. Generally, in investigation of structural and functional brain correlates of retrieval, the problem of re-encoding has to be considered (Tulving, 2001) since every new retrieval of an information potentially re-activates encoding, consolidation and storage-related brain structures (see also Johnson & Chalfonte, 1994). For example, Nyberg, Habib, McIntosh, and Tulving (2000) found in a $H_2^{15}O$-positron emission tomography (PET) study that retrieval of words from previously learned word-tone-associations reactivated auditory cortices although retrieval of the tones was not demanded. The authors suggested that single fragments of a complex stimulus are probably sufficient to trigger retrieval of the entire memory (see also Fig. 5: SPI model). More recently, attempts have been made to control for this confound (e.g. Lee, Robbins, Graham, & Owen, 2002).

Retrieval of perceptual, priming and procedural memory contents relies on similar structures as those involved during their acquisition and storage. Depending on the nature of the tasks, different polymodal association areas are implicated in priming and perceptual memory. For example, perceptual priming has been associated with extrastriate activations of the visual system (Buckner & Koutstaal, 1998), whereas in conceptual priming left (pre-) frontal cortex is involved (Demb et al., 1995)[3]. Once procedural and priming memory contents are successfully consolidated, retrieval requires less activity in initially involved brain regions (cf. Schacter & Buckner, 1998; Ungerleider, 1995). Concerning episodic and semantic memory, Tulving, Kapur, Craik, Moscovitch, and Houle (1994) have proposed a recently revised (Habib, Nyberg, & Tulving, 2003) model of hemispheric encoding/retrieval asymmetry (HERA). The HERA model suggests that, stimulus-independent, the right hemisphere is specialised for episodic retrieval, whereas the left hemisphere is more involved in retrieval of semantic (and encoding of episodic and semantic) information. Brain regions most critically involved in retrieval from both memory systems comprise prefrontal cortex and temporal lobes/anterior temporal pole (e.g. Kroll, Markowitsch, Knight, & von Cramon, 1997; Noppeney & Price, 2002; cf. Markowitsch, 2000c).

Reanalysing previous neuroimaging results with healthy subjects, Cabeza and Nyberg (2000) found left hemispheric regions within prefrontal cortex, temporal lobe and in anterior cingulate gyrus to be involved in retrieval of semantic memories. Further differentiating semantic

[3] In perceptual priming, learning occurs from sensory perceptual features of the materials. An example is simple word-stem completion. For encoding, words are presented and have to be read or their syllables have to be counted. In later retrieval, stems of the formerly encoded words are shown and have to be completed. Priming can be seen, if subjects retrieve words from the learning trial at an above average rate. In contrast, in semantic priming, encoding is assured by deepened processing of the stimuli during the initial presentation. Here, subjects are supposed to form meaningful associations (e.g. ‘summer – winter’) or cluster the primes into meaningful categories (e.g. ‘living – non-living’) during encoding.

retrieval paradigms, the authors separated categorisation tasks and generation tasks[4]. Whereas categorisation tasks more frequently involved ventromedial prefrontal regions, generation tasks revealed activity in more posterior and dorsal prefrontal areas. The authors suggest from their analysis that generation tasks require additional language processing and working memory beyond long-term memory retrieval. Furthermore, within temporal lobes, left middle temporal and inferior temporal regions (see also Lee et al., 2002; Pilgrim, Fadili, Fletcher, & Tyler, 2002) as well as bilateral occipito-temporal lobe activations were consistently observed. Independent of the nature of the to be retrieved semantic materials, left hemispheric middle temporal activation was observed in the Cabeza and Nyberg (2000) meta-analysis (see also Booth et al., 2002), whereas occipito-temporal activations in fusiform gyrus was more frequently seen during retrieval of visual stimuli (cf. Wheeler & Buckner, 2003). Cingulate cortex activations were most often revealed in generation tasks (e.g. Abrahams et al., 2003) probably pointing to enhanced attentional demands such as task switching (e.g. Swainson et al., 2003).

Generally, memory retrieval can be tested by different paradigms which are, however, associated with separable brain regions and underlie a differentiable vulnerability to deteriorations. Among these paradigms, free recall is the most challenging variant, followed by cued recall and recognition. Accordingly, in brain damaged patients, impairment in free recall is often accompanied by intact recognition performance (e.g. Hildebrandt, Müller, Bussmann-Mork, Goebel, & Eilers, 2001; Vargha-Khadem et al., 2001; Vargha-Khadem et al., 1997). Also, healthy subjects show a performance discrepancy between weaker free recall and better recognition performance, and in normal ageing free recall degrades earlier than recognition (cf. Wingfield & Kahana, 2002). While free recall substantially relies on executive functions such as monitoring, search strategies or source memory, recognition may result from feelings of familiarity only and thus, for example, perceptual memory. Patients with frontal lobe damage are repeatedly reported to suffer from disproportionately impaired free recall versus recognition performance. In this context, Kopelman and Stanhope (1998) observed that frontal lobe patients disproportionately benefited from supply of additional retrieval strategies compared to patients with temporal lobe or medial-diencephalic lesions. The authors concluded that frontal lobe patients may be unable to organise their retrieval strategies for themselves and therefore may be impaired in structuring the learned materials for retrieval.

Reanalysing previous neuroimaging results of episodic memory retrieval in healthy subjects, Fletcher and Henson (2001) distinguished control processes and assigned them to different regions within prefrontal cortex. Specifically, the authors suggest that ventrolateral

[4] Categorisation tasks require subjects to sort their retrieval products according to certain semantic categories (e.g. 'living – non-living'). In generation tasks, semantic information is to be generated. This requires retrieval of information, e.g., according to certain semantic criteria such as generating words with the initial letter "A".

prefrontal is involved in all kinds of generation tasks and therefore also implicated in specifying search parameters for episodic memory retrieval. Similar to its involvement in working memory tasks, dorsolateral prefrontal cortex is suggested to be responsible for monitoring functions and maintenance of information. Finally, anterior prefrontal cortex is proposed to control and co-ordinate processes such as shifts between task demands and monitoring of one's own performance.

A further classification of forms of episodic retrieval concerns the concepts of *retrieval mode, retrieval effort,* and *retrieval success* (e.g. Rugg & Wilding, 2000). Retrieval mode describes a state in which one consciously focuses on the act of episodic memory retrieval (e.g. focusing attention to a certain past experience, treating incoming and online information as retrieval cues, becoming aware of retrieval products). It is thought to rely on right hemispheric regions within prefrontal cortex (e.g. Düzel et al., 1996; Lepage, Ghaffar, Nyberg, & Tulving, 2000). Higher retrieval effort is associated with increased (left) dorsolateral prefrontal activity (cf. Buckner & Koutstaal, 1998; Fletcher & Henson, 2001). Successful retrieval of episodic memory contents was associated with left parietal activity (e.g. Konishi, Wheeler, Donaldson, & Buckner, 2000), probably accompanied by prefrontal cortex activation (e.g. Maril, Simons, Mitchell, Schwartz, & Schacter, 2003).

One can assume that the nature of semantic and episodic contents as well as the task demands and processes are associated with activations within (pre)frontal brain regions. Whereas some studies showed a lateralisation of episodic retrieval to the right hemisphere, others indicated left or bilateral involvement. This discrepancy may result from differences in the complexity of to-be-retrieved materials that covaries with retrieval effort which may engage left hemispheric control processes to a higher degree. Moreover, if the stimuli are emotional in nature, a right hemispheric involvement is likely as will be elaborated in the forthcoming section. Summarising previous results from patients and healthy subjects, brain structures and circuits associated with the aforementioned memory systems and processes are listed in Table 2 (cf. Brand & Markowitsch, 2003).

Table 2: Memory systems and processes and their associated brain areas (from Brand & Markowitsch, 2003)

	Procedural memory	Priming	Perceptual memory	Semantic memory	Episodic memory
Encoding and consolidation	Basal ganglia, cerebellum	Primary and association cortex	Posterior sensory cortex	Cerebral cortex, limbic structures	Limbic system, prefrontal cortex
Storage	Basal ganglia, cerebellum	Primary and association cortex	Posterior sensory cortex	Cerebral cortex (mainly association areas)	Cerebral cortex (mainly association areas), limbic regions
Retrieval	Basal ganglia, cerebellum	Primary and association cortex	Posterior sensory cortex	Fronto-temporal cortex (left)	Fronto-temporal cortex (right), limbic regions

1.3 Emotion and memory

Emotional connotation of information is of particular importance for their encoding and consolidation as well as for storage and retrieval. Reciprocally, current dysfunctions or permanent disorders of affect and emotional processing can significantly influence memory performance. In the next section the neurochemical basis for this interdependency is introduced and illustrated by the clinical syndromes of Major Depression and Post-Traumatic Stress Disorder (PTSD).

1.3.1 Emotional modulation of memory

Usually, memory enhancing effects are observed for emotional in contrast to neutral information (Brown & Kulik, 1977; Kleinsmith & Kaplan, 1963; Ochsner & Schacter, 2000). The more attention a stimulus receives, the better it will be later remembered (cf. Craik, Govoni, Naveh-Benjamin, & Anderson, 1996). This is especially likely if information is evaluated as personally relevant or important (Lazarus, 1991). Moreover, once a stimulus is evaluated as emotionally relevant, it may subsequently be difficult to ignore it (Öhman, Flykt, & Lundqvist, 2000). Evaluation can occur unconsciously as well as under conscious control (Lazarus, 1991; Zajonc, 1998) wherein perception of any information may trigger unconscious evaluative processes. This phenomenon is also known as 'automatic evaluation effect' (e.g. Clore & Ketelaar, 1997). Studies on the automatic evaluation effect imply that perception of information instantly triggers memory retrieval of its affective-emotional characteristics probably providing the organism with basal information for approach or avoidance (cf. Lambie & Marcel, 2002; Ochsner & Schacter, 2000). Beyond triggering of automatised reactions, emotional (as well as neutral) information undergoes intentional processing such as causality checks. Dependent on the nature of the initially triggered emotion and related memories, this second step permits further attentional focussing on emotionally relevant internal (e.g. goals, plans) and external features (e.g. situations, tasks) (cf. Lazarus, 1991; Stein, Wade, & Liwag, 1997). The further evaluation of emotional information is influenced by momentary mood ('mood congruency' of memory; cf. Blaney, 1986) and other factors such as personality (cf. Ochsner & Schacter, 2000).

Brain areas associated with emotional processing and emotional memory comprise amygdala, prefrontal cortex (esp. ventromedial prefrontal, orbitofrontal cortex), anterior cingulate gyrus, ventral striatum, and insula (cf. Davidson & Irwin, 1999). Traditionally, processing of emotional materials is associated with right hemispheric lateralisation (cf. Hughlings-Jackson, 1879). This right hemispheric preponderance concerns perception, evaluation and retrieval of emotional materials as well as expression of emotions (Borod et al., 1998; Nagae & Moscovitch, 2002; Troisi et al., 1999; cf. Gainotti, Caltagirone, & Zoccolotti, 1993). For instance, studies with healthy subjects as well as brain damaged patients indicated predominantly right hemispheric contribution in identification of emotional facial expressions (e.g. Adolphs, Damasio, Tranel, & Damasio, 1996; Ahern et al., 1991; Anderson, Spencer, Fulbright, & Phelps, 2000; Suberi & McKeever, 1977) or affective prosody (Breitenstein, Daum, & Ackermann, 1998; Nicholson et al., 2003; Ross, Thompson, & Yenkosky, 19997; Starkstein, Federoff, Price, Leiguarda, & Robinson, 1994; but see Kotz et al., 2003). Also more complex emotional behaviours such as social cognition and emotional decisions were seen to involve more right hemispheric (ventromedial prefrontal) brain regions than left hemispheric areas (e.g. Tranel, Bechara, & Denburg, 2002)[5]. Accordingly, recall of autobiographical episodic memories, as they are mostly emotional in their nature, was associated with right lateralised activity patterns (cf. Fink et al., 1996; Markowitsch, Thiel et al., 2000, but see Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003).

Of the brain regions implicated in emotion processing, the amygdala is most intensively studied. Amygdaloid involvement has been observed in numerous emotion processing and emotional memory studies with animals and healthy human subjects (cf. LeDoux, 2000). Enhanced amygdala activity, induced by increases in emotional arousal, was associated with better memory for emotional information as observed in human $H_2^{15}O$-PET (Cahill et al., 1996;

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[5] The reason for the right hemispheric dominance in emotion processing is largely unresolved. Probably, the right hemisphere is generally more involved in regulation of autonomic and behavioural arousal than the left (Heller, 1993; Wittling, 1997). Furthermore, some researchers suggest that the left lateralised hemispheric specialisation for language in most humans may contribute to the right preponderance for emotion (cf. Buck, 1999).

Hamann, Ely, Grafton, & Kilts, 1999) or functional magnetic resonance imaging (fMRI) studies (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Canli, Zhao, Desmond, Glover, & Gabrieli, 1999). Furthermore as is seen in patients with Urbach-Wiethe disease, selective structural damage to the amygdalae can lead to deterioration of emotion processing and emotional memory (Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Markowitsch et al., 1994; Phelps et al., 1998; Siebert, Markowitsch, & Bartel, 2003). Likewise, in patients with affective disorders, enduring amygdaloid metabolic hyper- or hypoactivity critically contributes to memory deficits (von Gunten, Fox, Cipolotti, & Ron, 2000) (see **section I-1.3.2**).

The basolateral nucleus of the amygdala is considered a crucial brain structure for the modulation of memory through emotional arousal (Cahill & McGaugh, 1998). It possesses numerous systemic-hormonal afferents whose input is combined and distributed via efferents to subcortical and cortical memory relevant brain structures (e.g. the hippocampal formation) (Aggleton, 2000). This modulation has been suggested to be mediated by effects of stress hormones or glucocorticoids interacting with noradrenergic receptors in the basolateral amygdala (McGaugh & Roozendaal, 2002) as well as with other neurotransmitter systems (cf. Vallée, Mayo, Koob, & Le Moal, 2001). Glucocorticoids were found to enhance amygdala-dependent processes (emotional learning) while simultaneously inhibiting hippocampus-dependent processes (non-emotional learning) (Buchanan & Lovallo, 2001; Kim, Lee, Han, & Packard, 2001; McGaugh, 2002; Roozendaal, Nguyen, Power, & McGaugh, 1999). It is important to note that modulation of memory formation via glucocorticoids is dosage-dependent. Generally, memory enhancing effects are obtained with low to moderate doses over short periods of time whereas memory deteriorating effects are observed after higher and longer lasting exposition to glucocorticoids (cf. de Kloet, Oitzl, & Joëls, 1999; Kim & Yoon, 1998). Memory enhancing effects of moderate stress hormone elevation were observed in two experiments of Lupien et al. (2002). Following a learning experiment, they pharmacologically decreased cortisol levels and later restored baseline levels. Decreased cortisol significantly impaired memory recall, whereas restored cortisol levels also restored memory performance. In a second experiment, cortisol levels were pharmacologically altered dependent on circadian cortisol variations. Experimentally induced cortisol increases during the morning hours – which are associated with a circadian peak in cortisol levels (cf. Friess, Wiedemann, Steiger, & Holsboer, 1995) – had memory deteriorating effects. However, the same manipulation during the afternoon, a time associated with the lowest cortisol levels, enhanced memory. These results imply that, within normal ranges, glucocorticoids are essential for normal memory processing. However, since glucocorticoid manipulation did not exceed normal to near-normal doses, no conclusions can be drawn concerning possible neurotoxic effects of pathologically altered glucocorticoid levels. In this regard, long lasting glucocorticoid level increases resulting from chronic psychosocial stress were associated with learning impairments in rats (Park, Campbell, & Diamond, 2001). Moreover, chronic exposure to psychosocial or external stressors (Haines, Stansfeld, Job, Berglund, & Head, 2001) were associated with memory impairment also in humans (cf. Jameison & Dinan, 2001). Though the interaction between glucocorticoid levels and memory has been primarily studied in the context of memory formation, there is growing evidence for the importance of glucocorticoids also for retrieval modulation (de Quervain et al., 2003; Roozendaal, 2002). Outside the amygdala, glucocorticoid receptors are located in various memory relevant structures such as the anterior temporal lobes and the hippocampal formation turning them vulnerable to stress (Alderson & Novack, 2002; Bremner & Vermetten, 2001; Buwalda et al., 2001; McEwen, 1999; O'Brien, 1997; Patel et al., 2000; Yehuda, 2001a).

Though stress and glucocorticoids affect various kinds of memories, autobiographical episodic memory, as it is mostly characterised by its emotional nature, is particularly vulnerable to stress-related deteriorations. These are subsequently outlined by the examples of Major Depression and PTSD.

1.3.2 Memory deficits in Major Depression and PTSD

As aforementioned, emotionality of information and experiences can have a major impact on memory encoding as well as retrieval. However, emotional disturbances as seen in clinical syndromes such as Major Depression, can likewise be a cause of deteriorations in memory. Depression can be accompanied by multiple cognitive deficits, most of which centre around attentional, executive and mnemonic dysfunctions (cf. Ottowitz, Dougherty, & Savage, 2002). Reviewing previous studies, Austin, Mitchell, and Goodwin (2001) concluded that these deficits must not be seen as epiphenomena of the disease, but rather reflect functional brain disturbances (e.g. Kimbrell et al., 2002) as well as structural brain changes (e.g. Beyer & Krishnan, 2002). With regard to glucocorticoids, a general finding in depression is a so-called hypercortisolism. Parker, Schatzberg, and Lyons (2003) suggest acute depressions to be characterised by hypersecretion of hypothalamic corticotropin-releasing factor, pituitary adrenocorticotropic hormone (ACTH), and adrenal cortisol. In chronic depression, enhanced adrenal responsiveness to ACTH and glucocorticoid negative feedback are assumed to work complementary so that cortisol levels remain elevated while ACTH levels are reduced. Brain areas most consistently affected in depression comprise limbic, especially amygdalar, and paralimbic cortical regions such as the subgenual area of the frontal lobe (cf. Beyer & Krishnan, 2002; Drevets, 2003). Corresponding to the emotional changes in depressive patients' behaviour, a large body of memory research in depression focuses mood effects on the acquisition of information. In this vein, numerous studies have revealed mood congruency effects in learning and perception of emotional information pointing to an advantage in processing negatively valenced materials (e.g. Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Ellwart et al., 2003; Murphy et al., 1999; Murray, Whitehouse, & Alloy, 1999; Watkins, Martin, & Stern, 2000).

Concerning autobiographical episodic memory, a frequently reported finding in depression is a lack of memory specificity. Compared to healthy subjects, depressive patients tend to recall overgeneralised events and instead of reporting temporally and contextually distinctive episodes, they rather give categoric descriptions of summarised repeated occasions (Barnhofer, de Jong-Meyer, Kleinpass, & Nikesch, 2002; de Decker, Hermans, Raes, & Eelen, 2003; Park, Goodyer, & Teasdale, 2002; c.f. Williams, 1996). This retrieval style is further associated with poor recovery from the disease (Brittlebank, Scott, Williams, & Ferrier, 1993). A possible underlying mechanism is described by Williams (1996) and referred to as 'mnemonic interlock'. He suggests that overgeneral autobiographical retrieval is encouraged by a ruminative self-focus which in turn fosters overgeneral retrieval. Though also in healthy subjects overgeneral autobiographical retrieval serves to avoid memories for negative emotional aspects of events (Raes, Hermans, de Decker, Eelen, & Williams, 2003), in depressive patients it may develop early in life so that avoidance of conscious recollection becomes an automatised habit. Furthermore according to Williams, depressive patients show a tendency to retrieve negative self-referential categoric descriptions (e.g. "I have always failed"). If potentially negative retrieval cues are encountered[6], these categoric descriptions are triggered in an automatised way. Activation of related and frequently used self-descriptions is elicited only within this level of description stage (e.g. "I used to fail at school", "I never had friends" etc.) meaning that retrieval moves across the hierarchy rather than down to more specific levels. Thus, overgeneral memory emerges from a blockade or truncation ('mnemonic interlock') of the search for specific events and instead results in an overelaboration of self-related general categories (see Fig. 6).

[6] Given the aforementioned processing biases towards a negative direction, this may happen more likely than in non-depressed subjects.

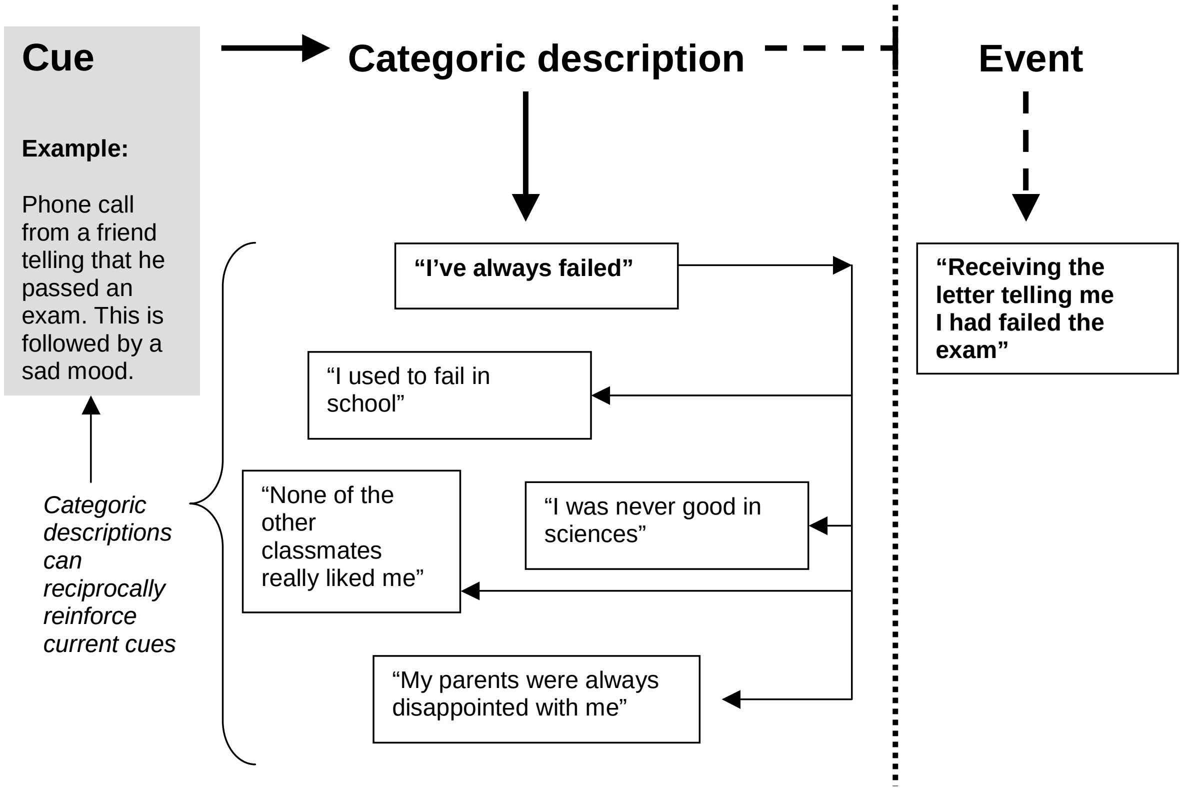

Figure 6: Truncated search for specific episodic memories in depression. Instead of retrieving event specific information, an iterated search within overelaborated categoric descriptions is instantiated; the dotted line indicates truncation (adapted from Williams, 1996, p. 261).

Williams further asserts that mnemonic interlocks can only be overridden at high costs of effort. Individuals with working memory or attentional impairments, either resulting from structural brain damage to the frontal lobes or functional metabolic disturbances in frontal brain regions (as seen in depression, cf. Beyer & Krishnan, 2002; Drevets, 2001), may show problems in inhibiting the automatised categoric search and therefore be particularly prone to impaired retrieval of specific memories. Thus, in Major Depression emotionally motivated overstable self views may prevent autonoëtic remembering of autobiographical episodes and instead foster noëtic retrieval of categoric events. It is not clear how this tendency develops in childhood and later on, but one of the most likely triggers is the experience of psychological trauma.

A large body of evidence emphasises the close relationship between stress and depression (e.g. Di Chiara, Loddo, & Tanda, 1999; Holsboer, 2001) and patients with PTSD show a heightened prevalence of comorbid depression (Breslau, Davis, Peterson, & Schultz, 2000; Franklin & Zimmerman, 2001) On the brain level, the common factor between both diseases can be seen in a dysregulation of glucocorticoid signalling while the processes in both diseases seem complementary (cf. Raison & Miller, 2003). In PTSD, specific changes of the hypothalamus-pituitary-adrenal axis are observed indicating hyperreactivity and hyperresponsiveness towards stress. This alteration contrasts with the chronic stress cascade in which corticotropin-releasing factor release results in attrition of negative feedback and down-regulation of glucocorticoid receptors. Thus, in PTSD a greater negative feedback inhibition of cortisol is observed, which may paradoxically serve to lower cortisol levels and which is secondary to an increased sensitivity of glucocorticoid receptors (Yehuda, 2001b, 2003). Taken together, glucocorticoids are required for reliable memory formation and retrieval, especially so if the memory contents is of emotional nature (see above). Therefore, hypersecretion of glucocorticoids and reduced responsiveness to glucocorticoids as seen in depression or hypocortisolism as in PTSD, may correspond to retrieval deficits of specific autobiographical episodes.

According to Ehlers and Clark (2000), acute traumatic stress or trauma is based on the subjective experience of a life-threatening situation for oneself or others (cf. Holbrook, Hoyt, Stein, & Sieber, 2001). For the later development of PTSD, the trauma and its circumstances are excessively negatively evaluated which probably leads to behavioural maladaptation (e.g. active avoidance) and changes in cognitive styles (e.g. rumination) (cf. Huether, Doering, Rueger, Ruether, & Schuessler, 1999). It may be of particular importance whether stress is subjectively perceived as uncontrollable or controllable. Huether et al. (1999) proposed that controllable stress triggers stabilisation and facilitation of neural networks for appropriate behaviours of appraisal and coping. Uncontrollable stress may favour extinction of inappropriate patterns but, additionally, neural connections underlying inappropriate behaviours are reorganised and eventually facilitated. Several factors predispose individuals to develop PTSD. Among these are socio-demographic variables such as membership of an ethnic minority (Al-Saffar, Borgå, Edman, & Hällström, 2003; Beals et al., 2002) or affiliation to occupational groups frequently dealing with extremely stressful situations (Feinstein, Owen, & Blair, 2002; Pole et al., 2001; Wagner, Heinrichs, & Ehlert, 1998). Traumatic experiences of the parents, familial instability as well as genetic predispositions may also account for development of adult PTSD (Bremner & Vermetten, 2001; Glaser, 2000; King, Abend, & Edwards, 2001; Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001; Yehuda, Halligan, & Bierer, 2001). A further critical factor may be the time during ontogenetic development when a trauma is experienced. Different cortical and subcortical brain structures mature in different time windows and accordingly, associated cognitive and social-emotional behaviours do as well (cf. Stiles, 2001). These functions' development can be significantly slowed, altered or impaired depending on the developmental stage at which a trauma is sustained. Underlying neural changes can include dysfunctional formation of synapses, deteriorations in migration of developing neurons or defective differentiation of functional neural associations (cf. Salmon & Bryant, 2002). In this regard, Anderson, Teicher, Polcari, and Renshaw (2002) observed that adults who were repeatedly sexually abused in childhood, exhibited structural brain changes as well as behavioural aberrances in contrast to non-abused control subjects. In structural MRI, eight subjects with sexual abuse in childhood showed altered T2 relaxation times in the cerebellar vermis and heightened pathology in a psychological screening compared to a control group. Psychopathology in the screening instrument was in turn linearly related to substance use and depressive symptoms in a second sample of more than 500 adults. Furthermore, in Schore's review (Schore, 2002) an elevated vulnerability of basal right hemispheric brain regions (e.g. brain stem, limbic system) related to childhood trauma and stressful attachments during upbringing was observed. Resulting impairments of primarily right hemispheric functions such as attachment and relationship behaviour, affect regulation and stress modulation as well as autobiographical episodic retrieval may therefore further promote subsequent dysfunctional coping strategies and later development of PTSD and depression.

Elzinga and Bremner (2002) reviewed the specific memory disturbances commonly seen in patients with PTSD. Typically, memory for the traumatic event itself is at least partially impaired and trauma-related material is retrieved in a fragmentary way (Nadel & Jacobs, 1998). Patients further suffer from intrusive thoughts and memories of trauma-related material and impaired recall of neutral information. Implicit access of the trauma, however, may be spared or even enhanced as is seen in heightened priming of trauma-related material and conditioning of emotional responses (e.g. Morgan, Grillon, Southwick, Davis, & Charney, 1995; Pole, Neylan, Best, Orr, & Marmar, 2003). Brewin (2001) suggests highly emotional information such as in trauma experiences to trigger basic conditioned responses while at the same time conscious memory processes are impaired (cf. **section I-1.3**). Elzinga and Bremner, (2002) suggest these dissociable effects to depend on structural and functional alterations in amygdala, hippocampus and medial prefrontal cortex. Alterations in the hippocampal formation may account for explicit memory deficits whereas disrupted inhibitory transmission from medial prefrontal cortex to amygdalar nuclei probably account for enhanced emotional conditioning and intrusive trauma memories. Concerning early childhood trauma, the dissociation between explicit memories and fragmentary, often hardly verbalisable traumatic memories may be dependent on developmental stages of language. Since neural/functional development does not yet enable verbal encoding in early childhood, early traumatic experiences do not possess verbal descriptions and therefore cannot be retrieved in the same way as later experienced episodes (cf. LeDoux, 2000).

It is controversial whether trauma or depression is the determining factor for overgeneral autobiographical memory retrieval. Some studies suggest a major influence of traumatic experiences (de Decker et al., 2003; Harvey, Bryant, & Dang, 1998), whereas others found depression to be more relevant (Arntz, Meeren, & Wessel, 2002; Wessel, Meeren, Peeters, Arntz,

& Merckelbach, 2001). Likewise, both factors have been identified as possible precursors in dissociative or functional retrograde amnesia (Markowitsch, 1999a) which will be discussed in **section I-2**. First, autobiographical memory and its components in healthy subjects is introduced.

1.4 Autobiographical memory

In the following, an introduction to autobiographical memory and its theoretical bases in humans is given. Underlying neural correlates in healthy subjects will then be reviewed.

Remembering autobiographical events requires retrieval of episodic memory contents, related emotions and a sense of one's own self and past life history (cf. Tulving, 2001). The vivid recollection of personal episodes is – at least partly – related to the evocation of the formerly experienced emotional states (Dolan, Lane, Chua, & Fletcher, 2000; Markowitsch, 2000c). To assign events to autobiographical memory, episodic memory contents have to be integrated and bound with a sense of self-coherence and self-continuity across the individual time axis reaching to the past as well as to the future (Larsen, Thompson, & Hansen, 1996). Thus, autobiographical episodic memory comprises the emotional evaluation of personal life experiences with respect to one's own self. The relationship between autobiographical memory and self is considered powerful if not inseparable. Furthermore, autobiographical remembering involves the conscious recollection of one's own self in the past. In the following sections possible interdependencies among autobiographical memory, self and consciousness are specified.

1.4.1 Martin A. Conway: Interdependencies between autobiographical memory and self

As was pointed out by Conway and Pleydell-Pearce (2000), autobiographical knowledge may define the range of goals of the self by which the construction of new autobiographical memories is reciprocally modulated. In their view, emotional autobiographical memories are derived from experiences of goal attainment or failure, and retrieval or forgetting of emotional personal events may serve to reduce perceived discrepancies in self. In particular, the authors suggest that autobiographical memories are transient mental reconstructions that are generated from an underlying knowledge base. This autobiographical knowledge base is assumed to be sensitive to cues that trigger endogenous activation patterns not necessarily involving consciousness for one's own self. Instead, instantiation of memories into consciousness and integration into ongoing information processing is modulated by central or executive control processes which implement plans generated from currently active goals. Thus, an entity that actively holds current goals is proposed and labelled 'working self' (Conway & Pleydell-Pearce, 2000). The goals of the working self are suggested to form a subset of working memory control processes organised into interconnected goal hierarchies that serve to constrain cognition and behaviour into effective ways of operating on the outside world. The goal structure of the working self is a mental model of one's own capacities and ideal states of oneself. The autobiographical knowledge base in turn restricts and constrains the range of goals that an individual can realistically hold. Thus, the goals of a transient working self determine access to the knowledge base which reciprocally constrains and restricts retrieval in order to serve currently active goals and prevent self-destabilising memories (cf. Conway, 2001b). Goals differ in their range and complexity and therefore can comprise topics such as mastery, independence, or intimacy as well as narrower subjects such as learning how to drive a car, eating healthy food, or calling a certain friend. The following example may illustrate these ideas. Person A and person B both move out of their parents' homes and therefore both have to handle the current goal of living on their own. Person A has had loving though emotionally overprotective parents. Her current goal attainment mostly consists of how to master the lack of constant emotional support from her parents. She selectively accesses autobiographical knowledge for occasions when she was emotionally protected by her parents and may remember these events as a help and comparison for her current everyday situation. In turn, she may selectively integrate only those new events into her autobiographical knowledge base, in which she now masters feelings of loneliness or helplessness on her own. Her autobiographical knowledge base restricts the realistic range of her current goals in that she does not immediately try to go out to a party where she does not know anyone and try to make friends. On the other hand, person B has had independent but somewhat impractical parents. Her current goal attainment consists of how to manage everyday duties such as doing laundry, shopping at the grocery's and the like. Former events in her autobiographical knowledge base related to these topics may (or may not) be a help and useful comparison in her current situation (e.g. when her mother once did laundry). She subsequently may pay specific attention to those new events, in which she manages these practical obstacles on her own and these instances are integrated into her autobiographical knowledge base. Restriction with regard to realistically possible goals prevents her from starting to gamble on the stock exchange or from buying a derelict house which she had to renovate on her own.

The knowledge base itself contains knowledge of different levels of specificity: Lifetime periods, general events and event-specific knowledge[7] (see also Barsalou, 1988; Conway, 1996). Lifetime periods are the most abstract and temporally extended autobiographical memories. They contain knowledge about others, locations, activities and evaluations common to a lifetime period as a whole (e.g. "My childhood in city X"). They may be chunked into higher order units to form

[7] A more detailed description of Conway's ideas of differences between autobiographical knowledge and episodic memory is given in **section I-1.4.3.**

life story schemata which in turn form part of the self concept (cf. Bluck & Habermas, 2000; Habermas & Bluck, 2000). General events are narrower than lifetime periods and contain information about others, locations, activities and evaluations relating to more specific experiences. In Conway's terminology (Conway, 2001b) they can concern repeated events (e.g. "Every time I went to school"), extended events (e.g. "My first holiday in Spain") or more specific events (e.g. "The weekend trip to Hamburg"). Finally, a third category, event specific knowledge, is proposed. It refers to sensory-perceptual details of distinctive and unique events (e.g. "The moment I saw Mr. C. for the first time"). Under control of the current working self, retrieval from the knowledge base is triggered at differential levels of specificity. Figure 7 gives an overview of the outlined interdependencies as proposed by Conway and Pleydell-Pearce (2000).

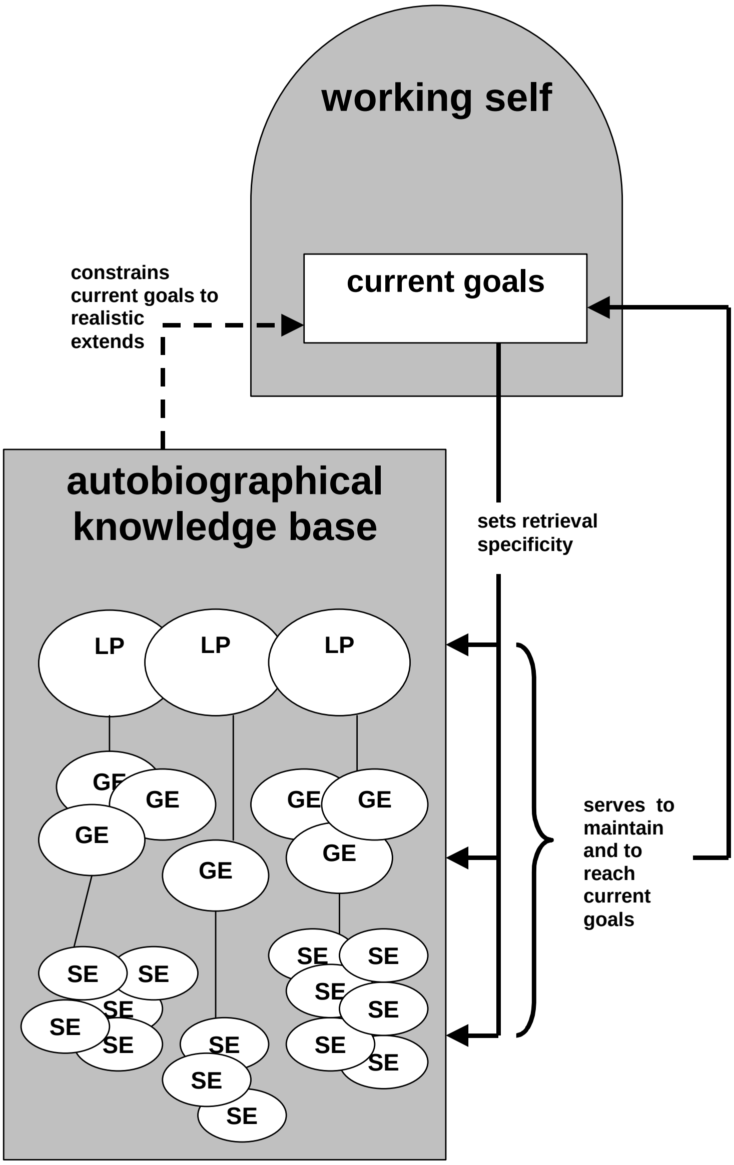

Figure 7: Interdependencies between autobiographical knowledge base and working self following Conway and Pleydell-Pearce (2000); LP: lifetime periods, GE: general events, SE: specific events.

Similar interdependencies are proposed by Wilson and Ross (2003). Their temporal self-appraisal theory claims a bi-directional relation between autobiographical memory and current identity. It suggests that autobiographical memory serves to enhance feelings of personal identity and consistency through time (see also Bluck & Habermas, 2000). The authors give evidence for self- and time-dependent memory biases and demonstrate how a tendency of perceived self-improvement over life time can distort autobiographical recall (e.g. Karney & Frye, 2002). On the other hand, current self views can be changed by the emotional connotation (Pasupathi, 2003) and temporal remoteness of retrieved autobiographical memories (Ross & Wilson, 2002). Mental concepts such as self or identity, require the ability to consciously experience oneself and one's past. Also, according to Tulving (e.g. Tulving, 2002), the experience of (autobiographical) episodic remembering is associated with a unique kind of consciousness, namely autonoëtic consciousness (cf. **section I-1.1.3.2**). Therefore, a neuroscientific elucidation of consciousness seems necessary which is given in the following section.

1.4.2 Antonio R. Damasio: Consciousness, self and autobiographical memory

Damasio (1994, 1999) challenged the view that 'consciousness' or 'the self' are metaphysical ideas separated from one's own body and any physical reality. In this vein, Churchland (2002) pointed out that a) conscious thinking results from activities of the physical brain, b) aspects of self-regulation and self-cognition can be non-conscious, and c) any introspective experience of the self is inseparable from the body.

In his theory of emotions and feelings, Damasio (1994, 2001) suggests that emotions are complex expressions of organisms' homeostatic regulatory systems. In his model, the basis of an emotion is the collection of changes in the body and mind mediated by several body organs and a limited number of brain circuits. This collection takes place under control of a brain system binding momentary thoughts with the current situation or event. Reactions resulting from this collection on the one hand involve bodily changes through a so-called body-loop, on the other hand, changes within the brain can be induced by minimally engaging the body via simulation through as-if-body-loops. An advantage of the latter mechanism is that organisms, on the basis of former experiences, can internally simulate internal and external events which then can be used in a generalised and therefore energetically economic way. Along these lines, Churchland (2002) pointed out that every system's efficiency may be linked to increasing abilities for internal emulation of future events, states, or outcomes.

Damasio (1999) proposes four stages of life regulatory mechanisms: basic reflexes, emotions, feelings and knowing of one's own feelings. These are associated with different levels of consciousness. On top of basic life regulation (e.g. reflexes), emotions are triggered if an object or situation occurs and is associated with specific somatic and mental changes. Furthermore, if an organism is capable of forming mental representations or images of the changes induced by emotions, a feeling is experienced. On the highest level, some organisms can consciously experience themselves as being the owners of their feelings. Reflexes, emotions and feelings do not necessarily require consciousness, whereas knowing feelings is a conscious process. Damasio (1999) suggests that emotions and feelings as well as increasing levels of consciousness provide the basis for survival-oriented behaviours. If organisms are capable of experiencing themselves as the owner of emotions and feelings, as-if-body loops are necessarily involved. Therefore, increasing levels of consciousness are associated with a higher degree of simulation capacity and therefore generalisation and adaptivity. Higher levels of consciousness are associated with increasingly complex forms of self representations. Along with this idea, Churchland (2002) claims that neuroscientific exploration of the self and its brain correlates requires a reformulation of the idea of the self as a singular entity into a concept allowing for a plurality of self-representing functions.

A possible classification of multiple hierarchically organised selves is given by Damasio (Damasio, 1999, see also Gallagher, 2000; O'Brien & Opie, 2003). On the most basic level, he suggests a non-conscious proto-self which is an ongoing collection of representations of the multiple dimensions of the current organism's state. On a higher level, he sets a core self being a transient but conscious reference or feedback to the organism in whom events are happening. The level of consciousness associated with the core self is labelled core consciousness. Core consciousness results from confrontation with an external or internal object or event automatically inducing mental representations experienced with a sense of ownership of these images. Core consciousness therefore is normally associated with a feeling of knowing oneself to be the owner of an experience. Due to its transient nature, the core self does not require embedding in a personal history or past experiences. Organisms without the ability to form autobiographical memories can, however, be conscious of their moment-to-moment core selves. Finally, on top of the hierarchy, so-called extended consciousness enables organisms to experience autobiographical selves. Extended consciousness is understood as the capacity to generate a sense of individual perspective and ownership over a larger range of knowledge than that surveyed in core consciousness. A substantial part of this knowledge is autobiographical memory. A summary of Damasio's model is given in Figure 8.

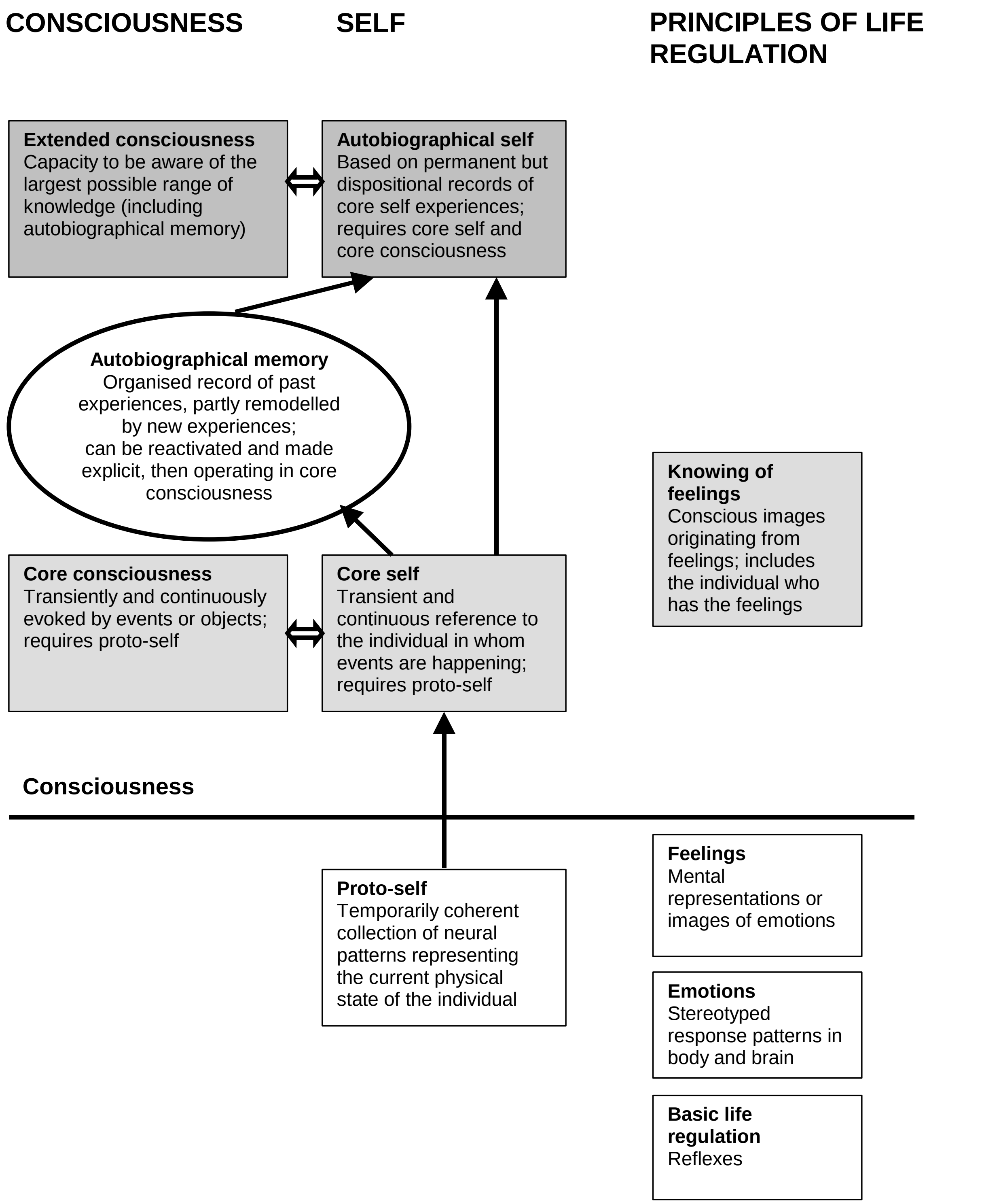

Figure 8: Classifications of consciousness, self and life regulatory systems according to Damasio (1999).

Due to the inseparability of the brain and body in Damasio's theories, neural substrates and representations of the body form the basis of emotion and proto-self (e.g. representation of the bodily internal milieu in brainstem, hypothalamus, and basal forebrain; representation of body posture and location in relation to the outside world in the somatosensory system). However, core and autobiographical self and associated core and extended consciousness require brain structures receiving converging signals from various sources capable of processing signals from the whole organism as well as from objects of the outside world. So-called convergence zones, a network comprising prefrontal cortex, cingulate cortex, thalamus, and superior colliculi, are assumed for this purpose (Damasio, 1999).

Though Damasio's assumptions may appear speculative, neurological and psychiatric patients who suffer from disturbances of autobiographical memory, emotion and self can provide concrete bases for the validity of the aforementioned classifications. Some of these will be described in the second part of this chapter. Neural bases of healthy subjects' autobiographical memory, which in Damasio's terminology is a major part of the knowledge used in extended consciousness are reviewed in the next section.

1.4.3 Functional neuroimaging of autobiographical memory

Given its complex nature and inherent variability between individuals, functional neuroimaging of neural correlates during autobiographical episodic memory retrieval is intricate and only a few studies have concentrated on this topic. Maguire (2001) reviewed the functional brain correlates of autobiographical episodic memory retrieval from nine functional neuroimaging experiments with healthy subjects (Andreasen et al., 1995; Andreasen et al., 1999; Burgess, Maguire, Spiers, & O'Keefe, 2001; Conway et al., 1999; Fink et al., 1996; Maguire, Henson, Mummery, & Frith, 2001; Maguire & Mummery, 1999; Maguire, Mummery, & Büchel, 2000; Ryan et al., 2001)[8]. Further, more recent studies have to be mentioned (Graham, Lee, Brett, & Patterson, 2003; Maddock, Garrett, & Buonocore, 2001; Maguire & Frith, 2003; Markowitsch, 2000b; Markowitsch, Vandekerckhove, Lanfermann, & Russ, 2003; Niki & Luo, 2002; Piefke et al., 2003; Tsukiura et al., 2002). Two preliminary experiments may as well be added (Botzung, Manning, Scheiber, & Paulos, 2003; Levine, in press). Taken together, these experiments revealed a distributed network of involved brain regions during autobiographical memory retrieval. Most consistently, this network comprised bilaterally ventrolateral, dorsolateral and ventromedial prefrontal cortex, temporal pole, lateral and medial temporal cortex including hippocampal and parahippocampal complex, temporo-parietal junction area as well as posterior cingulate/retrosplenial cortex and cerebellar regions. In the majority of studies a left hemispheric dominance was observed.

As Maguire (2001) noted, the findings from the reviewed studies may not provide a consistent delineation of functional neuroimaging correlates of autobiographical episodic memory due to differences in the experimental designs and scanning modalities (PET, fMRI) and

[8] The reviewed patient studies (Maguire, Vargha-Khadem, & Mishkin, 2001; Markowitsch, Thiel, Kessler, Stockhausen, & Heiss, 1997) are excluded here, since a more comprehensive overview of structural and functional brain correlates of autobiographical memory in patients is given in **sections I-2.2** and **I-2.4**.

methods (blocked fMRI, event-related fMRI). This also holds for the remaining recent studies. Concerning experimental designs, for instance, verbal materials (e.g. cue words: Botzung et al., 2003; Tsukiura et al., 2002; sentences: Fink et al., 1996; Piefke et al., 2003) or pictorial stimuli (e.g. Burgess et al., 2001) were either presented visually or auditory, and the time lag between stimulus acquisition and actual scanning comprised variable time ranges from 15 minutes (Andreasen et al., 1995) to several weeks (e.g. Maguire, Henson et al., 2001). Stimuli were mostly acquired through interviews of the subjects, but in one study some of the subjects' relatives were interviewed (Ryan et al., 2001). Moreover, the memory tasks themselves differed in their retrieval demands and the nature of their stimuli. For instance, in the study by Burgess et al. (2001), subjects were supposed to remember very recently experienced episodes of little personal involvement (artificial events in a virtual town learned immediately prior to scanning) whereas in other studies (Fink et al., 1996; Markowitsch et al., 2003; Piefke et al., 2003), to-be-retrieved information was explicitly emotional and the covered time range included the entire life history rather than only the very recent past (see also Maguire, 2001; Maguire & Frith, 2003).

Compared to other forms of memory, retrieval of autobiographical episodic memories implies several specificities concerning the task itself, the stimuli employed and accordingly associated brain activity. Firstly, a naturalistic task of autobiographical retrieval requires employment of events being differentially remote from the time of scanning. There is considerable debate about the time-dependent involvement of the hippocampal formation during retrieval of differentially remote memories. In line with memory consolidation theories that emphasise a time limited role of the hippocampus during engram formation, Niki and Luo (2002) and Piefke et al. (2003) observed activity in the hippocampal/parahippocampal complex to be restricted to retrieval of recent memories (cf. Rempel-Clower, Zola, Squire, & Amaral, 1996). However, other studies point to a time-independent (Maguire, Henson et al., 2001; Ryan et al., 2001) involvement. A critical approach to consolidation theory is the Multiple Trace Theory (Moscovitch & Nadel, 1998; Rosenbaum, Winocur, & Moscovitch, 2001) stating that the hippocampal complex contributes to the retrieval of all kinds of context-dependent information and therefore episodic memories of the entire life span. Such memory traces are thought to be represented as spatially distributed interactions between hippocampal complex and neocortex that persist for as long as those memories exist. On the other hand, context-free memories (e.g. semantic memories) are suggested to be independent of the hippocampal complex. By this logic, Rosenbaum et al. (2001) gave an alternate interpretation of differential hippocampal involvement across different time lags of remoteness of episodic memories. They suggested that its higher implication during recent compared to remote episodic memories may reflect an inherent lack of context and details in remote memories rather than a function of time passed (see also

Rosenbaum et al., 2000). However, even when richness of details was controlled across time periods, Niki and Luo (2002) revealed enhanced hippocampal activity during retrieval of recent in contrast to remote events. Further studies complicate the picture. For instance, Tsukiura et al. (2002) found the hippocampal complex to be inconsistently involved across time lags of remoteness of memories. Compared to a control condition, an increase of parahippocampal activity during recall of episodes from childhood and very recent events was observed, whereas retrieval of episodes from adolescence was not associated with enhanced parahippocampal activity. Finally, Maguire and Frith (2003) revealed hemispheric asymmetries of hippocampal activity covarying with remoteness of autobiographical episodes. They found a linear decrease in right hippocampal activity associated with remoteness of autobiographical memories, whereas the left hippocampus was invariably involved during remembering throughout the life span. So far, it can be concluded that probably both factors, time passed between memory formation and retrieval as well as differences in details across differentially remote episodes contributed to differential involvement of the hippocampal formation during remote autobiographical episodic memory retrieval.

A related issue concerning the specific nature of the stimuli and task in autobiographical episodic memory is raised by Conway (2001b). He suggests that a distinction be drawn between autobiographical knowledge and episodic memory assuming that episodic memory is largely sensory-perceptual in nature. In his view, during the process of episodic memory retrieval, these sensory characteristics trigger 'recollective experience' which he describes as the sense or experience of one's own self in the past. In contrast, retrieval of autobiographical knowledge, which in his view also contains personal semantics, is suggested to evoke feelings of familiarity. It may only then lead to a recollective experience, if this retrieval additionally activates interconnected episodic memories. For integration into autobiographical knowledge, these single episodes have to possess sensory-perceptual features and they have to be experienced in relation to the self and pre-existing autobiographical knowledge (see **section I-1.4.1**). Therefore, Conway proposes that sensory-perceptual episodic memory is associated with posterior sensory cortices while the more comprehensive autobiographical knowledge is suggested to involve broader networks of cortical and subcortical structures. The hypothesis that episodic memory retrieval reactivates posterior sensory brain regions was supported by an EEG study of Conway, Pleydell-Pearce, Whitecross, and Sharpe (2003). Herein, participants had to retrieve truly experienced events which was contrasted by processing of imagined events. Retrieval of true events was associated with higher activity shifts over occipito-temporal regions than processing of imagined events. However, an apparently conflicting result was revealed in a PET study by Markowitsch, Thiel et al. (2000). Here, activation of the precuneus region in the occipito-temporal junction area was observed during processing of imagined and fictitious in contrast to processing of true autobiographical events. Though the difference between real and fictive autobiographical episodes may reside in remembered sensory-perceptual characteristics of real episodes, it is unclear from the aforementioned results whether this is the most crucial differentiating variable. Possibly, re-experiencing of former self and emotions plays a similarly important role as was indicated by the results of the Markowitsch, Thiel et al. (2000) study. Generally, neuroimaging studies of autobiographical episodic memory employ stimuli which are episodic in nature, but, as a matter of definition, belong to the personal past of the subjects and thus to their general autobiographical knowledge. Therefore, while Conway's model (Conway, 2001b) is intriguing, no definitive neuroimaging evidence yet exists to confirm or disconfirm it.

Alternatively, emotional and self-related information processing can also be considered a crucial link to autobiographical episodic memory. Assuming that self-related processing is crucial for autobiographical episodic memory retrieval, medial and right prefrontal cortices seem prominent regions in which consistent overlap in activation has been observed in both, autobiographical episodic retrieval and self-processing tasks (cf. Markowitsch, 2003). A general right hemispheric preponderance for processing of one's own compared to other people's faces was found in laterality tasks by Keenan, Freund, Hamilton, Ganis, and Pascual-Leone (2000) and localised within the right prefrontal cortex in ERP and fMRI experiments (Keenan, McCutcheon, & Pascual-Leone, 2001). Similarly, in a PET study during which participants encoded trait adjectives either with reference to one's self or to other people, medial and right prefrontal cortex was involved only in the self-referential condition (Craik et al., 1999). Medial prefrontal engagement was also seen in fMRI experiments during self-referential cognition (Johnson et al., 2002; Kelley et al., 2002; Zysset, Huber, Ferstl, & von Cramon, 2002) with a possible differentiation of more ventral parts associated with emotional aspects and dorsal parts mediating attentional demands of the task (Gusnard, Akbudak, Shulman, & Raichle, 2001). In non-autobiographical episodic memory retrieval, medial and right ventral parts of the prefrontal cortex corresponded to active retrieval in contrast to automatic recollection (cf. Petrides, 2002). The results of (Lepage et al., 2000) concerning episodic retrieval mode and right ventral prefrontal activation (cf. **section I-1.2.3**) can be seen in the same light.

To reconcile the conflicting findings of right hemispheric activation in some autobiographical episodic retrieval studies (Fink et al., 1996; Levine, in press; Markowitsch, Thiel et al., 2000; Ryan et al., 2001), but medial and left prefrontal findings in others (cf. Maguire, 2001), the presence of perceived emotionality during the scanning session may provide a potential clue. Firstly, the emotionality of the used material itself cannot totally account for the lateralisation, since it was similarly associated with right (Fink et al., 1996), predominantly left

(Piefke et al., 2003) or bilateral prefrontal activations (Markowitsch et al., 2003). One can also consider whether the subjects' mood during the scanning session may have evoked a differential degree of emotional involvement across studies. In the Fink et al. (1996) experiment, participants were unaware of the purpose of previously conducted autobiographical interviews for stimulus acquisition. However, the same holds for Maguire's work (e.g. Maguire, Henson et al., 2001; Maguire & Mummery, 1999) in which predominantly left and medial prefrontal activity was revealed. It is nevertheless likely that in the two remaining studies (Levine, in press; Ryan et al., 2001), stimulus features led to greater emotional involvement. In Ryan et al. (2001), stimuli were partly acquired by interviews of spouses instead of participants themselves. Furthermore, in the (Levine, in press) study, participants were required to tape-record everyday experiences over a period of several months instead of reporting well-known and frequently recapitulated remote episodes as in the commonly used interviews (e.g. Maguire & Frith, 2003; Piefke et al., 2003). From those recordings only a small excerpt was taken as stimuli during scanning. Considering the effect this would have had on the participants, confrontation with autobiographical stimuli most probably invoked a higher degree of emotional involvement (e.g. feelings of surprise, ambiguity, emotional re-experiencing) as well as heightened visual attention to the stimuli during the scanning which may both correspond to right hemispheric activity (cf. Davidson, 2002, and Cabeza et al., 2003, respectively). In the same vein, a study by Fossati et al. (2003) directly compared self-referential reflection on emotional trait adjectives and found predominantly right anterior prefrontal activation in healthy subjects.

Taken together, it can be concluded that retrieval of autobiographical episodic memories is associated with a large network of memory related areas as well as brain regions specifically involved in processing of emotions and one's own self. Certain aspects of personal memories such as remoteness of an information may engage the hippocampal formation to a differential degree during retrieval which is, however, an ongoing controversy. Similarly, right hemispheric prefrontal lateralisation during self-related processing as well as autobiographical episodic retrieval is still under debate. Medial prefrontal areas are specifically engaged in processing of one's own self. These activations extend more ventrally and to the right prefrontal cortex, the more emotional the information is. This may be the case in autobiographical episodic memory studies, in which subjects are naïve to the stimuli and the stimuli themselves have an emotional impact. Though not consistent across studies, it is probable that if autobiographical episodes are re-experienced with a higher degree of emotional and visual/attentional involvement during the scanning, involvement of more right lateralised prefrontal areas becomes more likely. This may as well be applied to findings of autobiographical memory deficits in neurological and psychiatric patients, e.g., with right hemispheric frontal lesions or functional disturbances. These will be outlined in **section 2** of this chapter.

2. Disproportionate retrograde amnesia

In the second section of the Theoretical Background, behavioural, neuropsychological and neuropathological findings in disproportionate forms of remote memory loss are considered. Following a brief survey of organic focal retrograde amnesia, psychologically caused disproportionate forms of retrograde amnesia are exemplified in dissociative disorders. Subsequently, behavioural, neuropsychological and functional brain correlates are reviewed in a section on functional retrograde amnesia. To start this section, an explanation of the terminology used in previous and in the current study is given.

2.1 Terminology

Disproportionate loss of remote compared to new memories is a rare incident and diagnosis of organic and psychological mechanisms contributing to onset and maintenance of the amnesia is particularly difficult (see below). Therefore, such patients' deficits are inconsistently labelled in the literature. Commonly, if a clear neurological causation such as structural brain damage is observed, the label *focal retrograde amnesia* is used to indicate a relationship between focal brain lesion and memory deficit (e.g. Kapur, 2000; Kapur, Young, Bateman, & Kennedy, 1989). Furthermore, organically caused disproportionate forms of retrograde amnesia are also labelled *selective retrograde amnesia* or *isolated retrograde amnesia* (e.g. Levine et al., 1998; Miller et al., 2001; Yamadori et al., 2001) restricting the diagnosis to the overt behaviour instead of the brain lesion. Psychologically caused disproportionate retrograde amnesias are usually labelled *psychogenic, functional* or *dissociative amnesia*. Psychogenic amnesia clearly implies a relationship between memory deficit and underlying psychopathology (Kopelman, 2002b), which is even confined to a specific intrapsychic defence mechanism in dissociative amnesia (e.g. Porter, Birt, Yuille, & Herve, 2001). The term functional retrograde amnesia more generally points to dysfunctions of remote memory access in the absence of detectable structural brain damage (Kritchevsky, Zouzounis, & Squire, 1997).

These labels are not employed consistently across studies. Whereas most authors use the terms psychogenic and functional in an interchangeable way (e.g. Kopelman, 2002a), others apply 'functional retrograde amnesia' to cases in whom deficits were proposed to result from slight but undetectable brain dysfunctions (e.g. De Renzi, Lucchelli, Muggia, & Spinnler, 1997). For the latter cases, the labels *pure retrograde amnesia* or *pure focal retrograde amnesia* are used by certain research groups (Barbarotto, Laiacona, & Cocchini, 1996; Lucchelli, Muggia, & Spinnler, 1998; Lucchelli & Spinnler, 2002; Sellal, Manning, Seegmuller, Scheiber, & Schoenfelder, 2002).

In the current study, the label functional retrograde amnesia is used and applied to cases with disproportionate retrograde amnesia in the absence of structural brain pathology without inferring causal relationships between potential aetiology and amnesia.

2.2 Focal retrograde amnesia

In neurological diseases, the inability to acquire and retain new information, is more frequently and consistently reported than loss of remote memories (cf. Kopelman, 2002a). As aforementioned and pointed out by Kapur (1999), one reason for this discrepancy is that anterograde learning deficits can be caused by discrete lesions to diencephalic and limbic regions, whereas retrograde amnesia mostly results from significant involvement of subcortical and cortical brain areas. Accordingly, the majority of neurological patients suffering from retrograde amnesia also exhibit anterograde learning impairment due to broad lesions such as combined diencephalic and neocortical damage in Korsakoff syndrome (Kopelman, Stanhope, & Kingsley, 1999). Therefore, instances of focal retrograde amnesia accompanied by minor anterograde amnesia are rare and aetiologies differed to a large degree. In previous single cases, they encompassed severe traumatic brain injury (Goldberg et al., 1981; Hunkin, Parkin, Bradley, Burrows, Aldrich, Jansari, & Burdon-Cooper, 1995; Kapur, 2000; Kapur, Ellison, Smith, McLellan, & Burrows, 1992; Kapur et al., 1996; Kroll et al., 1997; Markowitsch, Calabrese, Haupts et al., 1993; Markowitsch, Calabrese, Liess et al., 1993; Markowitsch, Calabrese, Neufeld, Gehlen, & Durwen, 1999; Markowitsch, von Cramon et al., 1993; Mattioli et al., 1996; Rousseaux, Delafosse, Cabaret, Lesoin, & Jomin, 1984; case 1 of Yamadori et al., 2001), encephalitis (Calabrese et al., 1996; Carlesimo, Sabbadini, Loasses, & Caltagirone, 1998; Eslinger & Cermak, 1988; Eslinger, Damasio, Damasio, & Butters, 1993; Eslinger, Easton, Grattan, & Van Hoesen, 1996; Fujii, Yamadori, Endo, Suzuki, & Fukatsu, 1999; Hokkanen, Launes, Vataja, Valanne, & Iivanainen, 1995; Levine et al., 1998; O'Connor, Butters, Miliotis, Eslinger, & Cermak, 1992; Stuss & Guzman, 1988; Tanaka, Miyazawa, Hashimoto, Nakano, & Obayashi, 1999; case 2 of Yamadori et al., 2001; Yoneda, Yamadori, Mori, & Yamashita, 1992) as well as vascular pathology (Evans, Breen, Antoun, & Hodges, 1996; Evans, Graham, Pratt, & Hodges, 2003; Miller et al., 2001) or hypoxia (Manning, 2002)[9]. Similarly, lesion location or functional disturbance is variable and comprised thalamus (Miller et al., 2001), left temporal lobe (Hokkanen et al., 1995; Kapur et al., 1996), right fronto-parietal junction (O'Connor et al., 1992), bilateral fronto-parietal regions (Evans et al., 1996), bilateral temporo-parieto-occipital (Carlesimo et al., 1998; Manning, 2002) or parieto-occipital junction (Hunkin et al., 1995), as well as bilateral

[9] Further syndromes of excessive but usually transient retrograde memory loss comprise so-called Transient Epileptic Amnesia (TEA) (e.g. Kapur et al., 1989; Manes, Hodges, Graham, & Zeman, 2001) and Transient Global Amnesia (TGA) (Evans, Wilson, Wraight, & Hodges, 1993; Roman-Campos, Poser, & Wood, 1980).

medial temporal regions (Eslinger et al., 1996; Fujii et al., 1999; Mattioli et al., 1996; case 2 of Yamadori et al., 2001). Furthermore, the temporo-frontal connection may be a critical region for the retrieval of remote memories as it was implicated in several previous cases (Eslinger et al., 1996; Kapur et al., 1992; Kroll et al., 1997; Levine et al., 1998; Markowitsch, Calabrese, Haupts et al., 1993; Markowitsch et al., 1999; Tanaka et al., 1999). In this regard, Kroll et al. (1997) compared remote memory retrieval in two patients with bilateral temporopolar-prefrontal lesions with those in a patient with exclusively bilateral prefrontal damage. They found substantial episodic and semantic remote memory loss only in the patients with combined temporo-frontal lesions.

It was suggested by Markowitsch (1995) that information processing between prefrontal and anterior temporal lobes, interconnected via the ventral branch of the uncinate fascicle, is most critical for remote memory retrieval. This fibre tract connecting anterior and posterior regions of the brain (Ebeling & von Cramon, 1992), is assumed to allow backward and forward propagation of information stored in posterior association cortex (e.g. parietal lobes) while integration of retrieved information takes place within temporal lobes. Prefrontal areas may synchronise the search for specific details of the critical information and thus, only combined functioning of anterior temporal and prefrontal brain regions – additionally modulated via bi-directional connections to mediodorsal thalamus - may allow for appropriate remote memory retrieval (see also Kapur, 2000). In Greenberg and Rubin's view, (Greenberg & Rubin, 2003), anterior and medial temporal as well as (pre-)frontal brain structures, are necessary though not sufficient for the retrieval of remote (episodic) memories. Reviewing autobiographical memory loss and its possible brain correlates in organic diseases, Greenberg and Rubin (2003) suggested the underlying pathology to mainly comprise lateral temporal brain regions storing semantic knowledge combined with posterior cortices (e.g. occipital lobes) that process sensory features of episodic long-term memory information. The latter account is in good accordance with Conway's notion on episodic memory (Conway, 2001b; Conway & Pleydell-Pearce, 2000) especially requiring retrieval of sensory perceptual details of previous events (cf. **section I-1.4.1**).

In some disproportionate retrograde amnesia patients, neither corresponding structural brain damage nor psychological precursors were observed (e.g. Barbarotto et al., 1996; De Renzi, Lucchelli, Muggia, & Spinnler, 1995; Lucchelli et al., 1998; Sellal et al., 2002). In these cases, the amnesia was hypothesised to have been triggered by minimal cerebral damage that caused barely detectable functional/metabolic disturbances in memory relevant brain structures (e.g. De Renzi, 2002; De Renzi et al., 1997). Nevertheless, as was outlined by Kopelman (2000), many of these potentially organic forms of retrograde amnesia may have been entirely or partly caused by psychogenic mechanisms. In this regard he states (p. 614): "Given the difficulties in the attribution of causality, the social and psychological context needs to be presented for the reader to judge for himself or herself: [...] this can be just as crucial as presentation of the memory test scores. Psychogenic amnesia does exist, is important, deserves to be studied, and cannot be simply *dismissed*'. On the other hand, post-hoc determination of causational relationships is necessarily biased against the background that patients are seen past but not prior to their onset of amnesia. Whereas possible organic precursors are formally definable, social-emotional precursors and intrapsychic disturbances are subject to more speculative interpretation (Mayes, 2002). Under these circumstances, the finding of a presumed state of psychic discomfort preceding the amnesia is not sufficient to explain its entirety and comprehensiveness. Lucchelli and Spinnler (2002) argue that the heterogeneity of previously described potential psychological precursors and their high frequency of occurrence in everyday life cannot account for the rare instances of disproportionate retrograde amnesia. Given possible psychological precursors, it is therefore necessary for any attribution of causality that their exact nature, intensity and length are specified in detail (De Renzi, 2002; cf. Cortex (2002), 38 (4), 651-681; The Cortex Forum: Discussion on Retrograde Amnesia). However, since somatic and psychiatric problems commonly co-occur, the unequivocal distinction between either organic or psychogenic retrograde amnesia can be doubted (Kopelman, 2002a; Markowitsch, 1996).

Following an overview of clearly psychologically based disproportionate retrograde amnesia in dissociative disorders, the notion of a close interaction between somatic and psychological mechanisms underlying remote memory loss is resumed in the next section. Herein, previous cases of functional retrograde amnesia and probable neural correlates of the memory deficit are reviewed.

2.3 Dissociative disorders and memory

Already in early publications, patients were documented as suffering from psychological discomfort that was accompanied by memory disturbances (cf. Markowitsch, 1992). Among these, patients with hysterical or dissociative states such as the Ganser-Syndrome, Multiple Personality Disorder or 'Wanderlust', now labelled as Dissociative Fugue, were described (Ganser, 1898; Heilbronner, 1903; Pick, 1884). Today, dissociative disorders, sometimes filed under conversion disorders, comprise syndromes such as Dissociative Amnesia, Dissociative Fugue, and Dissociative Identity Disorder (American Psychiatric Association, 1994; World-Health-Organization, 1994). Dissociative Amnesia and Dissociative Fugue most often occur after the experience of psychological trauma or extremely stressful situations and time periods. Both syndromes involve the inability to retrieve the entirety or parts of the personal past. In Dissociative Fugue this retrieval failure is accompanied by a sudden and unexpected leave of one's usual environment for days, weeks, or even months and can include the assumption of a new identity. Awareness of basic life regulation is usually preserved (e.g. feeding, communication, use of common devices and transportation), so that patients do not give the clinical impression of disorganised thought as seen in schizophrenia. In Dissociative Identity Disorder, patients have the subjective and stable experience of at least two separable identities or personalities within their body. These are symmetrically or asymmetrically amnesic for each other. Each identity has its own perceptual, cognitive and communicative pattern relating to self and environment and at least two of the personalities repeatedly assume control of the behaviour. In Dissociative Identity Disorder symptoms of fugue and amnesia can co-occur and it usually results from experience of extremely traumatic (childhood) events.

Following van der Kolk and Fisler (1995) and van der Kolk (1994), dissociation enables the individual to fragment, de-realise and depersonalise traumatic experiences, yet this pattern of separating experiences from the self remains stable in everyday life. Acute dissociative reactions to a trauma can be predictive of later development of PTSD (Birmes et al., 2003; Marmar et al., 1999; Marshall & Schell, 2002). This indicates that dissociation – though a powerful psychological protection in the acute situation – is disadvantageous as a long-term stress coping mechanism. In this regard, Harvey et al. (1998) investigated a sample of motor vehicle accident survivors and found that inaccessibility of episodic memories for the trauma in the acute posttraumatic time accounted for PTSD severity at a six-months follow up. The probability of peritraumatic dissociations is determined by several factors. Marmar et al. (1999) and Marshall, Orlando, Jaycox, Foy, and Belzberg (2002) summarise these as follows: Extent of trauma exposition, duration of the trauma, subjectively perceived life-threat, existence of appropriate psychic regulatory behaviours, perceived power of external control, social support, flight- and avoidance reactions as well as emotional self-regulatory mechanisms. As was already described in early reports, memory impairment in dissociative disorders is relatively selective within the remote memory domain, often affecting only episodic-autobiographical memory (e.g. Heilbronner, 1903). Until today, patients with dissociative disorders represent a group of patients in whom disproportionate remote memory loss can most definitely be traced back to psychological causation (e.g. Glisky, Ryan, Reminger, & Hardt, in press; Markowitsch, Fink, Thöne, Kessler, & Heiss, 1997; Schacter, Wang, Tulving, & Freedman, 1982).

A common basis of dissociative disorders and further syndromes formerly labelled as *hysterical* (e.g. somatoform disorders) is specified by Oakley (1999). In his model of autosuggestive disorders, he refers to similarities across symptoms that can be induced by hypnotic procedures and those occurring in the context of hysterical disorders. In detail, he lists somatic and psychic phenomena such as paralysis, numbness, pseudoseizures and partial or extensive amnesic syndromes. In both, hypnosis and hysteria highly similar behavioural characteristics can be observed including a lack of concern towards one's own symptoms ('la belle indifférence'), subjectively perceived involuntariness as well as persistence of implicit knowledge in the face of absent explicit knowledge. The latter observation can, for instance, be made in patients with hysterical or functional blindness, who, regardless of their behavioural signs of blindness, avoid potential threats such as streets, bypass obstacles in experimental settings or otherwise implicitly use visual information (cf. Bryant & McConkey, 1989; Seligman & Rosenhan, 1998). In psychogenic amnesia, a similar dissociation of indirect and direct access to remote memories has been considered. While deliberate cueing failed to evoke past memories in some patients, more indirect questioning has been successful (Campodonico & Rediess, 1996; Kopelman, Christensen, Puffett, & Stanhope, 1994; Markowitsch, Fink, et al., 1997). For instance, Markowitsch, Fink et al. (1997) describe a 37 year old man (patient B.T.) suffering from extensive autobiographical-episodic amnesia following Dissociative Fugue. This patient was administered an implicit memory task comprising word fragments of names of formerly significant others (e.g. previous co-workers whom the patient did not explicitly recognise after the onset of his amnesia). When B.T. was asked to complete these word fragments, his performance was strikingly weak and even fell below guessing at a chance level. This result can be interpreted as implicit usage of explicitly inaccessible information, in this case contributing to worsening of the test performance.

Generalisability of this phenomenon to hypnosis is illustrated by a study Barnier (2002). She tested the implicit usage of to-be forgotten memories in high- and low-hypnotisable volunteers. She induced amnesia for one autobiographical event by hypnotic suggestion and tested retrieval both explicitly and implicitly. High-hypnotisable subjects showed impaired explicit recall of the critical autobiographical information compared to intact implicit access. Her results further give rise to the assumption that functional-psychogenic memory deficits may be caused by autosuggestive mechanisms (cf. Kihlstrom, 1997). In this regard, the results of Halligan, Athwal, Oakley, and Frackowiak (2000) and Marshall, Halligan, Fink, Wade, and Frackowiak (1997) are of particular interest. In a patient with conversion paralysis of the right leg, Marshall et al. (1997) investigated brain activity during the attempt to move the paralysed leg. By $H_2{}^{15}O$-PET, they found activation in right orbitofrontal cortex and right anterior cingulate gyrus. Applying the same paradigm, an almost identical activation pattern was observed in a control subject with hypnotically induced right leg paralysis (Halligan et al., 2000). Halligan et al. (2000) argued that in both individuals, activation within these areas may correspond to an active suppression of the voluntary attempt to move the paralysed leg. These results further support Oakley's (1999) model of a general similarity of hypnotic and hysterical symptoms and extend his notion to probable common underlying brain correlates. Summarising his view, he states that behavioural similarities concern the major areas of motor, sensory and memory- or identity-related symptoms. In this regard, symptoms of dissociative disorders can primarily be seen on the memory level whereas conversion disorders concern mostly sensory and motor symptoms. As outlined in Figure 9, within all major categories, positive and negative symptoms (i.e. pathological overproduction versus reduction of behaviours and thoughts) can emerge.

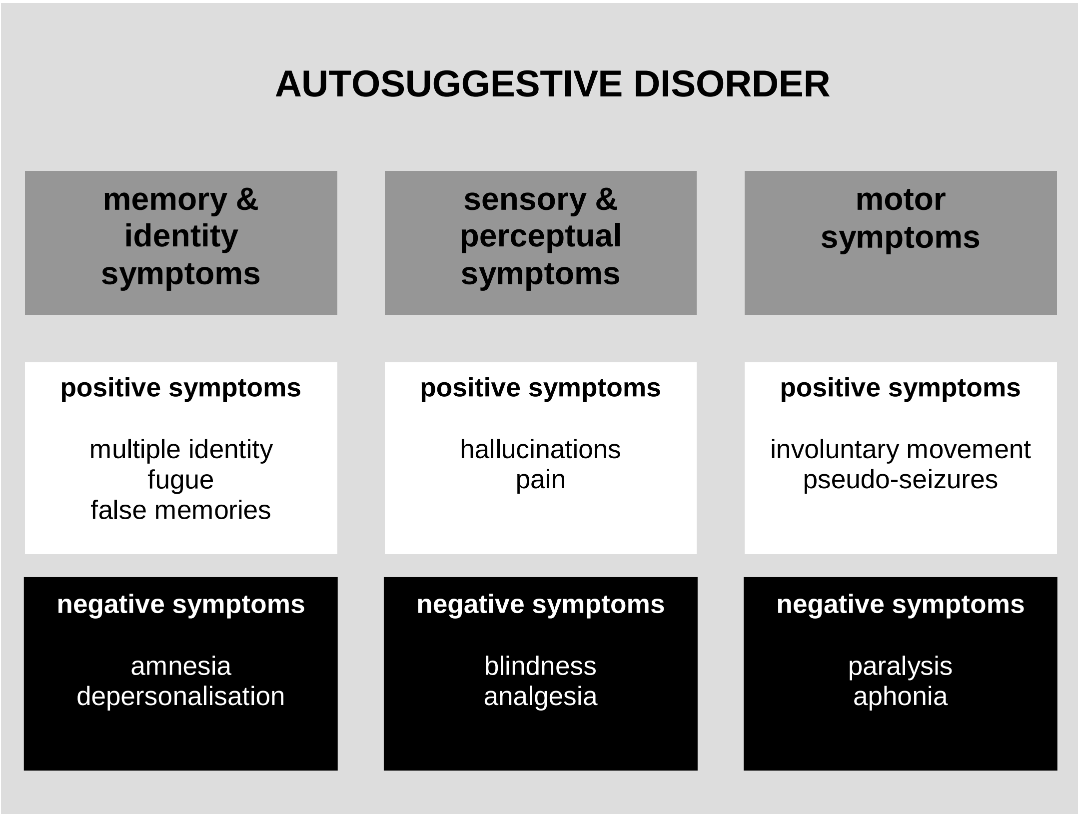

Figure 9: Oakley's scheme for classifying positive and negative symptoms of conversion disorders and dissociative disorders under the heading of autosuggestive disorders (modified from Oakley, 1999)

To conclude, in dissociative disorders disproportionate retrograde amnesia can be traced back to psychological triggers such as psychological trauma or massive stress yielding at de-realisation and de-personalisation of those traumatic experiences as a stress coping mechanism. There may be a considerable overlap of somatic symptoms in conversion disorders and memory-related symptoms in dissociative disorders and both may originate from mechanisms of (self-)suggestion. Though these processes are usually seen on a psychological level only, brain correlates of these behavioural disturbances have been observed. Therefore, disproportionate forms of retrograde amnesia can emerge from primarily organic aetiologies as in focal retrograde amnesia as well as from psychic trauma as in dissociative disorders. However, there is a considerable overlap of organic and psychological factors in many previous cases of disproportionate retrograde amnesia, especially in functional retrograde amnesia. In the following section, previous single cases of functional retrograde amnesia are reviewed and, if available, neural correlates of the amnesia are provided.

2.4 Functional retrograde amnesia

Patients with functional retrograde amnesia suffer from disproportionate remote memory loss and relatively intact anterograde memory in the absence of structural brain damage. Several behavioural and neuropsychological features have been isolated to differentiate these patients from individuals with disproportionate retrograde amnesia following structural brain lesions. Beyond the aforementioned implicit usage of explicitly inaccessible memories and a lack of concern towards one's own amnesic symptoms, other studies revealed 'reversed' temporal gradients in functional retrograde amnesia (i.e. relatively unimpaired retrieval of recent information with massive deterioration of childhood memories), a pattern which is usually not seen in organic amnesia (Kopelman et al., 1994; Kritchevsky et al., 1997; cf. Kopelman & Kapur, 2001). Furthermore, secondary gain or benefit from the amnesia can indicate psychological mechanisms (e.g. De Renzi et al., 1995; Papagno, 1998).

However, the unequivocal distinction between organic and psychogenic retrograde amnesia is questionable since somatic and psychiatric problems commonly co-occur (Kopelman, 2002b; Markowitsch, 1996). For instance, Kisely, Goldberg, and Simon (1997) demonstrated in a multi-centre study employing more than 25,000 participants from 14 different countries that somatic symptoms with and without clear organic causation were associated with additional psychiatric symptoms. Somatic and psychiatric disorders were positively linearly related if somatic symptoms were medically unexplained, but also if a clear somatic explanation of medical symptoms was given, the incidence of additional psychiatric disorders was increased. In this case, a sharp increase of additional psychiatric symptoms was observed, if a threshold of 11-12 medically explainable somatic symptoms was exceeded. Transferred to disproportionate retrograde amnesia, Kapur (2000; p. 629) revised the diagnosis of the aforementioned focal retrograde amnesia patient who was initially studied in 1992 (Kapur et al., 1992). Though this patient suffered from bilateral temporal lobe pathology, it turned out later that she developed additional psychiatric symptoms (conversion-like leg weakness) and that her initial retrograde amnesia was preceded by stressful events. Thus, even in the presence of brain pathology, psychological processes may influence onset, severity and recovery of amnesic symptoms (cf. case PN of Costello, Fletcher, Dolan, Frith, & Shallice, 1998). The common underlying bases of organic and psychogenic forms of retrograde amnesia have recently been specified by Kopelman (Kopelman, 2000, 2002a, 2002b). The author proposes that social factors (e.g. stress), previous amnesia-related experiences (e.g. previously experienced Transient Global Amnesia) and current emotional state (e.g. depression) can be seen in close interaction with brain systems processing autobiographical episodic memory retrieval as well as a personal semantic belief system or 'self'. In Kopelman's model of psychogenic retrograde amnesia (Kopelman, 2002b), severe precipitating stress, current emotional state and past experiences of transient organic memory loss elevate the probability of retrograde amnesia by an interaction with frontal/executive systems resulting in inhibition of remote memory retrieval. In this regard, Anderson and Green (2001) revealed that executive inhibitory control processes can suppress unwanted memories also in healthy subjects. In a series of behavioural experiments, it was found that the deliberate suppression of explicit memory for one word of word pairs lowers its later accessibility. Moreover, the number of preceding suppression trials significantly decreased later memory performance for the target words indicating a possible executive inhibitory mechanism underlying memory suppression as suggested in functional memory deficits (see also Halligan et al., 2000; Marshall et al., 1997). While it can be questioned whether motivated forgetting of personally irrelevant information as in Anderson and Green (2001) parallels the unconscious inhibition of one's own past in functional retrograde amnesia (Kihlstrom, 2002), Anderson and Green's results give hints for possible cognitive mechanisms underlying repression (Conway, 2001a).

In functional retrograde amnesia, there are inconsistencies concerning potentially relevant aetiological or predisposing factors, characteristics of the amnesia, additional neuropsychological impairment and potentially underlying neural correlates. In Table 3, an overview of neuropsychological and – if available – brain correlates of previous cases with functional retrograde amnesia is given. Patients suffering from focal retrograde amnesia with a clear organic causation are excluded.

Table 3: Previous single cases of functional retrograde amnesia

Study	**Patient characteristics**	**Aetiology & predisposing factors**	**Neuro-psychological symptoms**	**Physiological measures & brain correlates**
Andrews, Poser, and Kessler (1982)	59 years, male	headache	mild AA; episodic and semantic RA for previous 40 years	EEG: normal

Study	Patient characteristics	Aetiology & predisposing factors	Neuro-psychological symptoms	Physiological measures & brain correlates
Barbarotto et al. (1996)	P.A.: 38 years, female	possibly a minor head injury, histrionic personality disorder	mild episodic and extensive semantic RA; implicit usage of remote memories	CT, SPECT: normal
Campodonico and Rediess (1996)	L.J.: 47 years, female	severe preceding stress deprived from sleep and ingestion for several days; anxiety disorder; history of paranoid behaviour	episodic and semantic RA; irregular neuropsychological profile language, attention; implicit usage of semantic knowledge	CT: normal
Costello et al. (1998)	P.N.: 'in his 40ies', male	stroke, haemorrhage, history of pseudoseizures, financial, professional and marital stress during preceding 15-20 years	episodic and semantic RA for preceding 19 years; sharp temporal gradient preserved memory for information that were older than exactly 19 years	MRI: left anterior dorsomedial prefrontal damage EEG: normal $H_2^{15}O$-PET: increased activity in left precuneus and decreased activity in right posterior ventrolateral/left superior frontal cortex contrasting retrieval attempt of pre-amnesic versus post-amnesic autobiographical episodes. Similar differences contrasting pre-amnesic episodes and impersonal information
Dalla Barba, Mantovan, Ferruzza, and Denes (1997)	R.M.: 17 years, female	unknown	episodic RA	EEG, CT, MRI, FDG-PET: normal

Study	Patient characteristics	Aetiology & predisposing factors	Neuro-psychological symptoms	Physiological measures & brain correlates
Della Sala, Freschi, Lucchelli, Muggia, and Spinnler (1996)	D.V.: 33 years, male	minor head injury, possibly preceding stress following a sexual maturation crisis	episodic RA, mild semantic RA	EEG, CT, MRI: normal; SPECT: diffuse bilateral cortical hypoperfusion
De Renzi and Lucchelli (1993	P.I.: 24 years, male	thoracal trauma, hypoxia	episodic and semantic RA; mild long term learning problems	MRI: normal, FDG-PET: bilateral posterior-superior temporal hypometabolism
De Renzi et al. (1995)	M.A.: 19 years, male	possibly minor head injury; loss of consciousness after traffic accident	episodic and semantic RA; implicit usage of semantic knowledge	CT, MRI, FDG-PET: normal
De Renzi et al. (1997)	Andrea: 58 years, male	head injury	episodic and semantic RA; procedural impairment reading, writing, arithmetic	CT, MRI, SPECT: normal

Study	Patient characteristics	Aetiology & predisposing factors	Neuro-psychological symptoms	Physiological measures & brain correlates
Glisky et al. (in press)	F.F.: 33 years, male	psychogenic fugue after being assaulted; 4 months before: secret departure from home country following legal and financial problems	episodic RA; executive dysfunctions; loss of native German language; gradual recovery over approximately 5 weeks	SCR: greater SCR elevation to falsely rejected autobiographical information compared to correctly recognised. No such dissociation between honest and pretended rejection of autobiographical sentences in control subjects. fMRI: enhanced parietal and decreased fronto-striatal activity processing German words contrasting enhanced frontal activity in bilinguals simulating amnesia for the German language
Gudjonsson and Taylor (1985)	Mr.A.: 40 years, Male	stressful previous life legal and relationship problems	AA; RA for 20 years; gradual recovery after 8-9 months	EEG: normal
Kapur and Abbott (1996)	P.P.: 19 years, male	fugue-like state after preceding stress university exams; acute headache	episodic and semantic RA; gradual recovery over 4 weeks	CT: normal
Kapur et al. (1996)	37 years, female	mild head trauma	episodic and semantic RA for the preceding 14 years; mild anterograde amnesia; sudden recovery after 4 months	CT: normal

Study	Patient characteristics	Aetiology & predisposing factors	Neuro-psychological symptoms	Physiological measures & brain correlates
Kopelman (2000)	A.: 58 years, male	fugue after preceding stress financial, marital	episodic RA; recovery after 4 days	not described
	B.: 52 years, male	several fugue-states after inflammatory encephalopathy, preceding stress	RA for fugue states	MRI; lumbar puncture: normal
	D.: 38 years, male	possibly mild head injury; preceding psychosomatic problems	episodic and semantic RA, AA; depression	CT, MRI: normal
	E.: 55 years, male	minor ischemic insult; abuse during childhood	episodic RA; functional left arm and leg weakness	CT: normal; MRI: slight bilateral signal changes resulting from diabetes
Kopelman et al. (1994)	A.T.: 43 years, female	fugue after psychic trauma	episodic and semantic RA; implicit usage of semantic knowledge	CT: normal
Lucchelli, Muggia, and Spinnler (1995)	M.M.; 24 years, male	traffic accident without loss of consciousness	episodic and semantic RA; sudden recovery after 1 month	CT: diffuse cerebral oedema; MRI: normal FDG-PET: bilateral posterior cingulate hypometabolism
Lucchelli et al. (1998)	C.D.A.: 20 years, male	minor head injury	episodic and semantic RA	EEG, CT, MRI: normal
	G.C.: 38 years, male	fugue state after the patient betrayed his employer	selective RA for job-related information about 7 years pre-incidental	EEG, CT, MRI, SPECT: normal
	A.F.: 15 years, male	minor head injury	episodic and semantic RA; sudden recovery after 7 days	EEG, CT: normal

Study	Patient characteristics	Aetiology & predisposing factors	Neuro-psychological symptoms	Physiological measures & brain correlates
Mackenzie Ross (2000)	J.J.: 56 years, female	minor head injury without loss of consciousness, stressful life history, abuse during childhood, marital violence, depression	global cognitive impairment: intellectual deficits; AA; episodic and semantic RA; executive dysfunctions	EEG, CT: normal MRI: white matter changes of a non-specific nature in the centrum semiovale indicative of small vessel disease
Maravita, Spadoni, Mazzucchi, and Parma (1995)	V.T.: 15 years, female	minor head injury	initially semantic and episodic RA; AA; residual episodic RA after two years; abnormal anterograde forgetting rate	CT: signs of left parietal hypodensity uncertain significance FDG-PET: hypometabolism in the same region
Markowitsch, Thiel et al. (1997)	D.O.: 59 years, female	sexual abuse in childhood	selective RA for life period 10-16 years of age trauma period	MRI: normal $H_2^{15}O$-PET: temporo-polar activation during exposure to trauma-related information without explicit access to this information
Markowitsch, Calabrese et al. (1997)	B.T.: 30 years, male	dissociative fugue; stressful experiences since childhood	episodic RA	CT, MRI: normal, possible sign of past meningitis SPECT: right temporo-frontal hypoperfusion $H_2^{15}O$-PET: abnormal processing of recently learned information

Study	**Patient characteristics**	**Aetiology & predisposing factors**	**Neuro-psychological symptoms**	**Physiological measures & brain correlates**
Markowitsch, Fink et al. (1997)	N.N.: 37 years, male	dissociative fugue; personality problems since childhood	episodic RA	EEG, MRI: normal $H_2^{15}O$-PET: left hemispheric temporo-frontal activation pattern during retrieval of autobiographical episodes; similar location of activations in the right hemisphere in healthy control subjects
Markowitsch et al. (1998) Markowitsch, Kessler et al. (2000)	A.M.N.: 23-25 years, male	childhood trauma; amnesia after exposure to an event resembling the stressful experience from childhood	episodic AA; episodic RA for preceding 6 years; begin of recovery 8 months after onset due to intensive pharmaceutical and psychological treatment	EEG, MRI: normal FDG-PET (1998): hypometabolism in bilateral hippocampus and fronto-basal cortex, right temporo-basal, and left temporo-medial cortex, left dorsal parietal region, insula, and cerebellum FDG-PET (2000): metabolic normalisation after about 1 year

Study	Patient characteristics	Aetiology & predisposing factors	Neuro-psychological symptoms	Physiological measures & brain correlates
Nakamura et al. (2002)	T.H.: 23 years, male	traffic accident with loss of consciousness	episodic and semantic RA; lexical/procedural impairment reading, writing, naming, object use	MRI: normal SPECT: bilateral hypoperfusion in temporal and occipital lobes
	K.N.: 27 years, female	fever of unknown origin; various preceding somatic and psychological problems anorexia, frequent hyperthermia, dyspnea, past right-sided motor disturbances and dysarthria without organic basis	episodic and semantic RA; AA; lexical /procedural impairment reading, writing, naming, object use	MRI: normal
Papagno (1998)	C.L.: 16 years, male	minor head injury, preceding stress	episodic and semantic RA; naming deficit; recovery after 10 days	CT, MRI: normal EEG: left temporal irritations
Sellal et al. (2002)	F.P.: 32 years, male	minor head injury	episodic RA, to a lesser degree semantic and procedural RA; recovery after 4 weeks	CT, MRI: normal EEG: right temporal irritations SPECT: right temporal hypometabolism
Schacter et al. (1982)	P.N.: 21 years, male	dissociative fugue after trauma	episodic and semantic RA; mild AA; recovery 24 hours later after seeing a television scene resembling the trauma	CT: mild signs of previous right temporal lobe damage
Starkstein, Sabe, and Dorrego (1997)	R.P.: 16 years, male	minor head injury	episodic and semantic RA	CT, MRI: normal SPECT: right frontal, parietal and thalamic hypoperfusion

Study	**Patient characteristics**	**Aetiology & predisposing factors**	**Neuro-psychological symptoms**	**Physiological measures & brain correlates**
Stracciari, Ghidoni, Guarino, Poletti, and Pazzaglia (1994)	M.L.: 20 years, male	minor head injury	episodic RA for 1 year; attentional deficits; gradual recovery after 6 months	EEG, MRI: normal SPECT: left frontal hypoperfusion
	D.R.: 20 years, male	minor head injury	episodic RA for preceding 10 months; gradual recovery after 1 year	EEG, CT: normal SPECT: left parietal hypoperfusion FDG-PET after recovery: normal
Yasuno et al. (2000)	33 years, female	suicide attempt sedatives after stress, depression	episodic and semantic RA	CT, MRI: normal $H_2^{15}O$-PET after 2 months: right anterior medial temporal and amygdala activation during exposure to famous faces vs. bilateral hippocampal activation in control subjects; hyperactivation in anterior cingulate and prefrontal cortex $H_2^{15}O$-PET after 1 year: recovery of abnormal activation pattern

EEG: electroencephalography; CT: computer assisted tomography; MRI: magnetic resonance imaging; SPECT: single photon emission computed tomography; PET: positron emission tomography; FDG: ^{18}F-fluoro-2-deoxy-D-glucose; $H_2^{15}O$: radioactive water isotope; RA: retrograde amnesia; AA: anterograde amnesia; SCR: skin conductance response

In summary, the average age of the listed patients (mean age: 33.5 years) appears to be considerably younger than that of patients with organic amnesia (cf. Kritchevsky et al., 1997). The aetiologies reflect the two aforementioned groups of functional retrograde amnesia patients. One group had experienced stress or psychic trauma before the onset of the amnesia, whereas in the other group the deficit emerged after a minor head trauma. In both groups, however, psychological/psychiatric precursors or previous psychological problems were seen eventually, reinstating the close interaction of psychic and somatic processes.

In almost all cases, episodic autobiographical memory was impaired, and the majority of patients also suffered from partial semantic retrograde amnesia. Sometimes language and procedural skills were likewise deficient. Functional retrograde amnesia most often covered the entire prior life, while some patients showed more circumscribed amnesic gaps with regard to time periods or contents. Compared to the retrograde memory deficits, anterograde memory was most often spared or disproportionately impaired although in a few of the above listed cases, intellectual and learning deficits were clearly present (cf. Kopelman [2000] for an extensive discussion on this issue).

Per definition, relevant structural brain damage has to be excluded in functional retrograde amnesia, and the instances of organic pathology in some of the listed cases do not sufficiently explain the symptoms of the exhaustive remote memory deficit (e.g. Schacter et al., 1982). Referring to the aforementioned similarity of behavioural symptoms probably originating from intrinsically or extrinsically induced suggestion (cf. **section I-2.3**), it may be of particular interest that in some of the cases, symptoms emerged after altered states of consciousness (e.g. unconsciousness after mild head trauma). Information about recovery from amnesia was not given in all case reports, rendering prognostic estimates difficult. While there were cases of enduring retrograde amnesia, others recovered from their symptoms, sometimes in an abrupt manner resembling the onset of their amnesia (cf. Lucchelli et al., 1995). In a few documented patients, recovery from amnesic symptoms was accompanied by normalisation of resting state functional metabolic disturbances (Markowitsch et al., 1998; Markowitsch, Kessler et al., 2000) or memory retrieval-related functional brain abnormalities (Yasuno et al., 2000; see below). These latter cases indicate that even given clear psychological factors in the acute stage of the retrograde memory deficit, corresponding functional metabolic disturbances may be detected. Moreover, these functional irregularities reflect a plasticity whose purpose may be in resolving behavioural symptoms, a phenomenon which is also seen in (other) psychiatric disorders and their successful treatment (e.g. phobia: Paquette et al., 2003; conversion paralysis: Vuilleumier et al., 2001).

As can be derived from Table 3, some previous cases' functional brain correlates were investigated during resting states by EEG, SPECT or FDG-PET. Functional irregularities were found in temporal regions of the right (Sellal et al., 2002) and left hemisphere (Papagno, 1998), in bilateral temporal lobe regions (De Renzi & Lucchelli, 1993; Nakamura et al., 2002), in the right temporal-frontal junction area (Kroll et al., 1997), in frontal or parietal areas of the left (Stracciari et al., 1994) or right hemisphere (Starkstein et al., 1997), in the posterior cingulate gyrus (Lucchelli et al., 1995) as well diffusely cortical (Della Sala et al., 1996). However, in other studies no functional deviances were seen (Barbarotto et al., 1996; Dalla Barba et al., 1997; De Renzi et al., 1995, 1997). Thus, similar to lesion variety observed in organically caused disproportionate retrograde amnesias (cf. **section I-2.2**), functional metabolic disturbances can be considered as inconsistent.

A few previous studies concentrated directly on functional brain correlates during active states, namely the retrieval attempt of lost remote memories (Costello et al., 1998; Glisky et al., in press; Markowitsch, Calabrese et al., 1997; Markowitsch, Fink et al., 1997; Markowitsch, Thiel et al., 1997; Yasuno et al., 2000). In this regard, brain activation of patient N.N. (Markowitsch, Fink et al., 1997), suffering from autobiographical-episodic functional retrograde amnesia following a fugue, has been studied with $H_2^{15}O$-PET while the patient attempted to retrieve autobiographical episodic remote information. N.N. showed a largely left lateralised activation pattern of temporal-frontal regions compared to right lateralised activity seen in healthy control subjects (Fink et al., 1996). In the healthy subjects a lateralisation to the left hemisphere has been detected during retrieval of semantic information. Thus, N.N.'s activation pattern was supposed to reflect the processing of one's own autobiography as if it was personally irrelevant, semantic information. This may correspond to an emotional detachment from personal memories as was obvious on the behavioural level (Markowitsch, Fink et al., 1997).

On the other hand, an overly emotional processing of remote memories was hypothesised in the functional retrograde amnesia-patient of Yasuno et al. (2000). In a $H_2^{15}O$-PET paradigm, their patient processed semantic remote information (famous faces) with enhanced activation in right prefrontal cortex and right anterior medial temporal regions including the amygdala as well as decreased activity in the right anterior cingulate. In contrast, healthy control subjects showed bilateral hippocampal activity and – corresponding to the semantic nature of the stimuli – more left lateralised prefrontal activation. Due to the enhanced amygdala activity, the authors proposed an overly emotional, especially negatively valenced processing of semantic remote information in their patient. Moreover, after recovery from functional retrograde amnesia, the patient's right hemispheric limbic and cortical hyperactivity during this task resolved to normal at a one year follow-up examination.

In a series of experiments Glisky et al. (in press) examined patient F.F. suffering from functional retrograde amnesia after a dissociative fugue. His skin conductance responses (SCR) during the recognition of sentences depicting true autobiographical versus fictitious information was examined. To test the possibility that F.F. was malingering his symptoms, control participants were instructed either to correctly respond to the sentences (recognise true and reject fictitious sentences) or to lie intentionally (reject true and fictitious sentences). F.F. showed a greater elevation of the SCR to sentences he falsely rejected compared to those he correctly recognised while control subjects did not show a dissociation between honest and pretended rejection of true autobiographical sentences. Given this result, it was argued that F.F. still has implicit knowledge of his autobiographical information and that he was not intentionally malingering his symptoms. His deficits also included amnesia for his native German language. Therefore, in a lexical decision task mapped by event-related fMRI, English and German words and non-words were shown to F.F. and native English speaking monolingual or German-English bilingual control participants. To test for malingering of the symptoms in F.F., the latter controls were instructed to process the stimuli as if they were either able to understand German or to simulate an amnesia for the German language. F.F.'s activation pattern across frontal brain regions resembled that of the bilingual controls but he showed elevated activity in parietal areas and grossly reduced activity in fronto-striatal regions, especially compared to bilingual controls while they simulated being amnesic. It was proposed that F.F. relied on enhanced phonological processing of the language stimuli (parietal hyperactivity). When classifying German words as non-words, simulating bilingual controls displayed enhanced frontal activity indicating an involvement of additional source monitoring or control functions which was contrasted by a frontal hypoactivity in F.F. The fMRI results point in the same direction as the SCR results since F.F.'s physiological responses resembled those of comparable controls but differed from those of subjects who intentionally simulated being amnesic.

One further patient, studied by Costello et al. (1998), could be considered as well. This case is somewhat different from the aforementioned patients, since the onset of his amnesia was clearly an organic disease (stroke) and he sustained haemorrhage to the left dorsolateral prefrontal cortex. However, the patient also presented with signs of psychogenic rather than organic retrograde amnesia (e.g. unusual temporal gradient in remote memory loss, stressful life, pseudoseizures). $H_2^{15}O$-PET during retrieval attempt of remote autobiographical episodes contrasting newly acquired episodes or impersonal information, revealed increased activity in precuneus and decreased activity in right posterior ventrolateral frontal cortex and left superior frontal cortex in the region of the structural damage. The authors proposed that P.N.'s retrieval deficit may be caused by a lack of activation in the right ventrolateral frontal area, a region they suggested to correspond with recursive self-cueing during autobiographical retrieval (cf. Levine et al., 1998).

To conclude, disproportionate retrograde amnesia is a rare incident in neurological as well as in psychiatric diseases. It can be inferred from previous single cases that attribution of causality is difficult and may be blurred by the common co-occurrence of somatic and psychological problems. However, some behavioural and neuropsychological characteristics might be useful to differentiate somatic and psychological factors in the course of disproportionate retrograde memory loss. Structural brain pathology underlying this deficit in organic retrograde amnesia can be considered inconsistent as there were functional metabolic disturbances in some patients without brain damage. In organic cases, some evidence points to particular involvement of the right anterior lateral temporal lobe together with (pre-)frontal regions as being essential for the retrieval of personal past experiences. A few reports of functional brain correlates in functional retrograde amnesia support this view. However, the picture is far from clear, which may primarily result from the fact that almost all previous studies were single cases. Thus, lesion location and extent in organic cases varied as did the applied functional neuroimaging methods and paradigms in functional cases. This makes it particularly difficult to draw direct comparisons across patients. The current study therefore compares five patients suffering from functional retrograde amnesia by means of their personal background, behavioural characteristics including emotional processing and personality, as well as their neuropsychological profiles. Furthermore, functional brain correlates during remote autobiographical-episodic memory retrieval were investigated by fMRI in patients A.B., C.D., and E.F. Since patients G.H. and I.J. had non-removable metal items in their bodies preventing them to participate in magnetic resonance imaging, a $H_2{}^{15}O$-PET investigation was conducted with them.

Given the inconsistent clinical pattern in previous cases, definite hypotheses about the outcome of this multi-case study seem inappropriate. However, in the following section, questions and assumptions of the study are outlined.

II. Questions and Assumptions

The following questions are addressed in this study of five functional retrograde amnesia patients:

- How do personal history, neuropsychological profile, and current emotional state of the patients relate to the retrieval deficit?
- Can neuropsychological test results and current emotional state be interpreted as contributing to aetiologically relevant factors in terms of organic, psychogenic, and malingering-related aspects of the amnesia?
- What are commonalties of symptoms and precursors across different cases of functional retrograde amnesia and is it possible to classify cases along organic, psychogenic and malingering-related factors?
- Given an impairment in remote episodic memory and unimpaired retrieval of anterograde episodic memory, is there a neural correlate differentiating both time periods?
- If fictitious information about hypothetical episodes is given to such patients, is there a differential brain involvement during retrieval attempt within amnesic and non-amnesic time periods?
- It is assumed that if fictitious information highly resembles true episodic memories, differentiation between true and fictitious is more difficult within amnesic than in non-amnesic time periods. This can be seen both, in behavioural responses as well as in functional brain correlates.

III. Case Histories

The five patients included in this study gave written informed consent for neuropsychological and neuroradiological examinations. The study was approved by Ethics Committees of the Heinrich-Heine University, Düsseldorf, University of Cologne, and Research Centre, Jülich. Additional to investigation of the patients themselves, interviews were conducted with the patients relatives and, additionally in case of patient A.B., with a friend of her. Table 4 gives a short overview over notation and demographic variables of the five patients.

Table 4: Summary of the patients' notation, demographic background

	PATIENT				
Demographic variables	**A.B.**	**C.D.**	**E.F.**	**G.H.**	**I.J.**
Age	17	30	33	35	34
Gender	female	male	male	female	male
Handedness	right	right	right	right	right
Years of education	11 (still in school by the time of test)	10	10	10	10
Professional background	high school student	engineer	lock-smith	house wife	sales worker
Marital status	single	married	married	married	married
Number of children	none	one	none	three	two

In the following section, detailed background information per patient is given. This information was derived from the patients' anamneses, interviews with the patients' relatives and friends, previous medical records and by interviewing their doctor's at the time the study was conducted.

1. Patient A.B.

Patient A.B. is a 17-year-old right-handed girl who, for unknown reasons, suddenly became unconscious while on an apprenticeship away from home (June 2001). After an unknown period of time ($\leq$1 h) she awoke and was disoriented in person, place and time as well as profoundly retrogradely amnesic. It is reported that she might have fallen to the right side of her forehead. A.B. was brought to a nearby hospital where neurological, neuroradiological and neuropsychologial investigation (EEG, evoked potentials, MRI, lumbar puncture, and neuropsychological screening) did not point to any brain pathology. A psychiatric report stated hypomania, problems in sexuality and an elevated score in the Minnesota Multiphasic Personality Inventory validity scale indicating exaggeration of psychiatric symptoms. Following discharge after two days, the retrograde amnesia persisted and comprised autobiographical episodic information and some semantic facts covering her entire previous life. It is reported that A.B. was unable to recognise significant others as well as her home and belongings. However, already in the very beginning of the amnesia it is reported that she accessed a few autobiographical facts such as knowledge about one friend's family. Anterograde and procedural memory and language were described to be intact. For instance, A.B. was spontaneously able to respond in English and French which she had learned in school. Due to unimpaired anterograde learning, A.B. rapidly re-learned personal and public semantic information. Though few vague images or fragmented episodic memories were reported to have returned, re-learning generally did not evoke the actual re-experiencing of autobiographical events. Interviewing A.B.'s relatives and friends revealed that her personality had not been significantly changed besides the fact that she lost her depressive tendencies (see below). However, several every day habits were reported to be different from the time before the onset of the amnesia. For instance, it was reported that she became vegetarian after the onset of amnesia. Though she herself emphasised this behavioural change during the test sessions, it was reported by her relatives and friend that during the months following her amnesia, she slowly returned to her previous food preferences. After approximately one year, her initial refusal of meat entirely resolved according to her psychotherapist and her mother.

Previous medical and psychological records revealed that since October 2000 A.B. suffered from major depression until the incident. The depression was treated by selective serotonin re-uptake inhibitors and psychotherapeutical intervention. The depression is reported to have recovered after the accident. Furthermore, throughout the year 2000, there were four documented but not entirely clarified suicides in her circle of friends. In medical records of A.B., several paroxysmal states with sudden loss of consciousness are described preceding and following the accident. Continuous EEG recording conducted in July 2001 did not reveal epileptogenic activity. After the retrograde amnesia onset, several somatic complaints (headache, gastrointestinal pain) emerged whose organic causation remained obscure. A.B. gradually started to recover from functional retrograde amnesia after nine months. Following an appendectomy in February 2002, her somatic complaints extinguished and she is reported to be symptom free since then.

A.B. was first seen four months after the onset of the functional retrograde amnesia (October 2001).

2. Patient C.D.

Patient C.D. is a 30-year-old right-handed engineer. He was born in the UK, married, father of an adolescent son and has lived in Germany since 1989. The present condition arose from a car accident during a foreign assignment in June 2001. C.D. reported that he was penned in a truck for 2 hours during which helpers tried to rescue him. Due to the high temperature and the still strapped seat belt, breathing started to get difficult until he lost consciousness. After the rescue, he was taken to a nearby hospital where he stayed for two days. He sustained a fractured right wrist and elbow, a spinal disc prolaps as well as profound retrograde amnesia. Subsequently, he was transferred to another hospital in the same city where he stayed for an additional 14 days. MRI investigation revealed no structural lesions to the brain. After he was transferred back to Germany, additional EEG and MRI investigations were carried out and showed normal results. It is reported that in the beginning, C.D. was entirely disoriented with respect to person, situation, and time. Though his native English language was unimpaired, he initially did not believe that he could speak and understand German. His deficit included also loss of knowledge about the usage of common tools (e.g. razors). In the weeks and months after the injury, re-learning of formerly known information and activities occurred so that he was able to start his former position again in August 2001. Besides sporadic flashbacks and a few vague feelings of familiarity, he reported being amnesic for all remote memories prior to the incident. In contrast, the acquisition of new information is reported to be spared, permitting him to fill in memory gaps. However, during restoration of his autobiography and past public life, no information returned spontaneously and he did not re-experience past events. C.D.'s wife reported that his personality underwent major changes after the accident. She reported that, from one moment to the next, he now loses contact with his surroundings giving the impression of temporarily being blocked and far away. She further reports a general slowing of behaviour, which, according to a note in the medical records, she might have noticed also before onset of the amnesia in April 2001. She further reports that following onset of the amnesia C.D. developed a tendency to misinterpret behaviour of others giving him a distrustful appearance. According to her, this behaviour is in contrast to his previous personality which she describes as sociable and rather credulous. Due to his behavioural changes, a conjoint therapy was initiated by C.D.'s wife and terminated after a few sessions due to C.D.'s refusal to continue. Furthermore, in the time after he started working again, C.D. reported experiencing several social problems with co-workers and colleagues which finally led him to quit his job. Beyond these occurrences it is reported that C.D. changed his food preferences in that after the onset of amnesia he more frequently tried unfamiliar or unusual dishes.

The medical history of C.D. revealed several precursory incidents. C.D. suffered from at least two closed head injuries (1993 after an assault; 1999 after falling from stairs) both followed by short periods of coma (< 1 day). Following the first head trauma, a prolonged period of anterograde amnesia was reported. Other symptoms described were decreased visual acuity on the right, a coarse tremor/twitch of the right arm and decreased power of the right upper limb. Reflexes were normal. Since neuroradiology (CT, MRI) appeared normal, a hypnotic procedure to reduce amnesic and ataxic symptoms and conversion hysteria was diagnosed. The symptoms recovered approximately four months after the incident, while the recovery process remains unclear at least from the given documents. The second head trauma in 1999 was followed by somnolence and possibly a convulsion. In the course of trauma diagnosis, a right fronto-parietal venous angioma was detected. The bleeding risk of the angioma was diagnosed as minimal, and thus its treatment was conservative. Also this head injury was followed by symptoms of paralysis (right arm paresis, weakness of the limbs) lasting approximately 4-6 months. Structural and functional brain imaging (CT, MRI) and neuromonitoring (EEG), however, could neither reveal any organic basis for these symptoms not gave indication of paroxysmal activity. Since the right hemisphere venous angioma did not correspond to the body side of the motor symptoms, a psychogenic causation of the paralyses was suspected. It is further reported that since November 1999 the patient suffered from strong chest pains and shortness of breath. Examination in February 2000 revealed no pathological signs of ischemic/cardiac disease. In March 2001, C.D. also suffered from acute Salmonella infection with 'probable meningeal involvement'. A resting state FDG-PET was carried out after the onset of the amnesia in March 2002. This examination revealed no pathological signs. Resting state cerebral glucose distribution was normal.

C.D. was first seen eight months after the onset of the functional retrograde amnesia (February 2002).

3. Patient E.F.

Patient E.F. is a 33 year old right-handed locksmith. He is married without children. The current condition arose from an incident while he had a morning shower and for unknown reasons went unconscious (January 2002). After an unknown period of time (max. 4 hrs.), he awoke and was disoriented in person, time and situation. In this state he was found by his wife who immediately brought him to a nearby hospital. Here a profound retrograde memory loss was diagnosed in the absence of any pathological signs in CT, MRI, and EEG. Initially, he reported being amnesic for almost everything including also knowledge about objects and common devices and actions (e.g. riding on a tram). In the first 2-3 days he regained memory for childhood and young adulthood while he stayed amnesic for remote memories occurring during the most recent 12-14 years. Unimpaired anterograde learning abilities enabled him to quickly re-learn facts and events from his previous personal life as well as public events, while he did not re-experience autobiographical events. He reported isolated fragments of memories from the amnesic period which, however, did not trigger exhaustive re-experiencing of remote autobiographical episodes. Intensive questioning of the patient's relatives and searching medical records did not reveal any past neurological or psychiatric aberrance. In the time following the onset of the amnesia, E.F. experienced headaches when starting to work again in his old work place where he had minor contact with chemicals. He successfully changed his position within the same company. E.F. and his wife reported that his personality and cognitive skills, except remote memory access, did not change to a major degree following the onset of his amnesia. However, his food preferences were changed. His wife reported that after the onset of amnesia, E.F. started eating meals he formerly disliked. Concerning relationships, E.F. reported feeling uneasy with one circle of his former friends. He basically ascribed this discomfort to the fact that he had been in contact with these people due to their common hobby of motorbike riding. He reported that after the onset of the amnesia he was scared to use his motorbike, and thus felt somewhat inappropriate within a circle of motorbike fans. Thus, his private life has changed to a certain degree since he and his wife now avoid these former friends. A resting state FDG-PET was carried out after the onset of the amnesia in March 2002. A slight overall cortical and a significant cerebellar hypometabolism was found.

E.F. was first seen two months after the onset of functional retrograde amnesia (March 2002).

4. Patient G.H.

Patient G.H. is a 35 year old right-handed house wife. She is married and mother of three adolescent daughters. The present condition arose after an anaesthesia for gynaecological surgery (August 2002). While the anaesthesia was reported to have been unproblematic, G.H. awoke disoriented in time and situation. She experienced herself to be in the year 1989 and was extremely anxious about her current state for she had no memory of the reason for her surgery. She reported that her last memory was exactly dated by a day in the end of May 1989 which she could describe in high detail. This day, however, did not appear to bare significant relevance for her life neither before the onset of her amnesia nor – according to her husband – following the amnesia. All episodic and semantic remote memories since then were reported to have vanished. When her husband and eldest daughter came to the hospital for a visit, she recognised him but was surprised about his seemingly elder appearance. She did not recognise her daughter who – in her memory – was supposed to be 1.5 years old. Neuroradiology and neuromonitoring (CT, EEG) did not reveal any pathology. In the time after the onset of the amnesia some sporadic flashbacks and vague memory fragments occurred while she reported to have stayed largely amnesic for the 13 years preceding the incident. G.H. experienced major problems in her social environment after the amnesia started. She reported to be often overwhelmed by the emotional and relational demands of others. She and her husband described her as being extremely sensitive and emotionally unstable since the onset of the amnesia. Due to the fact that she was unable to remember two of her children she suffered from feelings of guilt regarding her role as a mother and at the same time felt emotionally detached from her family. The psychological strains caused by her situation motivated her to start psychotherapeutic intervention in January 2003.

The medical history of G.H. revealed several incidents. Since her adolescence G.H. suffered from bradycardia and hypotonia. After a series of collapses she started wearing a cardiac pacemaker in 1990. An angina pectoris was diagnosed in 1994. Furthermore, she suffered from various gynaecological and gastrointestinal diseases and complications for which she underwent a considerable number of surgical interventions dated between 1991 and 2002 (e.g. for hysterectomy, endometriosis, tumour removal). Furthermore, since the age of 20 (1987) she experienced severe migraine attacks occasionally involving 'altered states of consciousness', during which she was disoriented in time and space. In the context of these attacks she experienced paralysis of one half of the body. The migraines were successfully treated by acupuncture in 1996.

According to information provided by G.H. and by her husband, G.H.'s childhood and young adulthood were extremely stressful. She reported numerous incidents of paternal violence against her mother and the children. Her parents were heavy drinkers and she described incidents when she witnessed and was even supposed to assist in suicide attempts by her mother. According to G.H.'s husband, her personality underwent major changes since the onset of the amnesia. He describes her behaviour as childish and more egocentric than before the amnesia. Her interpretation of other people's reactions and behaviours are now often faulty which leads to misunderstandings with others and frustration in herself as well as in the family. Moreover, many of her every day habits (e.g. choice of clothes, hobbies) are reported to have changed to a major degree. Moreover, her food preferences changed. G.H. herself stated that she started to eat generally less after the onset of amnesia and her husband reported that she preferred dishes she had been used to consume during the early 1990ies.

G.H. was first seen two months after the onset of functional retrograde amnesia (October 2002).

5. Patient I.J.

Patient I.J. is a 34 year old right-handed man working for an import-export company. He was born in Kazakhstan and has lived in Germany since 1993. He is married and father of two sons (nine and eleven years old). The present condition arose after he left his home to drive a friend to the airport of a city approximately six hours away from his home town. After this drive he intended to visit a former business partner in another city on the way back home. The cause for this visit was to receive a large amount of money from their corporate business to build up a new company. However, on this day (February 2002) I.J. did not return home and it could not be clarified, whether he arrived at his partner's place or not. After three weeks, a guard found him sleeping in a train in Russia. When the train guard woke him up, he was unable to remember any autobiographical information. He was not in possession of any of the money that he had intended to receive from his former business partner. Instead, he was asked by the train guard to pack some clothes in a bag lying near him. He could not remember either the bag or the clothes in his train cabin. Later he noticed that these clothes were not even approximately his size. According to I.J., the train guard then asked him to leave the train at the next stop and addressed the words to him that 'he would then notice why he had to get off'. After I.J. had left the train at the next stop, he reported to have wandered around the city neither knowing where he was nor who he was. He also experienced severe headache. After approximately one hour he returned to the railway station intending to clarify his location. He further reported that at the station, he accidentally entered a police compartment where he asked for advise. At this office, he collapsed without loosing consciousness. A medical, who had been called by the police, stated that I.J. would have died from high blood pressure if he had not immediately been treated by antihypertensives. As I.J. also did not carry any legal documents, his identity was unclear and he was brought to a nearby psychiatric hospital where he stayed the following months. In this hospital, concentration deficits, a 'strong will' and the 'ability to suppress feelings and discomfort' as well as symptoms of PTSD were stated.

In May 2002, his story was reported in Russian television which his wife in Germany became aware of. By the end of May 2002, his wife and brother went to Russia to bring him back home. Since they were told that I.J. had lost all his memories, they brought private photos and videos to show him. However when they met, I.J. was unable to recognise either his wife and brother or any of the documents they presented. In June 2002 they went back to Germany. EEG and CT conducted in the same month did not reveal any pathological signs. Already in the hospital, I.J. began to reconstruct his former life with the help of his relatives. Since his anterograde learning abilities were reported to be unimpaired, he was able to rapidly acquire facts about his life, but in the course of this process, autobiographical memories did not return spontaneously. It was reported that until today, his remote memory deficit remained basically unchanged. Although his knowledge of the German language slowly returned, he did and does not speak as fluently as before the onset of the amnesia. Intensive questioning of the patient's relatives and searching medical records did not reveal any precipitating neurological or psychiatric aberrance. I.J. reported that beside his retrograde amnesia, he now suffers from concentration deficits that prevent him from sustaining concentration over periods longer than two hours. His wife reported that his personality is unchanged since the onset of the amnesia though some alterations of daily habits occurred (e.g. food preferences). Since the family moved to another town after he came back, their former social life has changed to a major degree. Due to these circumstances, however, it is by now impossible to clarify to what extent I.J.'s amnesia contributed to these changes.

I.J. was first seen 13 months after the onset of functional retrograde amnesia (March 2003).

IV. Methods

All patients underwent standardised neuropsychological testing in order to evaluate cognitive domains: intelligence, anterograde memory, attention and executive functions as well as Theory of Mind abilities. Current mood, psychiatric symptoms, and personality were assessed by questionnaires. Retrograde memory was examined with standardised and experimental tests of semantic and episodic remote memory. Due to cultural and language-related differences in the non-German patients C.D. and I.J., adaptive changes to the test battery were applied if necessary and possible. This included the omission of some of the tests for I.J. or application of standardised English versions for C.D., respectively. Translations were only given if necessary since both patients are able to speak and understand German. For technical reasons, patient E.F. could not be tested with the entire neuropsychological test battery. The test battery and its adaptive changes per patient is summarised in Table 5 (see **section IV-3**).

Functional brain correlates during autobiographical episodic memory retrieval were measured by fMRI or $H_2^{15}O$-PET. In the fMRI study conducted with patients A.B., C.D. and E.F., changes were measured in the regional blood oxygenation level-dependent (BOLD) signals associated with the retrieval attempt of actual autobiographical episodic memories inside the amnesic time period (True Old) and after the onset of the amnesia (True New). These two conditions were paralleled by retrieval attempt of fictitious episodic memories constructed as if they had happened within the amnesic time period (Fictitious Old) and after the onset of the amnesia (Fictitious New). Patients G.H. and I.J. could not participate in magnetic resonance imaging and therefore were enrolled in a PET study. The $H_2^{15}O$-subtraction method was applied for studying regional cerebral blood flow (rCBF) changes associated with the retrieval attempt of true autobiographical episodes within the amnesic time (Old) and following onset of the amnesia (New).

Behaviour during scanning sessions was controlled by questionnaires immediately after the scanning sessions. The patients were required to self-evaluate their reactions to the stimuli during the scanning. The questionnaires comprised a pseudorandomised sequence of all stimulus sentences presented during the scanning.

1. Neuropsychological background evaluation

1.1 Intelligence

Intelligence was tested with a German version of the Wechsler Adult Intelligence Scale-Revised, WAIS-R (Wechsler, 1981; 'Hamburg Wechsler Intelligenztest für Erwachsene', HAWIE-R

[Tewes, 1991]) and/or a German adaptation of the National Adult Reading Test, NART (Nelson, 1982; 'Mehrfachwahl-Wortschatz-Intelligenztest', MWT-B [Lehrl, Merz, Burkhard, & Fischer, 1991]). Additionally, subtest 'Reasoning' from the intelligence test 'Leistungsprüfsystem', LPS-4 (Horn, 1983) was applied to assess fluid intelligence[10].

The WAIS-R provides a comprehensive measure of verbal and non-verbal intellectual abilities. It contains six verbal and five performance tests, the latter of which are administered under time limitations. Beside a measure of general intellectual functioning that is derived from all subtests and expressed as normalised IQ score (mean=100, standard deviation= 15), IQ-scaled levels of verbal intellectual abilities and performance IQ can be assessed separately to examine lateralised abilities (cf. Lezak, 1995). The NART provides an estimation of premorbid intellectual abilities on the basis of identification of successively unusual or unorthodox words. The LPS-4 requires logical reasoning to identify odd items in increasingly difficult sequences of numbers and/or letters. This test is administered under time restriction. It correlates highly with the entire LPS (r=.84) and therefore provides an estimate for general intellectual abilities (Horn, 1983).

1.2 Anterograde memory

As tests for anterograde memory, all patients performed the Wechsler Memory Scale-Revised, WMS-R (Wechsler, 1987; German version [Härting et al., 2000]; English version was used for patient C.D.). Furthermore, a German version of the California Verbal Learning Test, CVLT (Delis, Kramer, Kaplan, & Ober, 1987; English version for patient C.D.) was conducted, as well as a 30-minutes delayed recall of the Rey Osterrieth Complex Figure Test, Rey Osterrieth CFT (Osterrieth, 1944). As a measure for priming, the 'Fragmentierter Bildertest', FBT, an incomplete picture task, was applied (Kessler, Schaaf, & Mielke, 1993).

The WMS-R provides measures of immediate general, verbal and visual memory as well as indices for delayed general memory. Furthermore, assessment of an attentional-concentration index can be derived by visual and verbal short- and working-memory tasks (Digit Span and Block Span forward and reversed). All WMS-R indices are IQ-scaled. In the CVLT, verbal memory is assessed by learning a word list of 15 words by auditory presentation in five learning trials. Short- and long-term free recall and recognition of the words provide measures of short-term and long-term verbal memory[11]. The purpose of the Rey Osterrieth CFT is to assess visuospatial constructional ability (accuracy of copy of the figure) and visual long-term memory

[10] In the forthcoming sections, abbreviations of the English versions are used. If no corresponding English versions of tests exist, German abbreviations are given.
[11] Further indices can be assessed (e.g. performance in cued recall, use of strategies). These are not analysed in the current study.

(delayed recall of the figure after 30 minutes). In the FBT, subjects are required to identify successively completed fragmentary drawings of common objects. After a delay of 15 minutes, the identification trial is administered again. The number of complemental information required for successful identification serves as a measure for priming.

1.3 Attention and executive functions

Attention was tested with the Trail Making Test Part A, TMT-A (Spreen & Strauss, 1998), Concentration Endurance Test d2 (Brickenkamp, 1994) and/or subtests Alertness, Divided Attention, and Selective Attention of the computerised Test Battery for the Assessment of Attention (Fimm & Zimmermann, 2001). Executive functions were assessed with the Modified Card Sorting Test, MCST (Nelson, 1976; norms by Obonsawin et al., 1999), Trail Making Test Part B, TMT-B (Spreen & Strauss, 1998), and a German version of the Stroop-Test (Stroop, 1935; 'Farbe-Wort-Interferenztest', FWIT [Bäumler, 1985]; English translation for patient C.D.). Lexical and categorical fluency were examined with the FAS-Test and Animal Naming Task (Spreen & Strauss, 1998).

The TMT-A measures attention, speed of information processing, visual search and motor function, and TMT-B provides a measure of cognitive flexibility. The Concentration Endurance Test d2 assesses sustained attention and visual scanning abilities. It further gives evidence for subjects' information processing speed and levels of response accuracy. Subtest Alertness of the Test Battery for the Assessment of Attention measures basic attention and alertness, whereas in subtest Divided Attention, cognitive flexibility and the capacity to simultaneously process two concurring incoming stimuli is required. Subtest Selective Attention assesses the ability to selectively attend to task relevant stimuli and suppress responses to irrelevant stimuli. The purpose of the MCST is to assess the ability to form abstract concepts, to shift and maintain set, flexibly change mental rules, and utilise feedback. It is a shortened and computerised version of the original Wisconsin Card Sorting Test (Berg, 1948). The Stroop Test measures the ease with which a shift of perceptual set to conform to changing task demands is accomplished. Furthermore, it assesses susceptibility to interference between a habitual response that is to suppress in favour of an unusual one. Besides language functions lexical and categorical fluency, FAS-Test and Animal Naming Task measure the production of individual words under restricted search conditions. Therefore, they also assess subcomponents of executive functions (Bryan & Luszcz, 2000).

1.4 Theory of Mind

Theory of Mind (ToM) abilities were examined with the Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, & Hill, 2001; all patients except C.D. received a German adaptation [Kalbe, Brand, Fleck, & Kessler, in prep.]).

ToM refers to the ability to infer and interpret other people's mental and emotional states. In the Reading the Mind in the Eyes Test, subjects are given extracts of photographs of other people's eyes and have to chose from lists of adjectives, what they think the person shown in the picture is currently thinking or feeling.

2. Psychological screenings

Current mood, psychiatric symptoms and personality were screened by questionnaires. No translations were applied to these screenings.

The Beck Depression Inventory, BDI (German version by Beck, Steer, & Hautzinger, 1995) measures current depressed mood and depressive symptoms. Symptom severity comprises three stages: no depressive symptoms, mild to moderate depression and severe depression.

The Symptom Checklist-Revised SCL-90-R (Derogatis, 1992; German version by Franke, 1995) assesses psychological stress and psychiatric symptoms with nine different scales. These include *somatisation* (simple bodily strains to functional disorders), *obsessive-compulsive* (slight concentration deficits to severe compulsiveness), *interpersonal sensitivity* (mild social uncertainty to feelings of exhaustive personal insufficiency), *depression* (sadness to clinically relevant depressive symptoms), *anxiety* (noticeable nervousness to profound feelings of fear), *anger-hostility* (irritability and psychic imbalance to significant aggressiveness with hostile aspects), *phobic anxiety* (slight feelings of threat to massive phobia), *paranoid ideation* (distrust and feelings of inferiority to pronounced paranoid thinking), and *psychoticism* (mild feelings of isolation and alienation to evidence of psychosis). Furthermore, a *global severity index* (GSI), derived from symptoms on all subscales, indicates general psychological stress.

The Freiburg Personality Inventory-Revised, FPI-R (Freiburger Persönlichkeitsinventar-revidierte Fassung [Fahrenberg, Hampel, & Selg, 1989]) assesses personality on 12 dichotomised dimensions. These include *life satisfaction* (confident/content versus dissatisfied/sorrowful), *social orientation* (socially responsible/cooperative versus self-dependent/self-oriented), *achievement motivation* (ambitious/competitive versus unmotivated), *inhibition* (inhibited/insecure versus self-confident/sociable), *excitability* (excitable/sensitive versus calm/placid), *aggressiveness* (aggressive/assertive versus chary/controlled), *stress* (stressed/strained versus not feeling stressed/strained), *physical complaints* (many complaints/psychosomatic tendencies versus few complaints/no psychosomatic tendencies), *worries about health* (fear of diseases/health-conscious versus being free of health worries/robust), *openness* (willing to admit minor weaknesses and violations of everyday conventions versus oriented to social norms/giving a socially desirable impression), *extraversion* (extraverted/impulsive versus introverted/prudential), and *neuroticism* (emotionally labile/many problems and bodily complaints versus emotionally stable/self-confident). The subscale *openness* operates as a validity scale. Low results (standard scores one to three) indicate socially desirable response tendencies. If a subject achieves a low result in this scale, interpretation of all other responses is limited (Fahrenberg et al., 1989).

Patients A.B. and C.D. were given a German version (Laux, Glanzmann, Schaffner, & Spielberger, 1981) of the State-Trait-Anxiety Inventory, STAI (Spielberger, Gorsuch, & Lushene, 1977). This questionnaires differentiates two components of anxiety. *State Anxiety* as a momentary emotional state is characterised by strain, nervousness, uneasiness and fear of future events. *Trait Anxiety* marks a stable individual trait to judge neutral or innocuous situations as dangerous and anticipate future "threatening" situations.

In patient G.H. only, a German version (Freyberger, Spitzer, & Stieglitz, 1999) of the Dissociative Experience Scale, DES (Bernstein & Putnam, 1986; German version: FDS) was administered. This instrument consists of the four subscales *amnesia* (fragmentation and compartmentalisation of memory), *absorption* (imaginative experiencing and thought absorption), *derealisation* (identity confusion and out-of-body experiences), and *conversion* (bodily conversion symptoms affecting voluntary movement, sensitivity and sensorial perception).

3. Overview of applied tests and questionnaires

In Table 5, an overview of the applied standardised neuropsychological tests and psychological screenings is given per patient. References are listed for those test versions given to most patients. For more detailed description, see **sections IV-1** and **IV-2**.

Table 5: Applied neuropsychological tests and psychological screenings per patient

Neuropsychological Domain and Test	Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Intellectual Abilities						
MWT-B (Lehrl et al., 1991); German adaptation of National Adult Reading Test NART (Nelson, 1982)		**X**	**n.a.**	**X**	**X**	**X**
Subtest 'Reasoning' from Leistungsprüfsystem (LPS-4; Horn, 1983)		**X**	**X**	**X**	**X**	**X**
Wechsler Adult Intelligence Scale-Revised (WAIS-R; Tewes, 1991)		**X**	**X**	**n.a.**	**X**	**X**

Neuropsychological Domain and Test	Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Anterograde Memory						
Wechsler Memory Scale-Revised (WMS-R; Härting et al., 2000)		**X**	**X**	**X**	**X**	**X**
Rey-Osterrieth Complex Figure Test (Rey CFT; Osterrieth, 1944)		**X**	**X**	**n.a.**	**X**	**X**
California Verbal Learning Test (CVLT; Delis et al., 1987)		**X**	**X**[a]	**X**	**X**	**n.a.**
Incomplete Figures Test (FBT; Kessler et al., 1993)		**X**	**X**	**n.a.**	**X**	**X**
Attention & Executive Functions						
Trail Making Test (TMT; Spreen & Strauss, 1998)		**X**	**X**	**n.a.**	**X**	**X**
Concentration Endurance Test d2 (Brickenkamp, 1994)		**X**	**X**	**n.a.**	**X**	**X**
Subtests Alertness, Divided Attention, Selective Attention from Test Battery for the Assessment of Attention (Fimm & Zimmermann, 2001)		**n.a.**	**n.a.**	**X**	**X**	**n.a.**
Stroop-Test (FWIT; Bäumler, 1985)		**X**	**X**[b]	**n.a.**	**X**	**X**
Lexical Fluency (FAS-Test; Spreen & Strauss, 1998)		**X**	**X**[c]	**X**	**X**	**X**[b]
Categorical Fluency (Animal Naming Task; Spreen & Strauss, 1998)		**X**	**X**[c]	**n.a.**	**X**	**X**[b]
Modified Card Sorting Test (MCST; Nelson, 1976)		**X**	**X**	**X**	**X**	**X**
Theory of Mind						
Reading the Mind in the Eyes Test (Kalbe et al., in prep.)		**n.a.**	**X**	**X**	**X**	**X**
Psychiatric Symptoms and Mood						
Beck Depression Inventory (BDI; Beck et al., 1995)		**X**	**X**	**X**	**X**	**X**
Symptom Checklist (SCL-90-R; Franke, 1995)		**X**	**X**	**X**	**X**	**X**
Freiburg Personality Inventory-Revised (FPI-R; Fahrenberg et al., 1989)		**X**	**X**	**X**	**X**	**X**
State-Trait-Anxiety Inventory (STAI; Laux et al., 1981)		**X**	**X**	**n.a.**	**n.a.**	**n.a.**

Neuropsychological Domain and Test	Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Dissociative Experience Scale (FDS; Freyberger et al., 1999)		**n.a.**	**n.a.**	**n.a.**	**X**	**n.a.**

X: administered; n.a.: not administered; [a]: English version; [b]: ad-hoc translations to English or Russian; [c]: conducted in German and English

4. Assessment of remote memory

Standardised and experimental tests were applied to assess remote semantic and episodic memory performance. Since the patients emanated from diverse social-cultural backgrounds, for each individual adaptive changes were applied to all semantic remote memory tests. The tests were administered to five comparison subjects matched to the patients as closely as possible (see Table 6). However, since no appropriate control subjects for patients C.D. and I.J. were found (i.e. not being relatives of the patients and at the same time having the same nationality and having spent the same amount of time in Germany), for these patients two German males were chosen with comparable educational background and age. Table 6 summarises demographic variables of the comparison subjects (cf. Table 4 in **section III**).

Table 6: Summary of the comparison subjects' demographic background (cf. Tab. 4 in **section III.**)

	COMPARISON SUBJECT FOR :				
Demographic variables	**A.B.**	**C.D.**	**E.F.**	**G.H.**	**I.J.**
Age	17	33	38	34	32
Gender	female	male	male	female	male
Handedness	right	right	right	right	right
Years of education	11 (still in school by the time of test)	10	12	12	10
Professional background	high school student	bicycle mechanic	sound engineer	student	sales assistant
Marital status	single	single	married	single	married
Number of children	none	none	none	one	one

4.1 Semantic remote memory tests

Semantic remote memory tests comprised the Test of Semantic Remote Memory (Schmidtke & Vollmer-Schmolck, 1999), a Famous Events Test adapted from Leplow and Dierks (1997), and ad hoc designed Famous Names Test and Current Words Test. Patient E.F. was further tested with a Famous Faces Test (Fast, Fujiwara, & Markowitsch, in press). Example items of all tests are given in **Appendix A**.

In the Test of Semantic Remote Memory from Schmidtke and Vollmer-Schmolck (1999), basic world knowledge usually acquired in or before the first grades of school is requested. It comprises 81 questions about biology (36 questions), geography (20 questions), culture (14 questions), and fairy tales (11 questions). For cultural reasons, this test was not given to patients C.D. and I.J. (cf. **Appendix A-I.**).

In the Famous Names Test, subjects are asked to choose the correct name of a famous person out of a list of five names, including four fictive names. If correctly identified, subjects are asked to provide further details about the person (e.g. profession, nationality). Patient A.B. received a version of 47 names of German or Austrian celebrities. For C.D., some German names were excluded and either internationally famous persons or British celebrities were chosen (48 names). Patients E.F: and G.H. received a version of 48 German or international famous personalities. For I.J., two Russians constructed comparable items from their cultural background and therefore, I.J. was tested with a translated 48-item version of names of Russian (N=27) and international celebrities (N=21). Comparison with his comparison subject was based on recognition of international celebrities only (see **Appendix A-II.** for all versions).

In the Current Words Test, knowledge of the meaning of words, phrases or abbreviations that became common during roughly the last 20 years is asked for (e.g. 'Tamagotchi, yuppies, E.T., chat, snowboard'). Also here, words and phrases were exchanged for patients A.B., C.D. and I.J., whereas E.F. and G.H. received identical questionnaires. All four different versions comprised a total of 42 words or terms (see **Appendix A-III.** for words given to each patient). Patient I.J.'s performance was compared to the comparison subject's result in the German words.

In the Famous Events Test adapted from Leplow and Dierks (1997) subjects are given verbal descriptions of public news events ranging from years 1980 to 2001. Considering A.B.'s age, only items post-1989 were applied to test her. Due to cultural reasons, the number of items per time period was not evenly distributed either across time periods or across patients (see **Appendix A-IV.** for items given to each of the patients). The events for patient I.J. were mostly derived from a Russian background, and therefore it was inappropriate to compare his performance with a control subject. However, construction of the items was accomplished by two Russians and I.J.'s wife confirmed the validity of all items in that she acknowledged their commonness in Russia. Furthermore, she assured that I.J. had known the answers to most of the questions before onset of his amnesia. Table 7 shows the number of items per time period given to each patient.

Table 7: Famous Events Test: Number of event descriptions per time period for each patient

Patients **Time periods (years)**	**A.B.**	**C.D.**	**E.F.**	**G.H.**	**I.J.**
1980-1989	-	11	11	11	17
1990-1995	17	16	17	17	12
1996-2001	31	31	33	33	14
Total	**48**	**58**	**61**	**61**	**43**

With the help of the descriptions, the depicted news events have to be remembered and explained. Again, adaptive changes and/or translations were applied on this test for subjects A.B., C.D. and I.J. Since the events are specific to certain dates, this test serves for evaluation of temporal gradients in semantic remote memory.

Similarly, the Famous Faces Test (Fast et al., in press) provides the possibility to estimate temporally graded semantic remote memories. In this test, applied to patient E.F. only, subjects are given 50 black-and-white photographs of celebrities from various backgrounds (politics, culture, sports). Subjects are asked to freely recall the names of the persons as well as to report further details (e.g. profession, nationality). Following each unsuccessful free recall trial, a recognition trial is conducted. Herein, subjects are shown four names (three of which are fictive) and are asked to chose the correct name. Again, further details about the person of interest is requested (see **Appendix A-V.** for example items).

4.2 Episodic remote memory test

Episodic remote memory was assessed with the Autobiographical Memory Inventory, AGI (Autobiographisches Gedächtnis Inventar) that was developed on the basis of the Autobiographical Memory Interview (Kopelman, 1990). The AGI consists of a semi-structured interview on facts and incidents from the subject's life regarding specific time periods. Per time period, subjects are required to provide five autobiographical facts (e.g. names of former friends and addresses), two autobiographical episodic events and details on one of the two events. As a retrieval help for autobiographical episodic memories, a list of generic events and emotional states (e.g. 'first day in school', 'day of graduation', 'first kiss', 'sadness' etc.) is shown throughout the entire length of the interview. Time periods of 0-5 years of age, 6-10 years, and 11-17/18 years were considered in all patients. Additionally, the period ranging from age 18/19 years until the onset of the amnesia (age 30 to 34, respectively) was tested in patients C.D., E.F., G.H., and I.J. Per time period a maximum score of five points is given for correct autobiographical semantic information, two points are given for two exactly and vividly remembered autobiographical episodes and a maximum of eleven points for episodic details for one of the episodes can be reached. To control for originality and authenticity of autobiographical episodic memories, each detailed episodic event is followed by questions for details, vividness, preciseness, and imagery of the memory. Furthermore, subjects are asked to state the number of times that had been talked about the event, whether someone else had told about the event and whether there exist photographs of the event. These latter control questions do not add to the memory scores (see **Appendix A-VI.** for the list of generic events and an example time period).

5. Neuroimaging Methods – fMRI

Patients A.B., C.D. and E.F. participated in the fMRI experiment which was designed similar to the experiment of Piefke et al. (2003).

5.1 Stimuli

Individual stimuli were acquired by interviewing the patients' relatives who were asked to provide information about events that happened either in the patients' past preceding the onset of the amnesia (last 5-10 years) or following the onset. By this procedure, 10 true old episodes and 10 true new episodes were collected for each patient. Furthermore, 10 fictitious old and 10 fictitious new episodes were composed with the help of the patients' relatives. Fictitious episodes were designed to appear as plausible and realistic as possible meaning that names of formerly known places, friends and the like were included. To indicate the time when a fictitious event could have happened, time markers such as 'in summer 1996, last May, five years ago, last month etc.' were inserted into the events. Examples of the stimuli are given in **Appendix B**. By this procedure, it was intended a) to avoid fatigue during the scanning session as well as to prevent patients to readily and instantly refuse attending to fictitious events, and b) to indicate the individual time period (amnesic, post-amnesic) where the patients had to search for a memory. It was assumed that within the amnesic time, retrieval attempt of such kinds of fictitious events may be associated with more mental effort than reading fictitious events concerning a time period the patients can recall (cf. **Chapter II**). Furthermore, it was assumed that the differentiation between true events and highly realistic but fictitious events is more difficult within a time period which – on the behavioural level – cannot be remembered. Thus it may be associated with smaller differences in the involved brain activations than concerning the same differentiation within an accessible time period (cf. **Chapter II**). The patients' relatives were instructed not to discuss the provided events with the patients.

Six non-identical stimulus sentences were constructed for each true and fictitious episode, resulting in 60 individual sentences per condition. This material (240 non-identical individual German [A.B. and E.F.] or English [C.D.] sentences per patient) was visually presented during the fMRI scan.

5.2 Tasks and experimental design

Stimuli were presented in black on a white background. The display was set to a distance of 29 cm. Presentation and timing of stimuli was accomplished using Presentation 0.53 (Neurobehavioral Systems, Inc., San Francisco, USA). Six individual trials of one of the four conditions were blocked together (stimulus onset time SOT= 5.17 s, interstimulus interval ISI= 1.5 s, 1 block= 40 s) to evoke neural responses associated with retrieval attempt of true old (TO), true new (TN), fictitious old (FO), and fictitious new (FN) episodes. Conditions were separated from each other by low-level baselines (each lasting 16 s), during which the patients were instructed to try to remember the described events as vividly and emotionally as possible (cf. Piefke et al., 2003). The following instruction was given:

"Please remember the events and situations specified in the displayed sentences as vividly and emotionally as possible."

Per baseline, four (whole brain) volumes [TR (repetition time) = 4 s] were acquired. Per block of trials of each memory condition (TO, TN, FO, FN), ten (whole brain) volumes (TR = 4 s) were acquired. A total of five experimental runs each consisting of 9 baselines and 8 memory blocks were performed, leading to the acquisition of a total of 600 volumes per subject (120 volume images per run). This scanning paradigm resulted in two repeats per condition per experimental run, leading to 10 repeats per condition per subject. The order of the memory conditions was counterbalanced across runs and individuals and there was no repeat of the individual stimulus sentences.

To control for the patients' alertness during a block of trials a subordinate reaction time task was included into the retrieval task. During the ISI patients viewed either a blank screen for 1,5 s, or a checkerboard for 500 ms followed by a blank screen for the remaining 1000 ms. During each block of trials 2-3 checkerboards were presented to which patients were instructed to react on with a right index finger button press as quickly as they detected the checkerboard. The number of times a checkerboard was presented was kept identical across all conditions.

Prior to scanning, patients were familiarised with the experimental set-up and the tasks. Patients were informed that the reaction time task was subordinate to the retrieval task to prevent them from concentrating on the checkerboard. Patients were further told that fictitious episodes would be presented to them as well. Finally, they were required to read the instruction for the next block of trials repeatedly to make sure that the same cognitive task was performed in all baseline conditions.

5.3 Magnetic resonance hardware and technical parameters

Scanning was performed using a 1.5 Tesla whole-body scanner (Siemens Vision, Erlangen) with echo-planar imaging (EPI) capability. For transmit and receive a standard radiofrequency head coil was used. High-resolution anatomical images were acquired using a T_1-weighted 3D MP-RAGE pulse sequence with the following parameters: TE = 4.4 ms, TR = 11.4 ms, TI (inversion time) = 300 ms, flip angle = 15°, slice thickness = 1.25 mm, field of view (FOV) = 230 mm, matrix = 200 x 256, 128 sagittal slices. Functional MR images were acquired in axial plane with a gradient-echo EPI pulse sequence using blood-oxygen-level-dependent (BOLD) contrast (sequence parameters: TE = 66 ms, TR = 4 s, flip angle = 90°, slice thickness = 4 mm, inter-slice-gap = 0.4 mm, FOV = 200 mm, in plane resolution = 3.125 mm x 3.125 mm, matrix = 64 x 64, 30 transversal slices). These 30 slices covered a subject's brain from the cerebellar vermis up to the vertex and were oriented along the anterior-posterior commissure (AC-PC) line using a midsagittal scout image. Each of the five fMRI time-series was preceded by 4 dummy images to allow the MR signal to reach steady state.

5.4 Image processing

Image processing and all statistical calculations were performed on Ultra 20 workstations (SUN Microsystems Computers) using MATLAB (The Mathworks Inc., Natick, MA, USA) and SPM99 (Statistical Parametric Mapping software, SPM; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk). SPM99 was employed for image preprocessing (image realignment, co-registration, normalisation, and smoothing) and to create statistical maps of changes in relative regional BOLD responses corresponding to the four memory conditions and the baseline (Friston, Ashburner et al., 1995; Friston, Holmes et al. 1995).

The first four images of each time-series were discarded to allow the MR signal to reach steady state (see above). To correct for head movement between scans the remaining 116 volume images of each time-series were realigned to the first image – that is, to the fifth image of each time-series. Following realignment, all image sets were co-registered to the 3D anatomical images acquired prior to functional neuroimaging. Thereafter, images were transformed using linear proportions and a non-linear sampling algorithm into standard stereotactic space as defined by Talairach and Tournoux (1988) with the intercommissural AC-PC line being used as the reference plane (Friston, Ashburner et al., 1995). For this normalisation procedure a representative brain from the Montreal Neurological Institute (MNI) series provided by SPM99 was employed as the reference template (Evans et al., 1994). Subsequently, all data were expressed in terms of standard stereotactic x-, y-, and z-coordinates using the Friston, Ashhburner et al. (1995) stereotactic space convention. The resulting voxel size was 2 x 2 mm with an interplane distance of 2 mm. Following normalisation procedures, each subject's imaging data were smoothed with a Gaussian kernel of 6 mm (full width half maximum).

5.5 Statistical analyses

Following image pre-processing, statistical analyses of functional MR data were performed. Subject-specific low frequency drifts in signal were removed by a high-pass filter of 344 s. Data analysis was performed by modelling the experimental memory conditions (true old [TO], true new [TN], fictitious old [FO], fictitious new [FN]) and the baseline by means of reference waveforms which correspond to boxcar functions convolved with a haemodynamic response function (Friston, Ashburner et al., 1995). Accordingly, a design matrix which comprised contrasts modelling alternating intervals of "activation" (referring to the four different memory conditions) and "baseline" was defined. Additionally, because of strong movements of patient A.B., for each experimental run, six parameters obtained from the realignment procedure as additional regressors were included in the design matrix of this subject. These regressors consisted of six relative parameters describing rotation and translation of the subject's head during the experiment. After estimation of all model parameters, specific effects were assessed by applying appropriate linear contrasts to the parameter estimates for each condition and the baselines resulting in z-statistics for each voxel. Statistical Parametric Maps ($SPM_{\{Z\}}$) of differences between the memory conditions of interest were generated and interpreted in light of the theory of probabilistic behaviour of Gaussian random fields. Areas of activation were identified as significant only if they passed the threshold of $p<0.05$, corrected for multiple comparison at the voxel level.

Data were analysed contrasting all single conditions concerning true and fictitious episodes within and outside the amnesic time resulting in a total of eight comparisons of interest (TO>TN; TN>TO; TO>FO; TN>FN; FO>TO, FN>TN; FO>FN; FN>FO).

5.6 Localisation of activations

Standard stereotactic coordinates of pixels showing local maxima were determined within areas of significant relative changes in neural activity associated with the demands of the different memory conditions. These local maxima were anatomically localised by reference to a standard stereotactic atlas (Talairach and Tournoux, 1988). For validation of this method of localisation $SPM_{\{T\}}$-statistics of each individual patient were superimposed on the single subject's co-registered 3D MR image.

6. Neuroimaging methods – $H_2^{15}O$-PET

As mentioned in **section I-2.4**, patients G.H. and I.J. had non-removable metal items inside their bodies preventing them from participating in magnetic resonance imaging procedures. Therefore, a $H_2^{15}O$-PET investigation was performed.

6.1 Stimuli

Similar to the fMRI investigation, for each patient individual stimuli were acquired by interviewing their relatives, who were asked to provide biographical episodes of the patients' past from the time period covered by the amnesia (last 5-10 years) and from the non-amnesic time period following the onset of retrograde amnesia. By this procedure, four episodes before onset (Old) and four episodes after onset of the amnesia (New) were collected for each patient. Four non-identical stimulus sentences were constructed for each episode, resulting in 16 individual sentences per condition. Stimuli resembled those of the fMRI experiment (cf. **section IV-5.1** and **Appendix C**). This material (32 non-identical individual sentences per patient, Russian translations for I.J.) was visually presented during the PET scan.

6.2 Data acquisition

PET scans were performed on an ECAT Exact HR scanner (CTI/Siemens, Knowxville, TN; [Wienhard et al., 1994]) in three-dimensional mode after a 10-minute transmission scan. Because of the linear relationship between cerebral blood flow and tissue activity of ^{15}O-water (mCi/ml), measures of relative cerebral blood flow (CBF) were obtained (Raichle, Martin, Herscovitch, Mintun, & Markham, 1983). The measurement started after intravenous bolus injection of 370MBq of ^{15}O-water. Data acquisition began automatically when the detected activity exceeded 300% of background activity and lasted for 45 seconds. Twelve (4 x 3) subsequent scans were performed on each patient, with an interval of approximately 6 minutes between scans. Each scan was reconstructed to 47 slices (3.125 mm thickness and 2.16 mm pixel size within a 128x128 matrix) using the filtered back projection technique and a Hanning filter with cut-off frequency of 0.4 cycles per pixel. Prior to reconstruction corrections for random coincidence, scatter, and photon attenuation were applied.

6.3 Task and experimental design

We applied an autobiographical memory retrieval paradigm with four replications. The paradigm consisted of a resting condition (watching 16 different sets of Japanese characters) and two autobiographical memory retrieval conditions (reading sentences about personal episodes before [Old] and after the onset of the amnesia [New]). Stimuli were shown in 44 font/size on a 15" screen. Four sentences per condition were blocked together and were shown for 15 seconds each. The four sentences in each block depicted different episodes. During the experimental conditions, patients were instructed to try to remember the described episodes as vividly as possible (cf. **section IV-5.2**). The presentation of stimuli started with tracer injection and ended 45 seconds after scan start. Tasks were presented in a balanced sequence.

6.4 Image processing

Statistical parametric maps of significant individual CBF-differences between the conditions were obtained by using SPM 99 (The Wellcome Department of Cognitive Neurology, University College of London, UK; http://www.fil.ion.ucl.ac.uk)) implemented in MATLAB (Mathworks Inc., Sherborn, MA). All PET data were normalized to a standard stereotactic space (Talairach & Tournoux, 1988) by proportional scaling and smoothed with a 12mm full-width half-maximum (FWHM) isotropic kernel (Friston, Holmes et al., 1995). A single subject analysis was performed to map areas of increased CBF between the three different conditions. The resulting map of the t-statistics was transformed to the unit normal distribution $SPM_{\{Z\}}$ and thresholded at $p < 0.001$ and to a minimum extend of 10 voxels. The significance of resulting foci was accepted if peak height or cluster size reached the threshold of $p<0.05$, uncorrected for multiple comparisons.

7. Post-scanning debriefing

In the fMRI experiment, immediately after the scan patients were given two questionnaires including all stimulus sentences. In the first questionnaire, each of the 240 individual stimuli were randomised and patients retrospectively indicated, whether they could relate the stimulus to a personal past experience or whether the sentence depicted a fictitious event. Independent from answers to the first question, patients were further supposed to judge the quality of their memory. They had to decide whether each sentence triggered a vivid and precise memory ('remember'), a feeling of knowing ('know') or no memory at all. Finally, patients had to specify the source of their memory. They were asked to indicate whether they had known the described information by themselves or whether someone else had told them about it.

Furthermore, patients completed a questionnaire on characteristic features of autobiographical memory for each event separately. For this purpose, all six sentences depicting one episode were clustered together and all events were shown in randomised order. On a dichotomised scale, patients retrospectively rated their memory for each event during the scan with regard to the following characteristics: *mental imagery*, *personal relevance, role of language, emotionality, re-experience, and richness of details*. If an event was judged as emotional, it was further asked whether the episode was *negative* or *positive*.

In the PET experiment, a post-scanning debriefing was intended with patients G.H. and I.J. similar to the fMRI-experiment. However, patient G.H. was emotionally very upset after the scanning session, and therefore it was decided to omit the debriefing in her case. Accordingly, only patient I.J. received two questionnaires considering his memories during the scan. In the first questionnaire, each of the 32 individual stimulus sentences were shown in randomised order and, identical to the fMRI experiment, I.J. retrospectively indicated the quality of his memory per sentence ('remember', 'know', 'no memory') as well as the source of it ('self', 'others'). In the second questionnaire, all four sentences depicting one episode were clustered together and episodes were shown in randomised order. On a dichotomised scale, I.J. retrospectively rated the descriptions of each event with regard to the same autobiographical memory characteristics as described in the fMRI experiment's post-scanning debriefing.

Examples pages of the post-scanning questionnaires are given in **Appendix D** (fMRI experiment) and **Appendix E** (PET experiment).

8. Procedure

Following a detailed anamnesis, neuropsychological tests and psychological screenings were administered on at least two consecutive days. Per day, two to three test sessions were conducted, approximately lasting two hours each. If required, a third test day was added (patient G.H.). All patients were tested in their home environment. Interviews with the patients' relatives were held following the examinations, either on the test days or via phone.

For stimulus acquisition for the neuroimaging experiments, the patients' relatives provided the required autobiographical episodic information by mail. Each reported episode was scrutinised via phone conversations with the patients' relatives to allow appropriate reconstruction of the events. For the fMRI experiment, additional information about the patients' previous life was obtained with the help of their relatives to allow construction of fictitious but highly realistic events. All relatives were instructed not to talk to the patients about the information that they had provided to the stimulus construction.

All patients participated the functional neuroimaging experiments in a relaxed state during morning or early afternoon. Scanning sessions were conducted twelve months (A.B., C.D.), six months (E.F.), five months (G.H.), or sixteen months (I.J.) after onset of the amnesia. Table 8 gives an overview of the procedure and temporal sequence of the investigation's steps.

Table 8: Overview of the course of investigations in the current study

INVESTIGATION	TIME COURSE & DURATION
Neuropsychological investigation of the patients	duration: 2-3 days
↓	
Additional interviews of the patients' relatives	during and following the neuropsychological investigation; duration: several hours
↓	
Stimulus acquisition for scanning experiments: Patients' relatives provide written descriptions of events and additional information of the patients' past	approximately 1 month after the neuropsychological investigation
↓	
Verification of the provided information by phone interviews of the patients' relatives	immediately after receipt of the letters
↓	
Construction of the stimuli for the neuroimaging experiments	duration: approximately 2 weeks per patient
↓	
Scanning session	individually different time delays between first investigation and scanning session see **section IV-8.**
↓	
Post-scanning debriefing	immediately after the scanning sessions
↓	
At least two follow-up phone interviews with the patients	approximately 1 month after scanning session and 3 months after scanning session

V. Results

In the following chapter, behavioural observations are reported that were made during or outside the test sessions. These include general behavioural appearance and motivation during the test sessions as well as behavioural anomalies that seemed relevant in light of the amnesic symptoms. Subsequently, results of the neuropsychological investigation and psychological screening are reported. Results of the fMRI and the PET investigation are given separately. Both neuroimaging experiments are followed by results of the post-scanning debriefing.

1. Behavioural observations

Behaviour and motivation during the neuropsychological test sessions is reported and complemented by general observations made between test sessions and following the examination.

1.1 Patient A.B.

Patient A.B. was well motivated to participate in the study. She was alert, friendly and attentive throughout the entire neuropsychological examination. When asked for current complaints she did not report any cognitive limitations except a remote memory deficit for episodes that occurred prior to the onset of her amnesia. Furthermore, she stated that she occasionally experienced headaches. Regarding her current situation, she continuously mentioned that she is not very concerned about her amnesia. For example, she repeatedly stated that 'she is now simply and finally herself' and that 'the others may or may not accept her change'. While she described herself as being a different person (friendlier and more open compared to her previous life) after the onset of her amnesia, this could not be verified by interviews of her relatives and her friend. However, she lost her depressive symptoms after onset of the amnesia giving her a different emotional appearance. During semantic remote memory testing, A.B. involuntarily recalled fragments and details of former autobiographical events, a condition which was apparently threatening to her when she became aware of her performance.

1.2 Patient C.D.

Patient C.D. was well motivated to participate in the study. He was friendly and mostly alert throughout the neuropsychological examination though several breaks had to be interspersed due to attentional fluctuations. When asked for current complaints, C.D. reported various problems beyond a remote memory loss. He mentioned severe concentration problems stating that reading, writing and continuous activities such as watching TV were demanding for him since the onset of the amnesia. Concerning memory and learning he reported that sometimes the temporal order of events appeared difficult for him now. Thus, he stated that he occasionally confused who had told him what and when, and had problems in estimating time periods. He also reported sleep problems. Regarding his current situation, he claimed that while the gaps in memory sometimes scared him, he was as well anxious about getting his memory back. He also said that he quite successfully arranged his 'new life without a past'. He further reported suffering from pain in his back and in his elbow and mentioned a painful unstable right knee dating back to a previous injury. He supposed that these symptoms may have been re-awakened by the accident responsible for his amnesia. Several months after his participation in the current study, he quit his job and involved in litigation with his former employer to receive compensation. Furthermore, C.D. frequently presented his situation in public in interviews by several news magazines and TV stations. A behavioural anomaly occurred after the FDG-PET investigation. When he was confronted with the normal result, he reacted very upset and stopped contacting the Psychology Department for some time.

1.3 Patient E.F.

Patient E.F. was well motivated to participate in the study. He was alert, friendly and attentive throughout the entire neuropsychological examination. When asked for current complaints he did not report any cognitive deteriorations except a remote memory deficit for the last 12-14 years. However, he stated to occasionally experience headaches. During the test sessions he repeatedly mentioned his concern for his memory deficit. He stated that he felt very uneasy in everyday situations such as in road traffic or in unfamiliar places since he was not sure how to behave in several of these contexts. Also, he was afraid to be recognised by others whom he himself did not remember. When he was confronted with his FDG-PET results, he was concerned about the pathological finding of reduced cerebellar glucose utilisation.

1.4 Patient G.H.

Patient G.H. was motivated to participate in the study. She was friendly and mostly alert throughout the neuropsychological examination though several breaks had to be interspersed due to attentional fluctuations. When asked for current complaints, G.H. did not report any cognitive deteriorations except a remote memory deficit for the last 13 years. Except the emotional conflicts with her surroundings that were mentioned in the case history, G.H. reported some body-related problems that currently caused mood swings. She mentioned gastrointestinal and chest pain. She also reported a numbness concerning her general bodily states. G.H.'s husband reported that after the onset of amnesia, she started to behave in a childish and egocentric way, a behaviour that initially enabled her to avoid most of her daily duties. Her husband further reported that approximately 6 months after the onset of amnesia, G.H. started to vehemently express the wish to have another baby. Even following clarification by her husband that she is unable to become pregnant due to previous gynaecological surgeries (cf. **section III-4**), she kept denying her sterility. In the course of the testing sessions, some behavioural anomalies occurred which are outlined in the following. When tested with the Famous Events Test, G.H. misunderstood a question as if it was referring to an incident that had happened in 1988, prior to the time period covered by amnesia. This event actually had happened in 1990, that is, within the amnesic time interval. She correctly answered this item and provided additional details on the public event in question. When she noticed her misunderstanding, she instantly refused to answer the next questions, so that the test had to be interrupted and continued later. Another incident refers to the $H_2^{15}O$-PET investigation. Following the scanning, G.H. was emotionally very upset and had to be calmed by her husband. Therefore, the post-scanning debriefing had to be omitted in her case.

1.5 Patient I.J.

Patient I.J. was well motivated to participate in the study. He was alert, friendly and attentive throughout the entire neuropsychological examination. When asked for current complaints he reported minor concentration deficits and a short attentional span (<2 hours) beyond retrograde amnesia. He also stated that acquisition of new materials sometimes exhausted him, though he did not notice this problem in everyday life. He stated to experience headaches and sleep disturbances. During the test sessions, he repeatedly mentioned his concern for his remote memory deficit. For example, in the autobiographical interview he was startled and very distressed when he became aware of the extent of his amnesia. He repeatedly asked for possible explanations for his disease. Thus, the interview had to be interrupted and continued later. One information may be of further interest in this case. When I.J. and his wife were asked about seeking legal actions to regain the lost money (cf. **section III-5**), their answers were very evasive and they both stressed their demand for a current peaceful life.

2. Neuropsychological evaluation

In the next section, results of the neuropsychological tests and psychological screenings are listed.

2.1 Cognitive tests

Results in neuropsychological domains intelligence, anterograde memory, attention, executive functions, and Theory of Mind abilities are listed in Table 9. Unless otherwise stated, scores are given in percentiles derived from norm group data.

Table 9: Neuropsychological profile of the five patients

Neuropsychological Domain and Test	Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Intellectual Abilities						
MWT-B (German adaptation of NART)	estimated premorbid IQ	100	n.a.	114	91	124
Subtest 'Reasoning' from LPS (LPS-4)	IQ	97	96	113	103	98
Wechsler Adult Intelligence Scale-Revised (WAIS-R)	verbal-IQ	118	100	n.a.	116	117
	performance-IQ	126	110	n.a.	103	110
	full-scale-IQ	124	104	n.a.	112	120
Anterograde Memory						
Wechsler Memory Scale-Revised (WMS-R)	*IQ-scalea*					
	general memory	114	83*	129	99	91
	verbal memory	115	87	127	90	88
	visual memory	104	82*	116	119	99
	delayed memory	116	99	124	90	78*
Span Tasks from WMS-R	*percentiles*					
	Digit Span (forward)	37	87	87	88	68
	Digit Span (reversed)	73	92	56	73	56
	Block Span (forward)	18	60	97	32	56
	Block Span (reversed)	12*	3*	78	23	13*
Rey Complex Figure Test (CFT)	copy	48	24	n.a.	66	62
	delayed recall (30 min.)	82	31	n.a.	88	62
California Verbal Learning Test (CVLT)	*raw scores*					
	correct words (trials 1-5)	72/80	46/80*	52/80*	62/80	n.a.
	short delay free recall	15/16	10/16*	9/16*	13/16	n.a.
	long delay free recall	15/16	10/16*	10/16*	11/16	n.a.
	recognition hits	16/16	13/16*	13/16*	12/16*	n.a.
Incomplete Figures Test (FBT)	Trial A	58	73	n.a.	10*	73
	Trial B	79	62	n.a.	58	79
	Trial A-B	73	69	n.a.	9*	50

Neuropsychological Domain and Test	Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Attention & Executive Functions						
Trail Making Test (TMT)	Part A	73	31	n.a.	48	50
	Part B	8*	7*	n.a.	69	1*
Concentration Endurance Test d2	error-corrected total score	33	16	n.a.	21	54
Subtests from Test Battery for the Assessment of Attention	Alertness	n.a.	n.a.	0	0	n.a.
	Divided Attention	n.a.	n.a.	0	0	n.a.
	Selective Attention	n.a.	n.a.	21	1	n.a.
Stroop-Test (FWIT)	Word Trial	48	51	n.a.	24	66
	Colour Trial	69	71	n.a.	24	34
	Interference Trial	54	46	n.a.	1*	69
Attention/Concentration Index from WMS-R	*IQ-scalea*	90	113	113	104	94
Lexical Fluency (FAS-Test)		54	50	69	79	27
Categorical Fluency (Animal Naming Task)		50	10*	n.a.	85	93
Modified Card Sorting Test (MCST)	categories completed	>45	>45	>45	>45	>45
	errors	>65	35	>65	45-50	>65
	perseverative errors	>65	10*	>45	>45	>65
Theory of Mind						
Reading the Mind in the Eyes Test		n.a.	1-2*	0*	0*	50

n.a.: not administered; *: percentiles lower than 15 indicate deviation from norm groups

All patients exhibited normal to above normal intellectual abilities in the verbal and nonverbal intelligence measures applied here. Somewhat disparate results across intelligence tests and screenings were revealed in patients A.B. and I.J. Whereas A.B. had above average performance in the WAIS-R, her score in subtest 'Reasoning' of the LPS was only average. The differences across intelligence scores observed in I.J. may be due to the fact that in subtest 'Reasoning' subjects are given sequences of numbers and Latin letters in which an odd number or letter has to be found. Since I.J. is more familiar with the Cyrillic alphabet, his lower performance in this test might have arisen by this language-related characteristic.

While most attentional and executive functions were unimpaired, three of four patients in whom Trail Making Test part B was applied, showed deficient results (patients A.B., C.D., and I.J.). Patients E.F. and G.H., in whom parts of the Test Battery for the Assessment of Attention were applied, were severely impaired in tests Alertness and Divided Attention. G.H. showed comparably weak performance in Selective Attention, whereas E.F. exhibited low average performance. In patient C.D., categorical fluency measured by the Animal Naming Task, as well as categorisation and set shifting assessed with the MCST, were impaired. Furthermore, G.H. showed a highly elevated susceptibility to interference in the Interference Trial of the FWIT.

Anterograde memory assessed with the WMS-R was average to above average in patients A.B., E.F., and G.H., whereas patients C.D. and I.J. exhibited mild impairment. C.D. showed below average immediate learning with visual memory being weaker than verbal memory. I.J.'s immediate verbal memory index was somewhat low (percentile=88), which was mainly due to his weak performance in the subtest Logical Memory. His low result in 'delayed recall index' (index=78) was due to the low initial score in this subtest. Furthermore, C.D.'s immediate and delayed memory indices were somewhat unusual showing mild immediate memory impairment but average delayed memory.

Verbal and visual short-term and working memory was assessed by Digit Span and Block Span (WMS-R). Working memory was deficient in A.B., C.D. and I.J. Results in these four tests were disparate in patients A.B., C.D. and to a lesser extent also in patient G.H. All patients displayed a preference of verbal over visual material with patient C.D. showing the most pronounced discrepancy between above average verbal (percentile=92) and clearly impaired nonverbal working memory (percentile=3). In the four patients assessed by delayed recall of the Rey Osterrieth Complex Figure, no deficits were seen in visual long term memory. In the California Verbal Learning Test, C.D. and E.F. had mild problems in the acquisition of 16 words over five learning trials and their immediate and long-term delayed recall was slightly deficient. Long-term recognition of the words was below average in C.D., E.F. and G.H. without, however, a heightened false alarms rate (C.D. had no false positives, E.F. and G.H. falsely recognised one word).

Three of the four patients in whom ToM abilities were assessed, deficits were found indicating problems in the interpretation of other people's eye gazes referring to motivational and emotional states.

Considering the deficient results per patient, it can be summarised that A.B. and I.J. had deficits in visual working memory and mental flexibility, patients E.F. and G.H. showed problems in complex attentional tasks, slight verbal learning impairment in word list learning and

ToM-deficits, and patient C.D. exhibited a broader pattern mostly of minor impairment across neuropsychological domains attention/executive functions, anterograde memory and ToM.

2.2 Psychological screenings and personality

In Table 10, the patients' responses in psychological screenings and in the personality questionnaire are summarised.

Table 10: Results in psychological screenings and personality questionnaire

Psychological Screening	**Patients**	**A.B.**	**C.D.**	**E.F.**	**G.H.**	**I.J.**
Beck Depression Inventory (BDI)	Cut-offs: 12: mild to moderate depression 18: severe depression	2	9	7	14*	6
Symptom Checklist (SCL-90-R)	Cut-off: >60					
	somatization	73*	62*	50	56	41
	obsessive-compulsive	48	67*	57	57	26
	interpersonal sensitivity	33	64*	47	80*	33
	depression	46	64*	45	66*	38
	anxiety	35	60	37	60	38
	anger-hostility	56	58	38	70*	39
	phobic anxiety	41	61*	56	67*	53
	paranoid ideation	38	66*	53	66*	48
	psychoticism	51	59	50	79*	41
	global severity index	50	68*	48	69*	42
Freiburg Personality Inventory-Revised (FPI-R)	Stanines[1] (max. 9)					
	life satisfaction	5	4	4	4	5
	social orientation	7	4	8*	7	5
	achievement motivation	6	4	1*	6	2*
	inhibition	3	6	4	7	5
	excitability	7	5	6	6	2*
	aggressiveness	7	3	3	4	3
	stress	6	4	5	5	1*
	physical complaints	6	6	2*	8*	7
	worries about health	5	2*	3	1*	2*
	openness[2]	9*	1*[2]	3*[2]	5	1*[2]
	extraversion	7	5	3	4	2*
	neuroticism	9*	4	5	6	3
State-Trait-Anxiety Inventory (STAI)	Percentiles					
	State Anxiety	79	24	n.a.	n.a.	n.a.
	Trait Anxiety	69	31	n.a.	n.a.	n.a.

Psychological Screening		Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Dissociative Experience Scale (FDS)	Percentiles						
	amnesia		n.a.	n.a.	n.a.	>99	n.a.
	absorption		n.a.	n.a.	n.a.	>99	n.a.
	derealisation		n.a.	n.a.	n.a.	>99	n.a.
	conversion		n.a.	n.a.	n.a.	27	n.a.

n.a.: not administered; *: significant deviations from norm groups; [1]: Stanines 1-2 and 8-9 indicate significant deviations from norm group data; [2]: Stanines 1-3 on subscale *openness* indicate social desirability

Regarding mood and psychiatric symptoms, none of the patients showed severe depression in the BDI, although G.H. had a score of 14 points indicating mild to moderate depressive mood.

In the SCL-90-R, significant deviations from norm group data were found in patients A.B., C.D. and G.H. While A.B. showed elevated scores in subscale *somatisation* only, C.D. and G.H. exhibited a broader pattern of deviations as can be derived from Table 10. Patient G.H. had remarkably heightened scores in subscales *interpersonal sensitivity* and *psychoticism*, whereas C.D.'s deviations were less pronounced and more evenly distributed across subscales. Though some of the indicated problems might be explainable by the current situation of the patients (e.g. C.D. reported having been teased by some of his colleagues who told him fictitious facts about his past; this may have resulted in an overly paranoid attitude towards others), it cannot be clarified whether the symptoms are now experienced for the first time or whether they already existed before the onset of the amnesia. However, the global severity index GSI clearly indicates moderate current stress in patients C.D. and G.H. regardless of its origin and duration.

In the FPI-R, four of the five patients showed significant deviations from norm group data in subscale *openness*. In detail, patient A.B. described herself as being extremely willing to admit minor weaknesses and violations of everyday conventions (e.g. sometimes being late for appointments, behaving more casually at home than in public places), whereas patients C.D., E.F. and I.J. mostly negated these questions, indicating a tendency to act in socially desirable ways in the latter patients. Since *openness* operates as a validity scale, results on all other subscales is confined in these three patients. In patient A.B. an additional deviation was found in subscale *neuroticism* wherein she described herself as suffering from many psychosomatic complaints and as being emotionally labile, extremely sensitive, and anxious. Patient G.H. described herself as suffering from many physical complaints but at the same time being not at all worried about her health.

Patients A.B. and C.D. to whom the STAI was given, did not show heightened momentary or dispositional anxiety.

Patient G.H., who additionally received the Dissociative Experience Scale FDS, showed highly elevated scores in dissociative experiencing. Though some of the items have to be seen in the context of her retrograde amnesia (e.g. in the subscale *amnesia* it is asked whether writings, drawings and notes of oneself are detected which one cannot remember to have made), others do not necessarily relate to memory loss. In this regard, items of the *absorption* subscale can be considered validly heightened in G.H. (items include statements such as losing contact with the surroundings when focused on one's own thoughts; subjectively experiencing blurred boundaries between real events and those that were dreamt of). Whereas G.H. had an elevated score also in subscale *derealisation* indicating a sense of being outside her body, the score on *conversion* subscale was normal pointing to no clinically relevant conversion symptoms (e.g. pseudoseizures, unresolved somatic symptoms).

In summary, A.B. showed a tendency for somatisation, extreme openness to admit minor weaknesses in public and signs of emotional lability. C.D.'s general psychological profile was characterised by slight deviations in many psychiatric syndromes and complemented by a tendency to give socially desirable answers. The latter tendency was also seen in patient E.F. Patient G.H. showed mild signs of currently depressed mood. Similar to patient C.D. she presented with numerous psychiatric symptoms wherein interpersonal sensitivity was remarkably elevated. She further described herself as suffering from many physical complaints but not being worried about her health. Moreover, signs of dissociative experiencing were observed in G.H. Finally, similar to C.D. and E.F., patient I.J., showed a tendency to give socially desirable answers.

2.3 Remote memory

In the remote memory domain, results of the comparison subjects are reported to contrast with the patients' results. All results in remote memory tests were corrected for re-learned items after the patients' onset of their amnesia in that these were subtracted from the reached scores.

2.3.1 Semantic remote memory

Patients' and comparison subjects' test results in semantic remote memory evaluation are summarised in Table 11.

Table 11: Results in semantic remote memory tests

Neuropsychological Test	**Patients**	**A.B.**	**C.D.**	**E.F.**	**G.H.**	**I.J.**
Semantic Remote Memory Test						
	Cut-off < 89%	93.8%	n.a.	99%	96.3%	n.a.
Famous Names Test						
	name identification	91.7%	37.5%	48.0%	39.6%	27.1%
	comparison subjects	*91.7%*	*87.5%*	*95.8%*	*86.4%*	*93.8%*
	additional information	85.4%	31.3%	43.8%	33.3%	27.1%
	comparison subjects	*83.3%*	*83.3%*	*91.7%*	*83.3%*	*89.6%*
Current Words Test						
		90.5%	50.0%	47.6%	35.7%	52.4%
	comparison subjects	*92.9%*	*88.1%*	*97.6%*	*90.2%*	*88.1%*
Famous Events Test						
	years: 1980-1989	n.a.	0%	90.9%	27.3%	0%
	comparison subjects	*n.a.*	*72.7%*	*90.9%*	*81.8%*	*n.a.%*
	years: 1990-1995	88.2%	0%	5.9%	0%	0%
	comparison subjects	*88.2%*	*81.3%*	*82.4%*	*82.4%*	*n.a.*
	years: 1996-2001 (pre-amnesic time)	93.5%	29%	3%	6%	0%
	comparison subjects	*90.3%*	*83.9%*	*87.8%*	*81.8%*	*n.a.*
Famous Faces Test (percentiles derived by control group data from Jänicke, 2001)						
	years: 1980-1985					
	free recall	n.a.	n.a.	24	n.a.	n.a.
	recognition	n.a.	n.a.	54	n.a.	n.a.
	additional information	n.a.	n.a.	50	n.a.	n.a.
	years 1986-1990					
	free recall	n.a.	n.a.	10*	n.a.	n.a.
	recognition	n.a.	n.a.	16	n.a.	n.a.
	additional information	n.a.	n.a.	10	n.a.	n.a.
	years 1991-1995					
	free recall	n.a.	n.a.	13*	n.a.	n.a.
	recognition	n.a.	n.a.	10*	n.a.	n.a.
	additional information	n.a.	n.a.	5*	n.a.	n.a.
	years 1996-2000					
	free recall	n.a.	n.a.	12*	n.a.	n.a.
	recognition	n.a.	n.a.	13*	n.a.	n.a.
	additional information	n.a.	n.a.	2*	n.a.	n.a.

n.a.: not administered; *: significant deviations from norm groups

In the Test of Semantic Remote Memory from Schmidtke and Vollmer-Schmolck (1999) patients A.B., E.F., and G.H. in whom this test was applied scored normal.

In the Famous Names Test, except for A.B., all patients showed impaired performance in identifying the names of famous personalities and they exhibited problems to provide additional information. Interestingly, though this test is not suitable to map specific time periods, patient E.F. – who reported to be amnesic for the last 12-14 years (see case history) – provided precise details about some of the celebrities, however, only concerning early steps in their careers (e.g. he reported considerable details about the baseball career of O.J. Simpson but was entirely unaware of his accusation of murder and the following court cases).

Similar to the results in the Famous Names Test, in the Current Words Test all patients, except A.B., showed impaired performance in describing the meanings of words currently and formerly in use in everyday language. Patient G.H. had the lowest result correctly defining 35.7% of the items, patients C.D., E.F., and I.J. knew around 50% of the terms.

Remarkably impaired memory for news events as assessed by the Famous Events Test adapted from Leplow and Dierks (1997) was again found in all but patient A.B. Patient C.D. did not remember any events prior to the years 1996-2001. His slightly higher performance (29%) in this last time period could be traced back to his apparently intact memory for some events that had happened shortly before the onset of his amnesia. However, it was unclear whether he had re-learned these events and it can thus be concluded that his memory deficit was not temporarily graded. Patient I.J. exhibited a complete lack of memory for any of the public events in question. In contrast, E.F. showed a temporarily graded semantic remote memory loss with intact memory for events dating from time period 1980-1989 (90.9%) but almost no memory for events that had happened later (6% and 3%, respectively). Patient G.H. exhibited some memories for events dated between 1980-1989 (27.3%), but almost no memory for more recent events (0% and 6%). G.H.'s weak performance during time period 1980-1989 may underestimate actual memory performance but rather reflect a general lack of interest in news events which was emphasised by her husband.

As can be seen in Figure 10, the temporally graded semantic remote memory loss in patient E.F. was further supported by his results in the Famous Faces Test (percentiles derived by control group data from Jänicke, 2001).

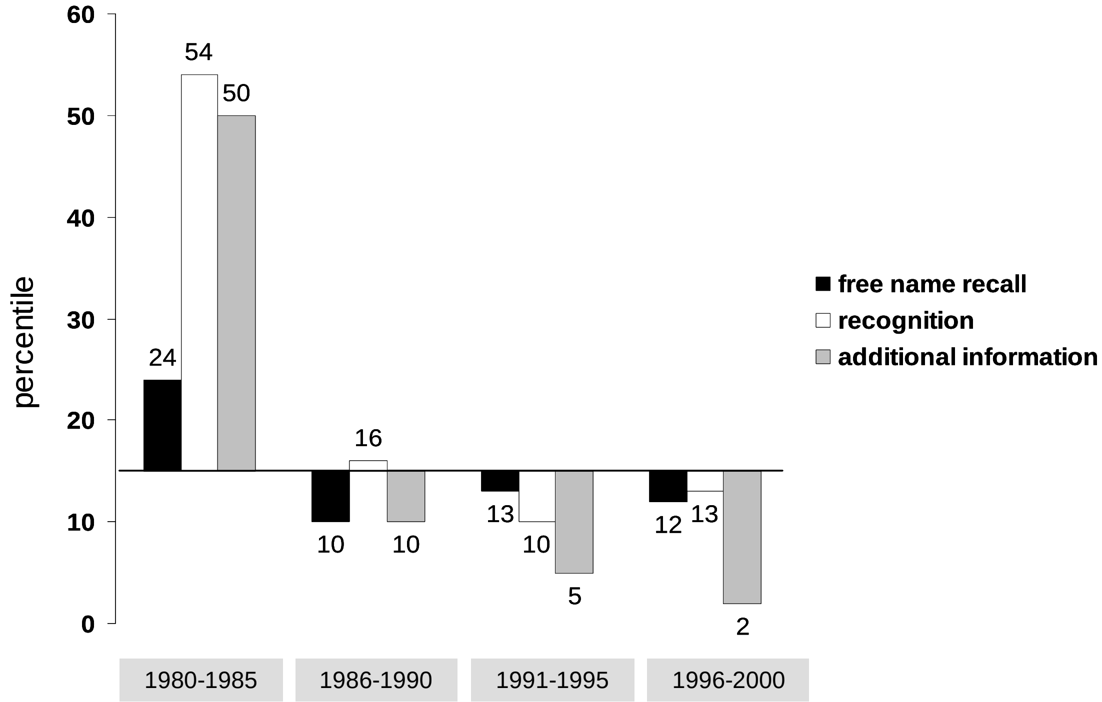

Figure 10: Patient E.F.'s results in the Famous Faces Test across four time periods between years 1980 and 2000.

A clear dissociation between preserved memory for famous personalities of the time period until 1985 and below average memory for celebrities from later time periods was observed. These results were seen in free recall of the names of famous personalities as well as recognition of their names from distractor lists. Even more pronounced impairment was observed in retrieval of additional information about the famous persons.

In contrast to all other patients, A.B. was not amnesic for remote semantic information. As can be seen in Figure 11., contrasting her performance with that of her comparison subject revealed strikingly similar results.

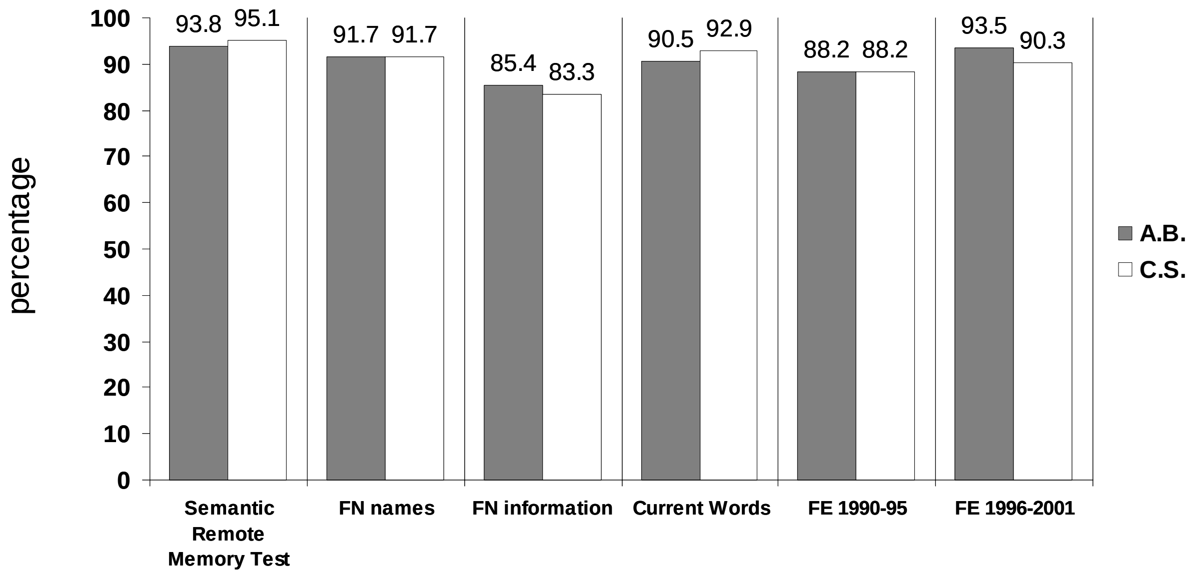

Figure 11: Patient A.B.'s and her comparison subject's remote memory performance across semantic remote memory tests. Scores are given in percentage; FN: Famous Names Test; FE: Famous Events Test; C.S.: comparison subject.

In summary, all patients except A.B. exhibited difficulties in parts of semantic remote memory. Whereas pre-school knowledge – testable in patients A.B., E.F. and G.H. originating from a German-Austrian background – was intact, deficits were observed in almost all other applied measures. Semantic remote memory loss was temporally graded in patient E.F. who showed difficulties in recall and/or recognition of news event and famous persons' names from time periods prior to the year 1990. It was unclear whether C.D. had relearned news events from recent years, rendering it difficult to make assumptions about a temporal gradient in his remote semantic memory. However, even assuming that he in fact remembered these recent events, his performance was still clearly below the results of his comparison subject. Therefore, his semantic remote memory can either be considered as showing a reverse temporal gradient or may be ungraded. Though patient G.H. provided some information about news events from the earliest time period, her performance was lower than her comparison subject's result. It has, however, to be considered that she might never have been interested in news events as was pointed out by her husband. Therefore, no definite assumptions about temporal gradients in her semantic remote memory can be made. Patient I.J. showed the lowest results in semantic remote memory compared to the other patients. His memory loss was temporally ungraded and comprised 47.6% of the word definitions from the Current Words Test, 72.9% of the names from the Famous Names Test, and all questioned news events. Though no appropriate comparison subject was available for controlling I.J.'s performance in the Famous Events Test, his wife emphasised that before the onset of his amnesia he would have known most of the events. Moreover, given his strikingly weak performance across all semantic remote memory tests, it is safe to state that he clearly exhibited semantic retrograde amnesia.

2.3.2 Episodic remote memory

Table 12 gives an overview of patients' results in the interview with the Autobiographical Memory Inventory (Autobiographisches Gedächtnis Inventar AGI).

Table 12: Results in autobiographical remote memory interview

	Patients	A.B.	C.D.	E.F.	G.H.	I.J.
Autobiographical Memory Inventory (AGI)	Age: 1-5 years					
	facts: max. 5	5	0	5	5	1
	episodes: max. 2	2	1	2	2	0
	details: max. 11	6	2	9	11	0
	Age: 6-10 years					
	facts: max. 5	5	2	5	5	1
	episodes: max. 2	1	2	2	2	0
	details: max. 11	8	7	8	11	0
	Age: 11-17/18 years					
	facts: max. 5	5	3	5	5	3
	episodes: max. 2	1	2	2	2	0
	details: max. 11	11	10	11	11	0
	Age: 18/19-29/34[1]					
	facts: max. 5	-	3	2	5	5
	episodes: max. 2	-	1	2	1	0
	details: max. 11	-	8	2	5	0

[1]: considering the individual age of the patients and time of the onset of the amnesia, this age period varied across patients

Patient A.B. was effortlessly able to provide semantic facts about her previous life in a consistent manner (e.g. names of former friends, class mates, teachers). However, this result may be overestimated since by the time of testing she still had daily contact with most of these individuals and also her domestic environment has been largely the same throughout her entire life. Considering the time up to the age of 10 years, A.B. was able to provide some fragmentary episodic information but all reported events were considerably lacking details and contextual embedding. In the time period between the age of 11-17 years, one of the two reported episodes was erroneous. As was confirmed by her friend, A.B. apparently confused three different previous episodes with regard to time and context. One detailed and contextually correctly recalled episode dated March 2001 (a holiday trip to New York). This represents a singular and isolated event that has already been remembered by A.B. in the very first time after the incident. The retrieval of this event, however, had not triggered retrieval of further autobiographical episodic information.

Patient C.D. had difficulties in retrieving autobiographical semantic information related to his entire previous life. For instance, C.D. could not provide the address of his home for about the first 14 years of his life, and he was unable to name friends or teachers from the time before the age of 10. In naming the addresses of the last eight to nine years he made errors in the temporal sequence of different locations due to information provided by his wife. Autobiographical episodes over his whole life span were either lacking emotional connotation or details. For instance, he remembered to have felt very uneasy while sitting in a train, but he could not tell the destination or the circumstances of the travel. Similarly, he described a very detailed and precise image of a certain door bell but could neither remember the place where it was nor why he was there, how he was feeling, whether he was alone or whether a specific event occurred there. Despite vivid imagery of single scenes, C.D. was unable to specify contextual (temporal and spatial) information regarding all but one episode at the age of 15. During examination, it was obvious that C.D. tried to retrieve episodic information through mental imagery without knowing which image belonged to which episode or life period. Thus, stringent reconstruction of events was remarkably difficult. In summary, in patient C.D. a dichotomy was observed in response behaviour. He reported either highly emotional but contextually confused episodes, or highly detailed but emotionless events.

Patient E.F. was able to provide autobiographical semantic and episodic information related to his life up to the age of about 20 years. However, retrieval of all later dated facts and events was impaired. The few semantic facts he reported were re-learned after the onset of the amnesia and despite his fragmentary memory for one event (New Year's Eve 2001), he did not retrieve any further events within this time nor did his memory fragment trigger any further details concerning the specific event. For instance, he did neither remember his current job nor his wife whom he is married with since 1997.

Similarly, patient G.H. could provide autobiographical semantic and episodic information about her previous life only until May 1989 (21 years of age). Though she was able to tell later dated semantic facts, she reported to have re-learned them after the onset of the amnesia. G.H. also reported some episodic information from the amnesic time but did so in a fragmentary and emotionally detached manner. Similar to the detailed but emotionally detached reporting style observed in patient C.D., she could precisely describe several visual/spatial details about the decorations for a party at her house dated March 1990 without being able to merge these details to the actual episode. During the interview, several of the aforementioned traumatic childhood events were discussed. G.H. could describe all of them in a consistent manner though she was obviously very distressed by her memories. Thus, the interview had to be interrupted twice and continued later.

Patient I.J. was unable to provide any autobiographical semantic or episodic information concerning his entire previous life. The few semantic facts he reported were re-learned after the onset of his amnesia and even with the help of extensive cuing there was no evidence for the retrieval of any episodic information in I.J. However, in a break during the neuropsychological examination and independent from the autobiographical interview, I.J. reported the autobiographical dream he had during his stay in the Russian hospital (cf. **section III-5**). He said, he had been dreaming of two small boys approaching him and giving him the intensive feeling of being a father in his 'previous life'. He stated that already in Russia, he had been convinced about this virtual fact of his autobiography. As aforementioned (cf. **section V-1.5**), I.J. was very distressed during the interview and repeatedly asked for possible explanations for his disease. Thus, the autobiographical interview had to be interrupted and continued later.

Summarising the individual patients' autobiographical remote memory deficits it can be stated that A.B. was selectively amnesic for autobiographical episodic information related to her entire previous life. Patient C.D. was almost completely amnesic for personal facts and events concerning the time prior to the onset of the amnesia. Patient E.F. was amnesic for all personal facts and events that had happened after about his 20th year of life (most recent 12-14 years). Similarly, patient G.H. was amnesic for 13 years preceding the onset of her amnesia (21st year of life). She could not retrieve the majority of personal facts and events that referred to the time after 1989. Similar to the pattern observed in C.D., patient I.J. exhibited extensive retrograde amnesia for his entire previous life.

Interestingly, all patients showed an islet of memory at least for one fragmentary episode from the amnesic time. However, this did never trigger either the retrieval of complementary context of the memory fragments or the retrieval of any further episode.

3. Neuroimaging experiments

3.1 fMRI experiment

3.1.1 Brain activity contrasting retrieval conditions

Six of the eight investigated contrasts revealed significant increases in neural activity ($p<0.05$, corrected) in at least one of the patients. Though areas of activation were identified at the voxel level (see **section IV-5.5**), additionally, the number of activated voxels in clusters is given for reasons of comparability to the results of the PET experiment (see **section IV-6.4**). Results of all patients participating in the fMRI experiment are summarised in Table 13.

Table 13: Relative increases in brain activity during retrieval attempt of autobiographical and fictitious episodes before and after the onset of the individual patients' amnesia

	Side	x	y	z	P-value (corrected)	Voxels in cluster	Z-score
True Old > True New							
A.B.							
Supramarginal gyrus	L	-64	-46	24	<0.001	*181*	6.34
Inferior parietal	L	-62	-38	30	0.010		5.33
Angular gyrus	L	-50	-64	34	0.001	*63*	5.66
Cerebellum	L	-38	-46	-32	0.001	*94*	5.67
	L	-36	-36	-24	0.033	*157*	5.10
C.D.							
					No significant differential activation		
E.F.							
Inferior frontal gyrus	R	52	36	-4	0.007	*68*	5.41
Gyrus rectus	R	2	36	-20	0.049	*67*	5.01
True New > True Old							
A.B.							
					No significant differential activation		
C.D.							
					No significant differential activation		
E.F.							
Fusiform gyrus	L	-28	-84	-18	0.016	*23*	5.25
True Old > Fictitious Old							
A.B.							
					No significant differential activation		
C.D.							
					No significant differential activation		
E.F.							
					No significant differential activation		
Fictitious Old > True Old							
A.B.							
					No significant differential activation		

	Side	x	y	z	P-value (corrected)	Voxels in cluster	Z-score
C.D.							
					No significant differential activation		
E.F.							
					No significant differential activation		
True New > Fictitious New							
A.B.							
Middle temporal gyrus	L	-54	-50	-2	0.001	*76*	5.68
Parahippocampal gyrus	L	-32	-38	-4	0.018	*55*	5.22
Cerebellum	L	-38	-74	-20	0.026	*230*	5.15
	R	44	-56	-20	0.032	*139*	5.11
Middle temporal gyrus	L	-48	-60	24	0.033	*39*	5.10
C.D.							
Insula	R	40	20	12	0.023	*77*	5.28
E.F.							
					No significant differential activation		
Fictitious New > True New							
A.B.							
Supramarginal gyrus	L	-64	-44	22	0.015	*44*	5.25
Cerebellum	L	-40	-50	-34	0.018	*87*	5.22
	L	0	-74	-30	0.046	*16*	5.03
C.D.							
Medial frontal gyrus	L	-10	34	-14	0.015	*34*	5.33
Inferior frontal gyrus	L	-52	38	-8	0.023	*106*	5.25
E.F.							
					No significant differential activation		
Fictitious Old > Fictitious New							
A.B.							
					No significant differential activation		
C.D.							
					No significant differential activation		
E.F.							
Inferior temporal gyrus	L	-46	-70	-2	0.001	*65*	5.84
Middle temporal gyrus	L	-58	-50	-8	0.011	*89*	5.32
Fictitious New > Fictitious Old							
A.B.							
					No significant differential activation		
C.D.							
					No significant differential activation		
E.F.							
Fusiform gyrus	L	-28	-84	-18	0.016	*23*	5.25

Brain regions showing relative significant BOLD signal increases associated with each comparison of interest. For each region of activation, the coordinates in standard stereotactic space are given, referring to the maximally activated focus within an area of activation as indicated by the highest Z-score. Additionally, the maximally activated focus within a cluster is given. x = distance (mm) to right (R; +) or left (L; -) of the midsaggital plane, y = distance anterior (+) or posterior (-) to vertical plane through the anterior commisure; z = distance above (+) or below (-) the inter-commisural (AC-PC) plane.

Contrasting retrieval attempt of true old episodes with true new episodes (TO>TN) revealed left hemispheric activation of lateral superior temporal/inferior parietal brain regions (supramarginal gyrus, angular gyrus) in patient A.B., whereas patient E.F. showed activation of inferior right and medial prefrontal cortex (see Fig. 12). No significant differential activation was detected in C.D.

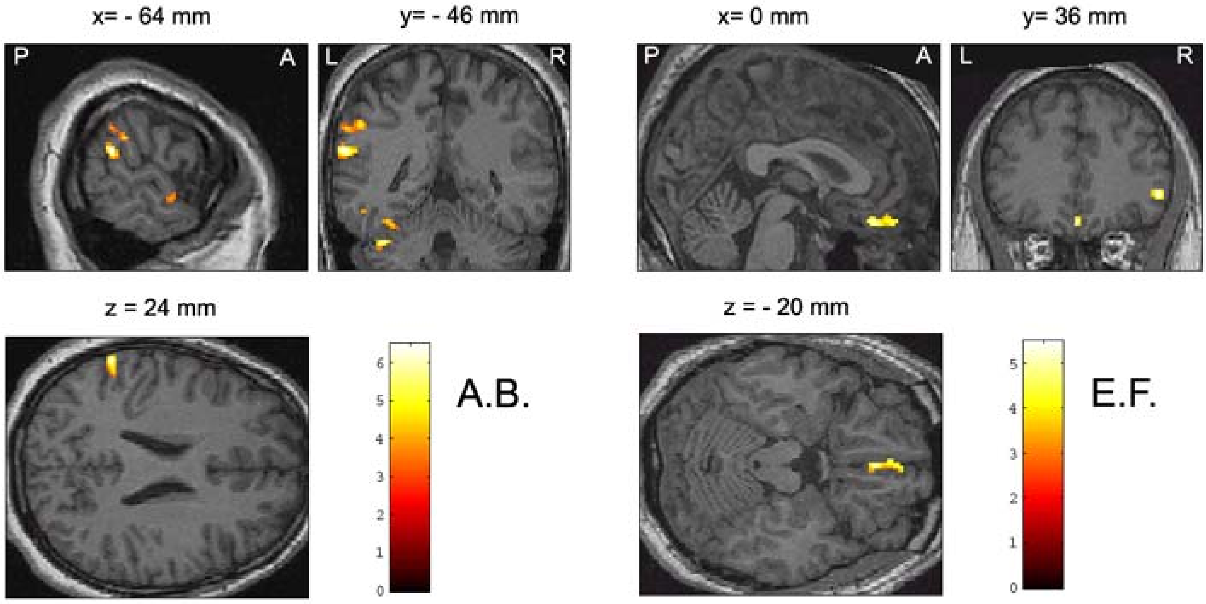

Figure 12: Relative increases in neural activity associated with retrieval attempt of true episodes from the individual amnesic time period compared with true episodes from the non-amnesic time. Statistically significant increases ($p < .05$, corrected for multiple comparisons) are superimposed on individual MRI sections of patients A.B. (left) and E.F. (right). In A.B., increased neural activity was seen in left supramarginal and angular gyrus, inferior parietal cortex, and cerebellum. In E.F. increases were seen in medial and inferior right prefrontal brain regions. The exact coordinates of the local maxima within the areas of activation and their Z-statistics are shown in Table 13. P= posterior; A= anterior; L= left; R= right.

The reverse contrast (TN>TO) revealed left fusiform activation in patient E.F. only as can be seen in Figure 13.

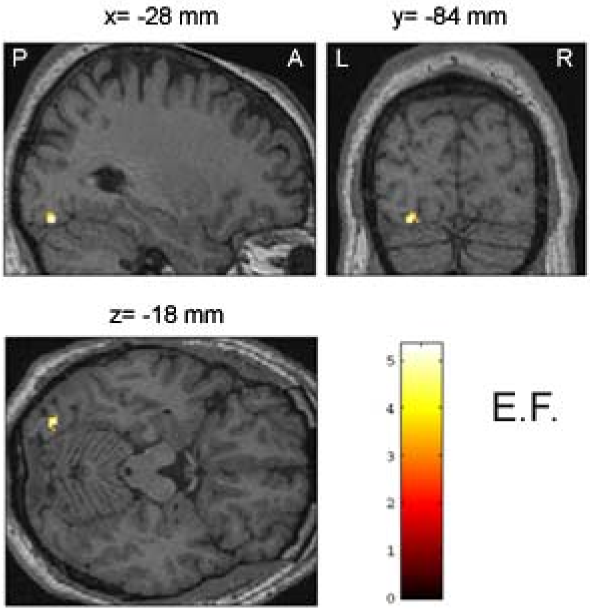

Figure 13: Relative increases in neural activity associated with retrieval attempt of true episodes from the non-amnesic time period compared with true episodes from the amnesic time. Statistically significant increases ($p< .05$, corrected for multiple comparisons) are superimposed on individual MRI sections of patient E.F. Increased neural activity was seen in left fusiforme gyrus. The exact coordinates of the local maximum is indicated by x, z, and z- Talairach coordinates. Z-statistics are shown in Table 13. P= posterior; A= anterior; L= left; R= right.

Significant increases in neural activity associated with retrieval attempt of true versus fictitious episodes before the onset of the amnesia (TO>FO) did not reveal significant differential brain activity in any of the patients. Likewise, the reverse contrast (FO>TO) did not show significant neural activity associated with retrieval attempt of fictitious versus true episodes within the amnesic time.

The analogous contrast concerning the time after the onset of the amnesia (TN>FN) revealed significant activations in patients A.B. and C.D. Patient A.B. exhibited left hemispheric activity in middle temporal, inferior parietal and parahippocampal regions, as well as bilaterally cerebellar. Patient C.D. showed right hemispheric activity in insular cortex. Though not significant, patient E.F. showed differential left anterior cingulate activation (p=.106 corrected) in this contrast (not shown in Table 13). Significant differential activations of patients A.B. and C.D. are given in Figure 14.

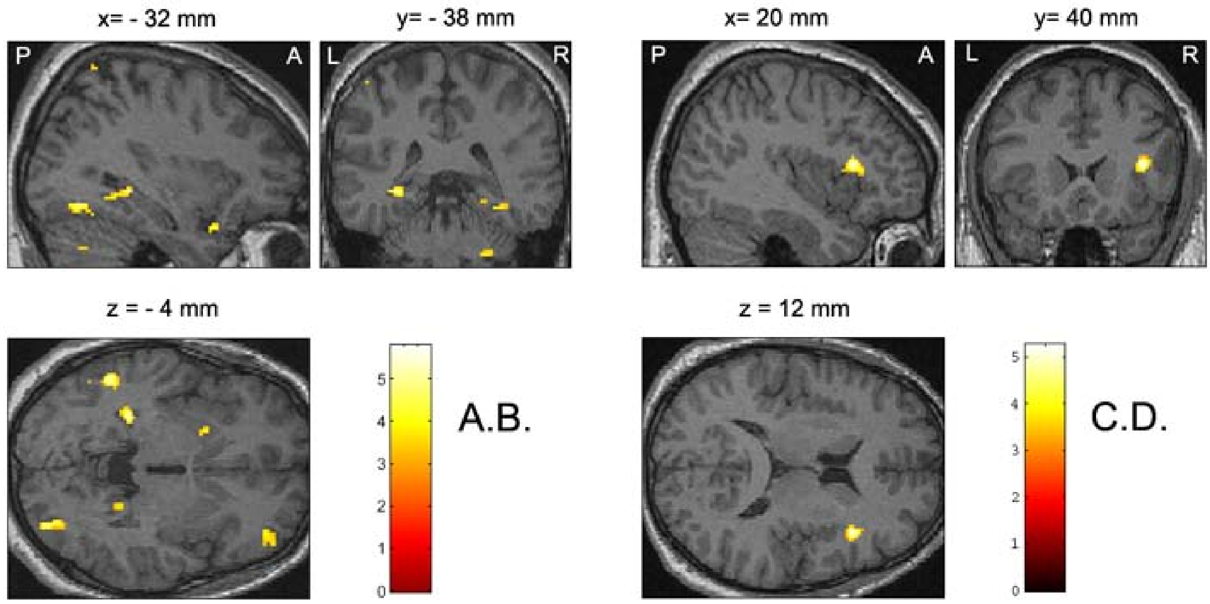

Figure 14: Relative increases in neural activity associated with retrieval attempt of true episodes from non-amnesic time period compared with fictitious episodes from the non-amnesic time. Statistically significant increases (p< .05, corrected for multiple comparisons) are superimposed on individual MRI sections of patients A.B. (left) and C.D. (right). In A.B., increased neural activity was seen in middle temporal gyrus, parahippocampal gyrus, and bilaterally in the cerebellum. In C.D. increases were seen in the right insular cortex. The exact coordinates of the local maxima within areas of activation and Z-statistics are shown in Table 13. P= posterior; A= anterior; L= left; R= right.

The reverse contrast (FN>TN) revealed left lateralised activation in A.B. comprising lateral temporal regions as well inferior and medial frontal activation in C.D. (see Fig. 15) No significant differential activation was found in E.F.

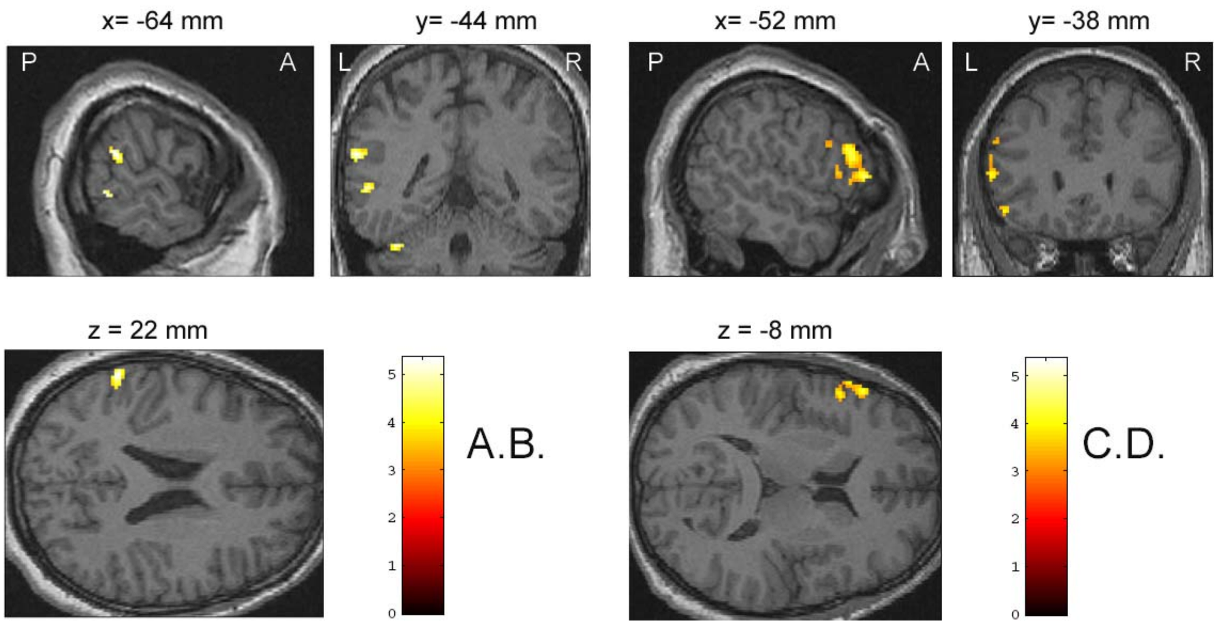

Figure 15: Relative increases in neural activity associated with retrieval attempt of fictitious episodes from the non-amnesic time period compared with true episodes from the non-amnesic time. Statistically significant increases ($p < .05$, corrected for multiple comparisons) are superimposed on individual MRI sections of patients A.B. (left) and C.D. (right). In A.B., increased neural activity was seen in left supramarginal gyrus and cerebellum. In C.D. increases were seen in medial and inferior left frontal gyrus. The exact coordinates of the local maxima within the areas of activation and their Z-statistics are shown in Table 13. P= posterior; A= anterior; L= left; R= right.

Contrasting retrieval attempt of fictitious episodes dated before and after the onset of the amnesia revealed significant activations in patient E.F. As can be seen in Figure 16, left hemispheric middle and inferior temporal gyrus activity was associated with retrieval attempts of fictitious old in contrast to fictitious new episodes (FO>FN).

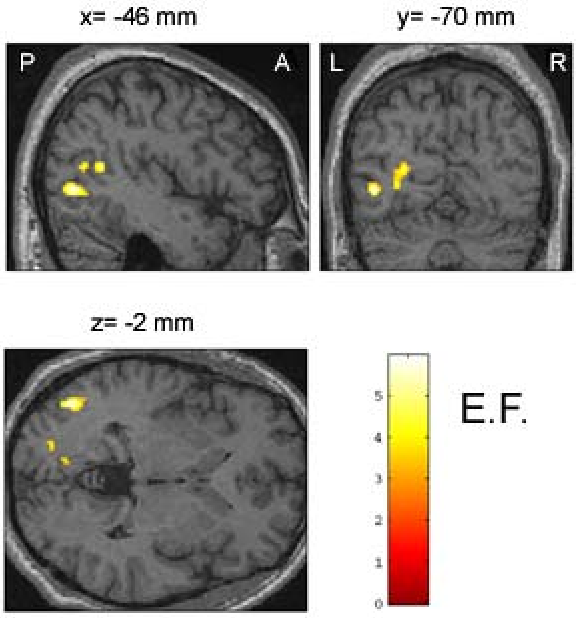

Figure 16: Relative increases in neural activity associated with retrieval attempt of fictitious episodes from the amnesic time period compared with fictitious episodes from the non-amnesic time. Statistically significant increases ($p < .05$, corrected for multiple comparisons) are superimposed on individual MRI sections of patient E.F. Increased neural activity was seen in left inferior and middle temporal gyrus. Exact coordinates of the local maxima within the areas of activation and their Z-statistics are shown in Table 13. P= posterior; A= anterior; L= left; R= right.

The reverse contrast, retrieval attempt of fictitious events from the non-amnesic time compared to fictitious events from the amnesic time (FN>FO) revealed left fusiform activation in patient E.F. (see Fig. 17).

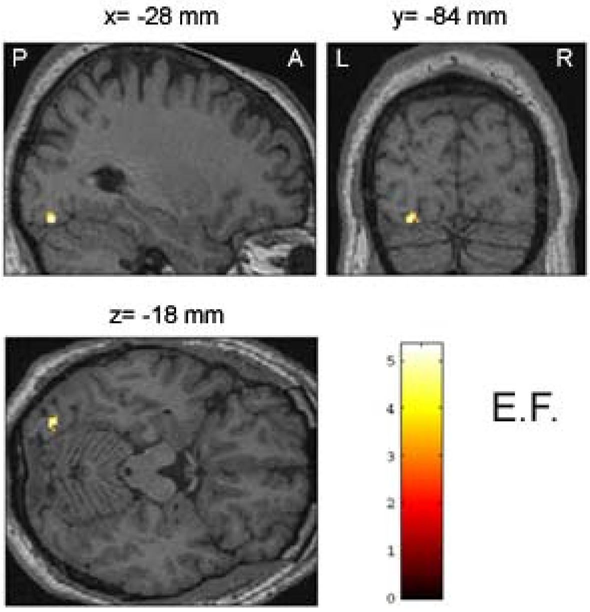

Figure 17: Relative increases in neural activity associated with retrieval attempt of fictitious episodes from the non-amnesic time period compared with fictitious episodes from the amnesic time. Statistically significant increases ($p < .05$, corrected for multiple comparisons) are superimposed on individual MRI sections of patient E.F. Increased neural activity was seen in left fusiforme gyrus. The exact coordinates of the local maximum is indicated by x, z, and z- Talairach coordinates. Z-statistics are shown in Table 13. P= posterior; A= anterior; L= left; R= right.

3.1.2 Alertness task during the fMRI experiment

After exclusion of extreme deviations (three reactions occurred > 7000 ms post stimulus probably reflecting artefacts), means and standard deviations of the reaction times in the subordinate alertness task were analysed across patients (mean= 662.08 ms; SD= 182.66 ms) following. Mean reaction times by patient and memory condition are shown in Figure 18.

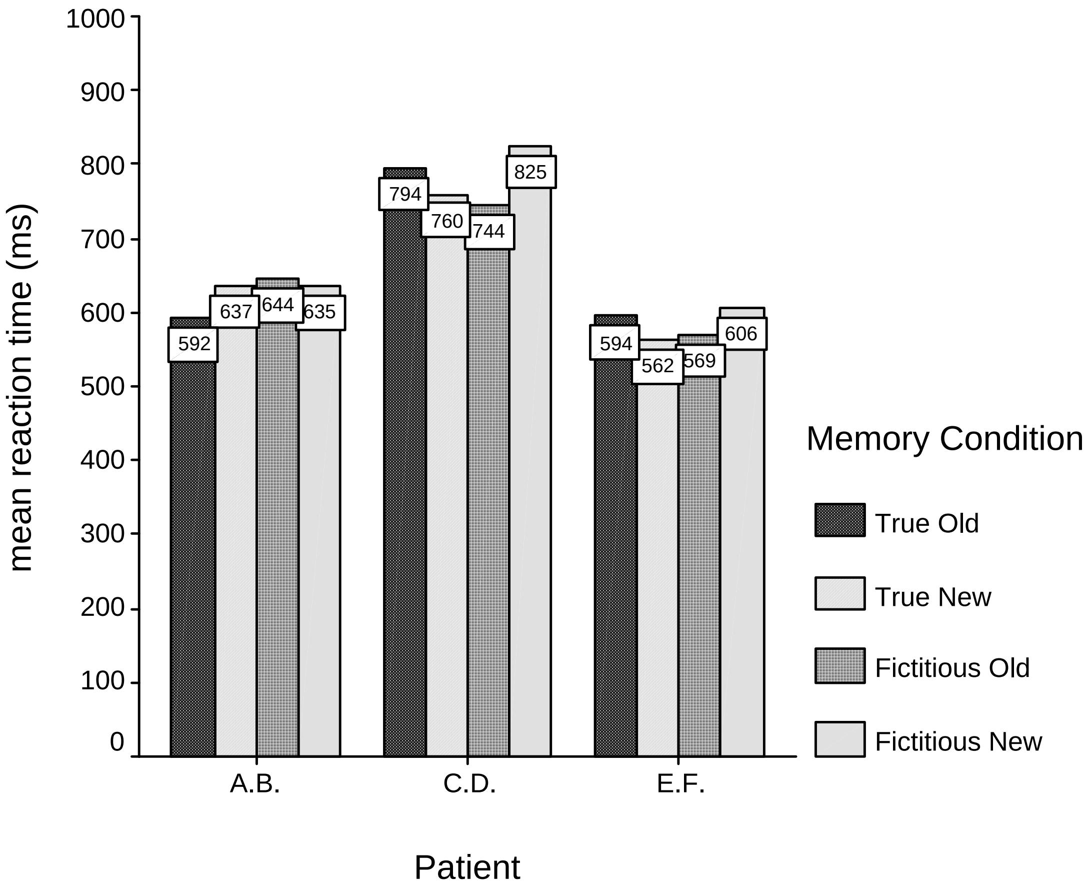

Figure 18: Alertness task: Mean reaction times (milliseconds) in all four memory conditions across patients.

Univariate analysis of variance of the reaction times by patient and memory condition revealed a significant main effect of patient (F= 59.3, df= 2, p< .001). Main effect of memory condition (F= 1.2, df= 3, p= .39) and interaction of patient by memory condition (F= 0.66, df= 6, p= .68) were not significant. The non-significant main effect and interaction indicate comparable levels of alertness across all memory conditions within individual patients. Concerning the different latencies across patients, post-hoc Scheffé procedures revealed longer reaction times in patient C.D. than A.B. (mean difference= 152.9 ms, standard error= 23.5 ms; p< .001) and E.F. (mean difference= 196.5 ms, standard error= 23.4 ms; p< .001), whereas the latter patients' latencies did not differ statistically (mean difference= 43.6 ms, standard error= 23.3 ms; p= .18).

3.1.3 Results in the post-scanning debriefing

In the post-scanning debriefing, patients A.B., C.D. and E.F. recognised approximately half of the sentences describing true episodes that had happened before the onset of their amnesia [TO] as belonging to their autobiography (A.B.: 56%, C.D.: 54%, E.F.: 41%). Sentences depicting events after the onset of the amnesia [TN] were recognised at a higher ratio (A.B.: 74%, C.D.:

77%, E.F.: 84%). The patients erroneously recognised fictitious events as being related to their own past between 1% and 19% ([FO]: A.B.: 1%, C.D.: 9%, E.F.: 19%; [FN]: A.B.: 11%, C.D.: 12%, E.F.: 16%). Combined boxplots of these results are given in Figure 19.

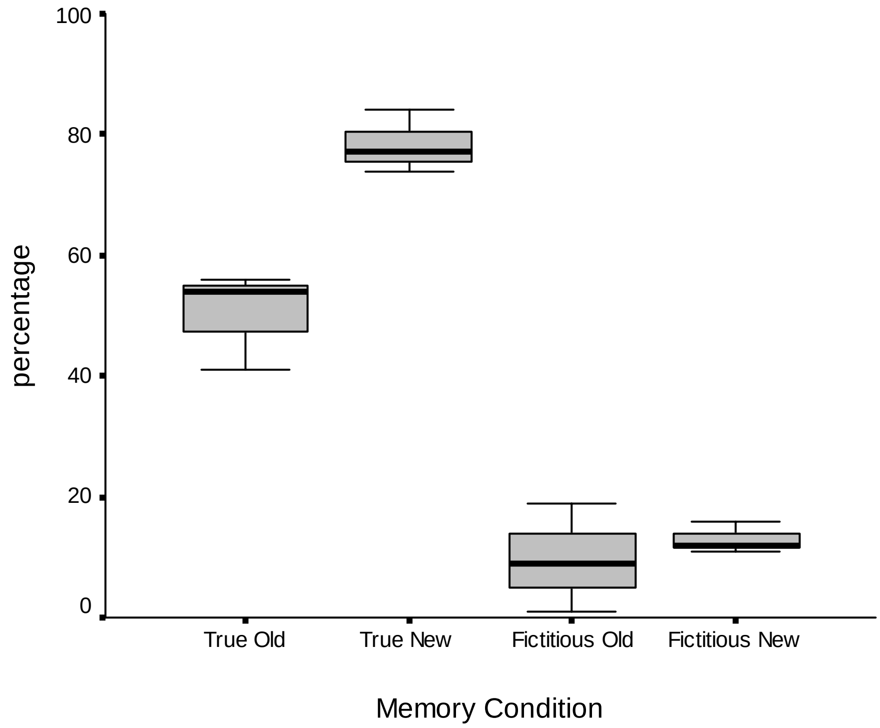

Figure 19: Post-scanning debriefing: Percentage of stimuli per condition judged to be autobiographical events. Scores are given in median and range for the four experimental conditions.

Regarding the quality of their memory, patients' judgements are summarised in Table 14. Patients indicated, (a) whether they had a precise and vivid memory ('remember') when they read a sentence during scanning, (b) whether reading evoked a feeling of knowing ('know'), or (c) whether a sentence did not trigger any memory at all ('no memory').

Table 14: Percentage of 'remember', 'know', and 'no memory' responses of patients A.B., C.D. and E.F. concerning stimuli of all four retrieval conditions

Patient	A.B.	C.D.	E.F.	range	mean
True Old					
remember	38.33	1.67	1.67	36.67	13.89
know	46.67	63.33	58.33	16.67	56.11
no memory	15.00	35.00	40.00	25.00	30.00
True New					
remember	86.67	88.33	98.33	11.67	91.11
know	3.33	1.67	1.67	1.67	2.22
no memory	10.00	10.00	0	10.00	6.67
Fictitious Old					
remember	0	1.67	0	1.67	0.56
know	6.67	6.67	20.00	13.33	11.11
no memory	93.33	91.67	80.00	13.33	88.33
Fictitious New					
remember	10.00	11.67	5.00	6.67	8.89
know	0	0	10.00	10.00	3.33
no memory	90.00	88.33	85.00	5.00	87.78

While on average patients made 'remember' responses to 13.89% of sentences depicting true old events, in the non-amnesic time they were able to vividly re-experience 91.11% of the described episodes. As patient A.B. already had started to recover from her amnesia (cf. **section III-1**), her higher percentage of remember responses (38.33%) within the amnesic time, compared to the other patients (1.67%), may be explainable and accounts for the high range of the results in this time period (range= 36.67%). Regarding the 'know' responses within and outside the amnesic time revealed that 56.11% of the sentences describing true old episodes evoked only a feeling of knowing contrasting 2.22% of the sentences outside the amnesic time. Thus, approximately half of the stimuli describing true old episodes were recognised by the patients on the basis of familiarity. Fictitious episodes evoked 'remember' or 'know' responses in approximately 10% of the sentences. Whereas 'know' responses were more frequent in the amnesic time, stimuli about fictitious events after the onset of the amnesia on average evoked more 'remember' responses which is in correspondence to the memory quality also for true events.

The patients' judgements of the source of their memory for true events by time period are summarised in Figure 20.

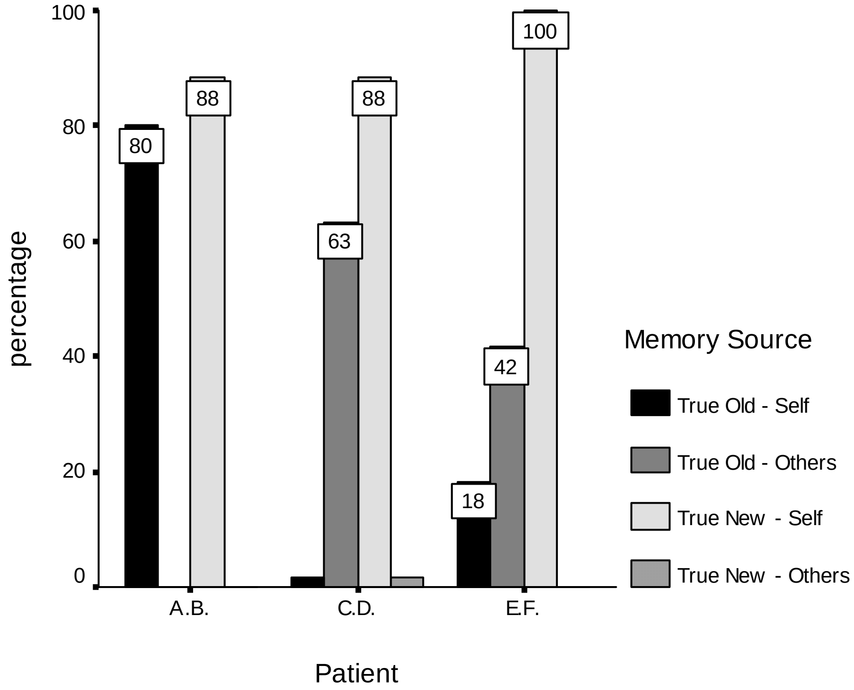

Figure 20: Post-scanning debriefing: Judgements of the source of a memory in the true memory conditions. Patients indicated information within each of the 120 sentences of the true memory conditions as remembered or known by themselves ('self') or as told by someone else ('others').

Patient A.B. judged 80-88% of all true memory sentences as remembered or known by herself without a differentiation across time periods. In contrast, patient C.D. indicated that 63% of events within the amnesic time period had been told by others while in the non-amnesic time, he remembered or knew 88% of the depicted events himself. Similarly, patient E.F. stated that he had been told 42% of the events from the amnesic time period, whereas he remembered or knew all events from the non-amnesic time. E.F. also indicated that he remembered or knew 18% of the true old events on his own.

The patients' responses in the second questionnaire are summarised in Figures 21 and 22. Their judgements represent experience of retrieval characteristics *mental imagery*, *personal relevance, role of language, emotionality, re-experience, and richness of details* when reading episodes from the amnesic time in contrast to the non-amnesic time.

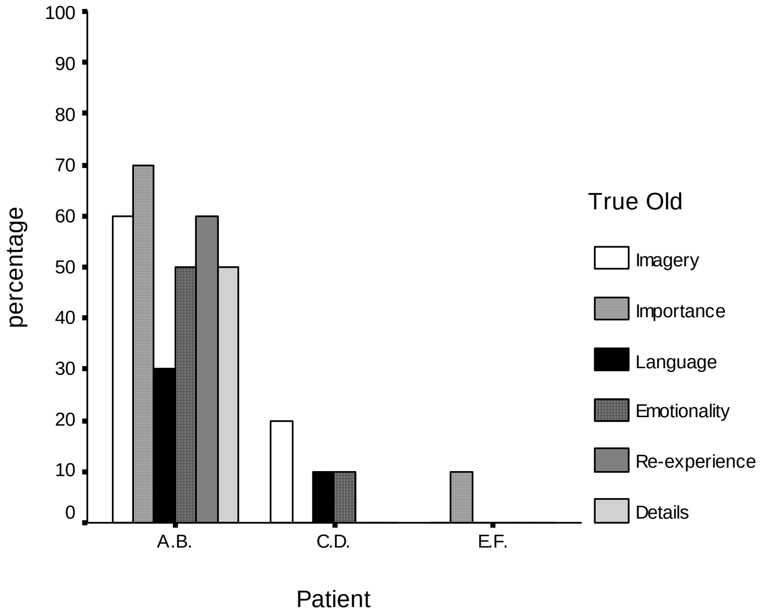

Figure 21: Post-scanning debriefing: 60 sentences about true old episodes judged by the patients regarding their subjective experience of episodic retrieval specific characteristics (imagery, personal importance, language relatedness, emotionality, re-experience in the sense of 'mental time travel', and detailed memories) during scanning. Answers are dichotomised and results are given in percentages.

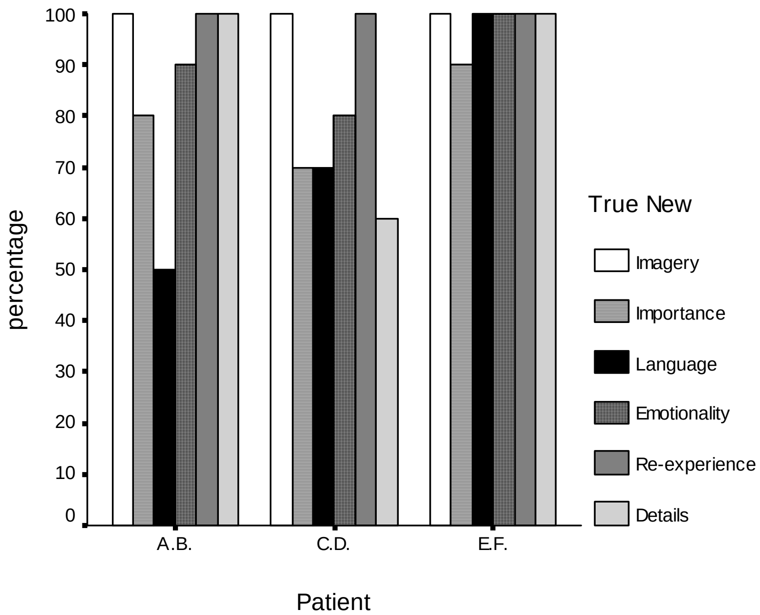

Figure 22: Post-scanning debriefing: 60 sentences about true new episodes judged by the patients regarding their subjective experience of episodic retrieval specific characteristics (imagery, personal importance, language relatedness, emotionality, re-experience in the sense of 'mental time travel', and detailed memories) during scanning. Answers are dichotomised and results are given in percentages.

Comparing the two time periods, patients C.D. and E.F. showed a clear dissociation reporting almost no retrieval specific characteristics when reading episodes from the amnesic time (C.D.: 6.7% indicating 4 points of the maximum of 60; E.F.: 1.7%) whereas for episodes after the onset of the amnesia, these characteristics were reported at a considerably higher ratio (C.D.: 80%; E.F.: 98.3%). Patient A.B. showed a somewhat different pattern with 53.3% of the retrieval characteristics for episodes from the amnesic time and 86.7% for new episodes. Again, her partly recovered amnesia may have contributed to the reported higher percentage of retrieval specific characteristics when confronted with episodes from the amnesic time.

To a considerably lesser degree, episodic retrieval characteristics were also reported for fictitious events. In summary, patients A.B. and E.F. did not report any of these memory characteristics when they read fictitious old events, C.D. reported one instance of imagery in one event from this condition (1.7%). Fictitious events from the non-amnesic time evoked episodic retrieval characteristics to a higher degree, ranging from 10% in E.F., to 8.3% in C.D. and 6.7% in A.B. All patients misjudged one fictitious event from the non-amnesic time as describing a true event.

Of the true events per time period that were judged to have emotional connotations (see Figures 21 and 22), negative and positive events were distributed as seen in Figure 23.

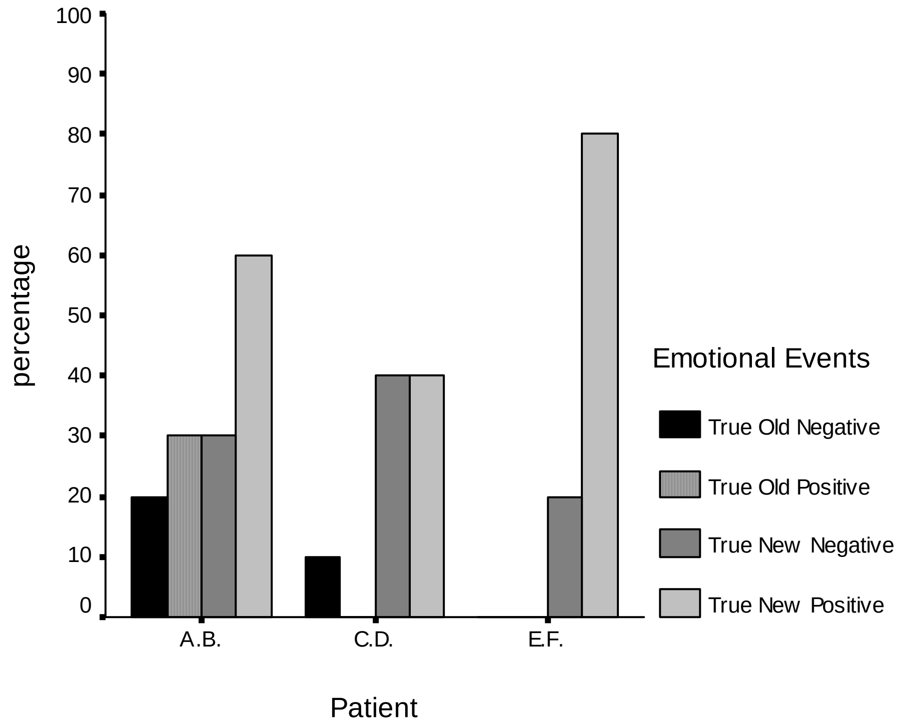

Figure 23: Post-scanning debriefing: Sentences that were judged to have triggered emotional memories were further evaluated with regard to their emotional valence as positive or negative. The total number of these sentences varied across patients (cf. Fig. 21 & Fig. 22).

Concerning episodes within the amnesic time, patient A.B. reported that 20% were negative events and 30% were positive. Patient C.D. reported 10% of the old episodes as negative. Within the non-amnesic time, the judgements were considerably higher. Patient A.B. reported 30% negative and 60% positive episodes, patient C.D. stated 40% as negative and 40% as positive, and patient E.F. indicated 20% as negative and 80% as positive events. Concerning fictitious events, the comparable numbers were negligible; none of the patients reported emotional significance in fictitious old events, and of the fictitious new events, patients A.B. and E.F. each reported 10% as negative.

3.2 $H_2^{15}O$- PET experiment

3.2.1 Brain activity contrasting retrieval conditions

Contrasting activity in the experimental conditions revealed significant differential activity ($p<0.05$, uncorrected for multiple comparisons) in the two patients participating the PET experiment. Results are given in Table 15.

Table 15: Relative increases in brain activity during retrieval (attempt) of autobiographical episodes before and after the onset of the individual patients' amnesia

	Side	x	y	z	Voxels in cluster	P-value (uncorrected)	Z-score
Old Episodes > New Episodes							
G.H.							
No significant differential activation							
I.J.							
Superior parietal	L	-30	-68	62	*39*	0.023	4.16
	L	-26	-64	54			3.62
Superior frontal gyrus	R	28	42	26	*34*	0.032	3.75
New Episodes > Old Episodes							
G.H.							
Cerebellum	R	48	-66	-36	*43*	0.024	4.47
Precuneus	L	-16	-62	26	*33*	0.044	3.71
Temporal pole	R	42	10	-36	*32*	0.047	3.49
I.J.							
Cerebellum	L	-42	-82	-40	*37*	0.026	5.12
Inferior parietal	L	-48	-64	50			4.59
Superior parietal	L	-42	-60	58	*68*	0.004	3.50

	Side	x	y	z	Voxels in cluster	P-value (uncorrected)	Z-score
Superior temporal gyrus	L	-44	22	-20			4.05
Inferior frontal gyrus	L	-38	34	-20	*71*	0.004	3.44
Gyrus rectus	L	-44	40	-12			3.23
Posterior cingulate gyrus	L	-2	-44	22	*41*	0.020	4.01

Brain regions showing relative significant regioinal cerebral blood flow increases associated with each comparison of interest. Areas of activation are given in cluster size. For each region of activation, the coordinates in standard stereotactic space are given, referring to the maximally activated focus within a cluster as indicated by the highest Z-score. x = distance (mm) to right (R; +) or left (L; -) of the midsaggital plane, y = distance anterior (+) or posterior (-) to vertical plane through the anterior commisure; z = distance above (+) or below (-) the inter-commisural (AC-PC) plane.

Comparing experimental conditions with each other revealed enhanced activity in retrieval attempt of old versus new episodes only in patient I.J. He showed increased perfusion in the left superior parietal lobe and right anterior superior frontal gyrus as can be seen in Figure 24.

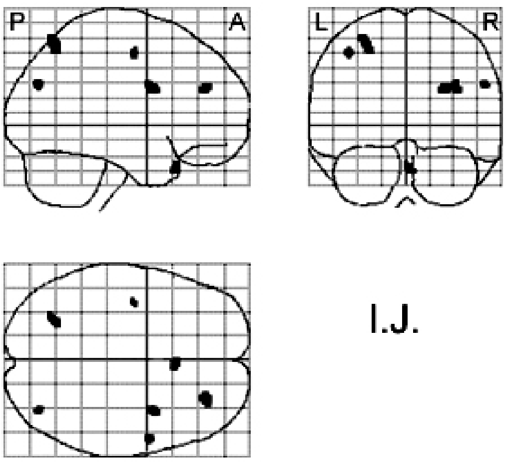

Figure 24: Orthogonal projections of brain regions showing increased activity (p< .05, uncorrected for multiple comparisons) for the Old-New comparison. In Patient I.J. only, significant activations were seen the left superior parietal lobe and right anterior superior frontal gyrus. The exact coordinates of the local maxima within the areas of activation and their Z-statistics are shown in Table 15. P= posterior; A= anterior; L= left; R= right.

As can be seen in Figure 25, the reverse contrast resulted in right cerebellar, left medial occipito-parieto-temporal activation as well as right anterior inferior temporal activity in patient G.H. In I.J., a left lateralised activation pattern was revealed comprising cerebellum, superior and inferior parietal lobe, temporo-frontal junction area as well as left/medial posterior cingulate gyrus.

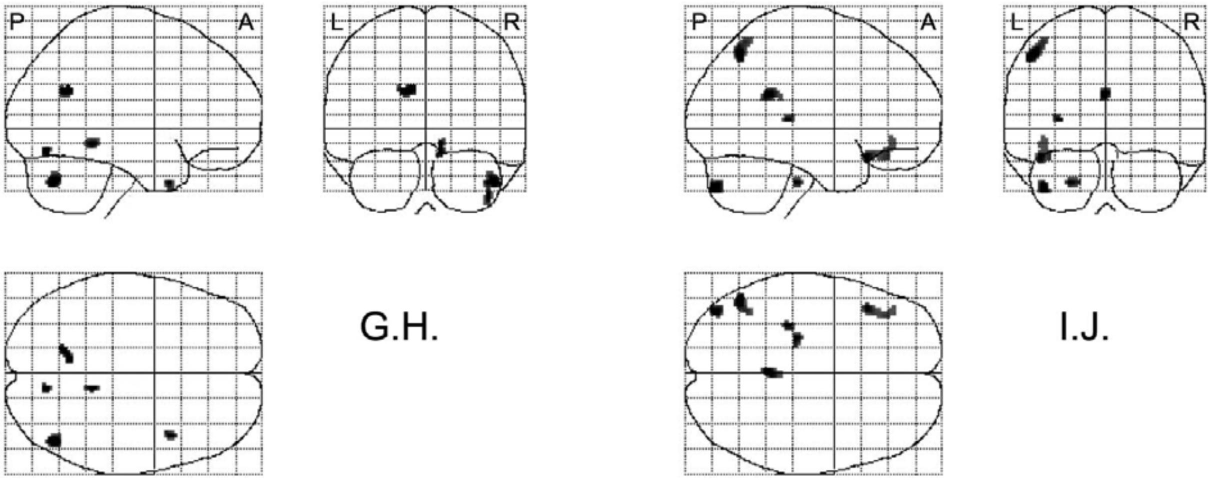

Figure 25: Orthogonal projections of brain regions showing increased activity ($p < .05$, uncorrected for multiple comparisons) for the new-old comparison. For patient G.H. (left), significant activations were observed in right temporal pole and cerebellum and in left precuneus. For patient I.J. (right), activations were seen in the left temporo-frontal junction area, in superior and inferior parietal cortex, in posterior cingulate gyrus, and in the cerebellum. The exact coordinates of the local maxima within the areas of activation and their Z-statistics are shown in Table 15. P= posterior; A= anterior; L= left; R= right.

3.2.2 Results in the post-scanning debriefing

As aforementioned, post-scanning debriefing had to be omitted in patient G.H. Therefore, I.J.'s results are reported only. He judged 15 of the 32 individual sentences to have evoked a precise memory ('remember'), 2 sentences triggered a feeling of knowing ('know'), and 15 sentences were not related to any memory for him. As can be seen in Figure 26, these responses were clearly differentiable between episodes that had happened before onset of the amnesia and those that had happened thereafter.

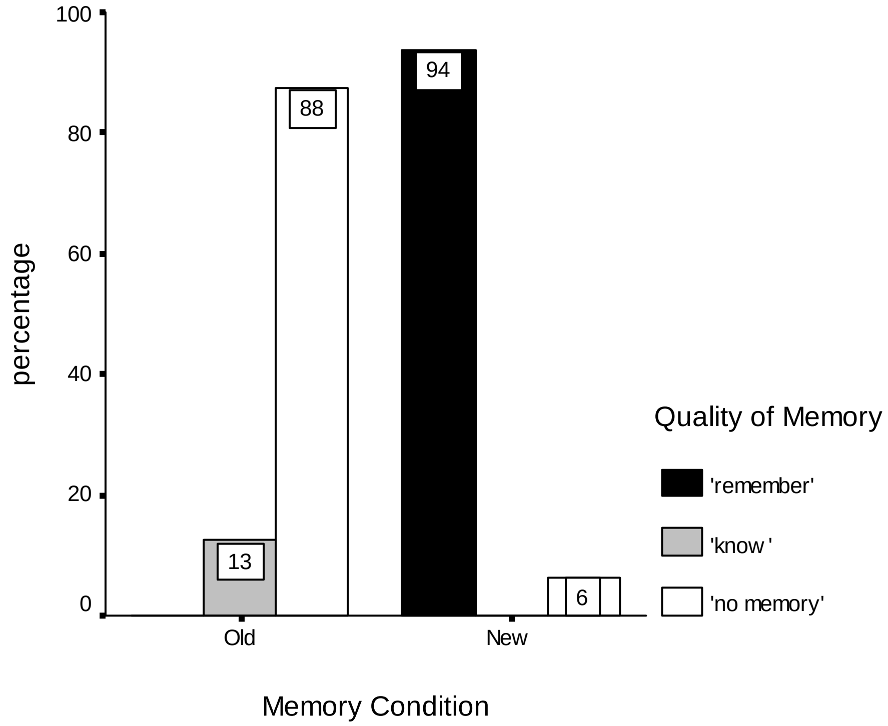

Figure 26: Post-scanning debriefing: 16 sentences about pre-onset (old) and 16 sentences about post-onset (new) episodes were judged by patient I.J. He indicated his subjective experience of remembering ('remember'), feelings of knowing ('know'), or not remembering or knowing ('no memory') while reading each sentence during scanning. Scores are dichotomised and given in percentage.

While I.J. precisely remembered almost all episodes from the non-amnesic time, he judged 14 of the 16 sentences describing episodes from the amnesic time to have not triggered any memories in him, and 2 sentences evoked a feeling of knowing only.

Patient I.J.'s responses in the second questionnaire are summarised in Figure 27. His judgements represent experience of retrieval characteristics *mental imagery*, *personal relevance, role of language, emotionality, re-experience, and richness of details* when reading episodes from the non-amnesic time only. He did not report a single episodic retrieval characteristic evoked by reading of sentences about episodes from the amnesic time.

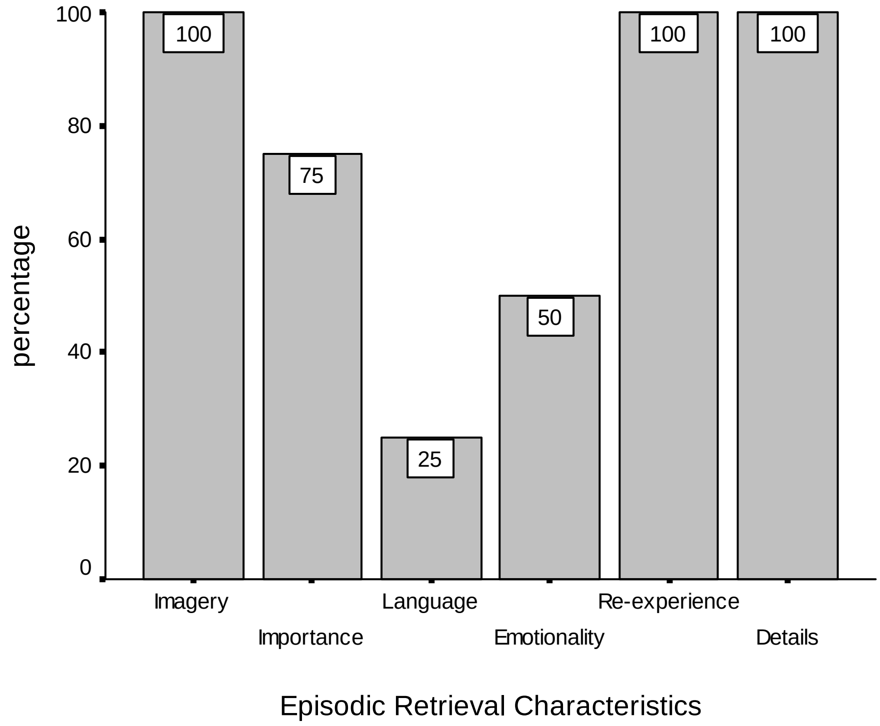

Figure 27: Post-scanning debriefing: Patient I.J.'s judgements of the four episodes from the non-amnesic time evoking episodic retrieval characteristics during the scanning session. Scores are given in percentage.

I.J. reported 18 of the maximum of 24 episodic memory retrieval characteristics when he read the four episodes from the non-amnesic time (see Fig. 27). In detail, I.J. reported that all four episodes evoked mental imagery, re-experience of the event and a detailed memory. Three episodes were personally important for him, two episodes were emotional and in one episode he remembered conversation and language related information of the past event.

VI. Discussion

In the absence of detectable structural brain damage, the investigated patients suffered from extensive retrograde amnesia covering either their entire life or the most recent 12-14 years. The retrograde amnesia encompassed autobiographical episodic information in all patients, and parts of semantic remote memory in all but patient A.B. Additional neuropsychological deficits accompanied the patients' amnesia**.** Though in all but patient I.J., the deficit arose from an organic condition, psychological factors are likely to account at least in part for the onset and maintenance of the retrograde amnesia. Regarding true memory conditions across all patients, retrieval of episodes from the amnesic time period revealed enhanced activation in right prefrontal brain regions in patients E.F. and I.J. and a left lateralised activation pattern of lateral superior temporal/inferior parietal brain regions in patient A.B. The reverse contrast, processing of new in contrast to old episodes, revealed differential activation in posterior association cortex in three patients (E.F., G.H., I.J.). Furthermore, in contrasting processing of true and fictitious episodes within both time periods, BOLD responses did not differ between attempts to retrieve true compared to fictitious episodes in the amnesic time period in the three patients investigated with fMRI. Concerning the non-amnesic time, however, significant differential activations associated with true relative to fictitious episodes were seen in A.B. and C.D., as well as a non-significant trend in the same direction in patient E.F.

To start the following discussion, the questions and assumptions underlying this study are addressed by an interpretation of the patients' personal history, behaviour, neuropsychological test results and psychological screening. Aetiologically relevant factors favouring organic, psychogenic or malingering-related interpretation are highlighted. Next, results of the neuroimaging experiments are discussed by synthesising the contrasts of the different memory conditions. Finally, individual patients are classified along their organic, psychogenic, or possible malingering-related characteristics.

1. Aetiologically relevant factors: Case histories, behaviour and test results

It is of particular interest in disproportionate forms of retrograde amnesia to clarify aetiologically relevant psychological and organic factors, since this knowledge may guide probable therapeutic interventions. However, clearly differentiating psychogenic and organic causes of retrograde amnesia was difficult in most of the cases in this study as well as in previously reported retrograde amnesia patients (e.g. Barbarotto et al., 1996; Mackenzie Ross, 2000). In fact, the clinical picture is even more complicated by the possibility of malingering. In the following sections, factors in favour of an organic causation are contrasted with those in favour of a psychogenic causation. Finally, the issue of malingering is discussed.

1.1 Factors in favour of an organic causation

None of the patients exhibited detectable structural brain damage. Even in those patients who were unable to undergo high resolution magnetic resonance imaging (G.H., I.J.), it is unlikely that they actually had structural brain pathology, since previously conducted CT scans and EEG measurements were normal. However, several characteristics pointing to organic factors were detectable in the majority of the patients. According to Lezak (1995) an organic aetiology of cognitive deficits is likely if:

1. Symptoms occur during or after an illness, intoxication, head trauma, etc.
2. Patients show neurological symptoms accompanying their cognitive deficits
3. Symptoms are medically reasonable and resemble those of other organic cases
4. The pattern of neuropsychological deficits includes lateralised abilities
5. Recent memory is more severely affected than remote memory
6. Functional recovery is partial rather than complete
7. Patients do not have a significant psychiatric background
8. There is no immediately preceding stressful life event
9. There is no evidence of secondary gain from the symptoms

The observed Theory of Mind disturbances cannot be unequivocally assigned to either organic or psychological factors. Since Theory of Mind abilities and autobiographical memory retrieval may share certain physiological components, they are added in this section (cf **section VI-1.1.10**). It should, however, be kept in mind that Theory of Mind disturbances cannot exclusively be interpreted as either an organic or a psychological phenomenon.

In the following, the aforementioned points are addressed and, if possible, specific characteristics indicating organic causation in retrograde amnesia are included as supplements.

1.1.1 Symptoms occur during or after an illness, intoxication, head trauma, etc.

In most of the patients, the onset of the amnesia was initiated by an organic condition (mild head injury, general anaesthesia) resulting in temporary unconsciousness. The probable exception may be case I.J. (see below). As outlined in the Theoretical Background, mild head injury is one of the most common precursors of functional retrograde amnesia. It can be argued that this physical harm may have caused minimal cerebral damage associated with barely detectable functional/metabolic disturbances in memory-relevant brain structures (e.g. De Renzi, 2002; De Renzi et al., 1997). The slight cortical and marked cerebellar hypometabolism observed by FDG-PET in patient E.F. could be such a metabolic disturbance in memory relevant brain structures. The cerebellum contributes to motor-related tasks (e.g. precise timing of movements, Liu, Gao, Liotti, Pu, & Fox, 1999) and many different kinds of cognitive processes (cf. Bower & Parsons, 2003), including memory (cf. Cabeza & Nyberg, 2000). Accordingly, it was involved also in autobiographical memory retrieval (Andreasen et al., 1999). However, since it is implicated in many different functions, its metabolic disturbance in patient E.F. may not be sufficient to explain his disproportionate remote memory deficit. In fact, his overall neuropsychological profile was rather superior, both, compared to norm group data as well as compared to the other patients (see Tab. 9). Therefore, his cerebellar hypometabolism may not entirely be seen as evidence for organic, focal retrograde amnesia[12].

A further characteristic related to the onset of amnesia refers to the fact that all patients exhibited initial confusion and instant amnesia after awakening, asking for explanations and seeking help. Kopelman (2002b) interpreted this kind of behaviour as typical for patients with TGA, a condition usually seen as organically caused memory loss.

1.1.2 Patients show neurological symptoms accompanying their cognitive deficits

Accompanying somatic complaints were observed in some of the patients, some of which were or resembled neurological symptoms. Patients A.B., E.F. and I.J. reported headache, A.B. and G.H. experienced gastrointestinal pain, and patient A.B. had several paroxysmal states following the onset of amnesia though these remained medically unresolved (continuous EEG recording was normal). In previous cases of organic retrograde amnesia, the deficit was eventually accompanied by neurological symptoms such as scotomas (Brown & Chobor, 1995), visual acuity loss (Carlesimo et al., 1998), complex partial and generalised epileptic seizures (Fujii et al., 1999; Hokkanen et al., 1995), hemiparesis (e.g. Goldberg et al., 1981), or hemiplegia (Hunkin et al., 1995). Severity and nature of the somatic complaints of the patients in the current study, however, do not resemble those clearly organic signs. Therefore, none of their somatic symptoms can be interpreted as reflecting a common underlying brain disturbance with the remote memory deficit.

[12] His entire cortical glucose metabolism was also slightly lowered. Since this reduction was not statistically significant from healthy subjects, it was not further discussed.

1.1.3 Symptoms are medically reasonable and resemble those of other organic cases

Given the pattern of brain damage observed in organic retrograde amnesia patients, commonly comprising extensive and bilateral region of frontal, parietal and temporal lobes (cf. **section I-2.2** and Kapur, 1999), the lack of underlying structural brain pathology the patients of the current study can be considered evidence against an organic hypothesis[13]. However, several characteristics of their amnesic symptoms resemble those of previous organic cases. For instance, the fact that all patients changed their food preferences after amnesia onset points to involvement of the limbic-cortical circuitry. In this regard, changes in food preferences can be induced in animals by lesions to the basal forebrain (Berger-Sweeney, Stearns, Frick, Beard, & Baxter, 2000), amygdala (Gilbert, Campbell, & Kesner, 2003), hippocampus (Tracy, Jarrard, & Davidson, 2001), thalamus (Reilly & Pritchard, 1996), and hypothalamus (Ganaraja & Jeganathan, 2000). These findings may not be entirely comparable to changes in food preferences in human amnesic patients, though psychogenic amnesia patient N.N. (Markowitsch, Fink, et al., 1997) was reported to have gained 15 kg in bodyweight after onset of his amnesia. At the same time N.N. stated he was never hungry and disliked most foods. One may speculate that due to emotional-motivational factors, proper functioning of the limbic-cortical neurotransmission may be affected also in the patients investigated here. It cannot be determined whether the observed changes in likes and dislikes stem mostly from the memory deficit or from motivational factors either induced by dysfunctions in limbic-cortical signalling or vice versa, potential molecular/hormonal changes result from changes in everyday emotional-motivational behaviour. Characteristics of the behavioural change itself point to both causal directions (e.g. it was reported that patient E.F. forgot his aversion for some food, patient C.D. started to try new and unusual dishes, A.B. gradually recovered from her vegetarianism during recovery from her amnesia).

In favour of an organic causation, the duration of the amnesia can be considered. In all patients, remote memory loss exceeded time intervals of weeks or months which is uncommon in psychogenic retrograde amnesia (Markowitsch et al., 1998; Markowitsch, Kessler et al., 2000; Stracciari et al., 1994; Yasuno et al., 2000) and only patient A.B. has so far recovered from the amnesia. However, note that there are exceptions of patients with prolonged retrograde amnesia of psychogenic origin (e.g. Campodonico & Rediess, 1996). Furthermore, in all but patient A.B., the amnesia comprised episodic as well as parts of semantic remote memory which is more frequently – though not exclusively (e.g. Barbarotto et al., 1996; Kopelman et al., 1994) – observed in organic retrograde amnesia (e.g. Carlesimo et al., 1998; Fujii et al., 1999; Tanaka et al., 1999). Patient C.D.'s neuropsychological profile showed global mild cognitive disturbances which

[13] Functional brain disturbance was obvious in patient E.F., whose resting state brain glucose metabolism showed aberrances (see **sections III-4** and **VI-1.1.1**).

is rarely seen in psychogenic retrograde amnesia. Concerning the diversity (not the severity) of accompanying deficits, his performance is comparable to that of case J.J. reported by Mackenzie Ross (2000). This patient's symptoms were supposed to be caused by a close interaction of both, organic and psychogenic factors, while it was impossible to exactly specify the extent to which psychogenic and organic factors contributed to her retrograde amnesia. Comparably, patient 'Andrea' studied by De Renzi et al. (1997) showed a broader cognitive impairment, e.g., also comprising verbal fluency and motor actions. Here however, the retrograde amnesia was proposed not to correspond with a psychiatric/psychological background (but see Mackenzie Ross, 2000). Further frontal lobe associated dysfunctions were observed in most of the patients. As these can also be seen in light of a psychogenic causation, they will be discussed below.

1.1.4 The pattern of neuropsychological deficits includes lateralised abilities

Neuropsychological signs for lateralised (dys-)functions can point to differential organic involvement of the cerebral hemispheres (Lezak, 1995). These kinds of dissociations between verbal and visual intellectual and memory functions were observed in some of the patients. As such, patients A.B., C.D., and E.F. showed better verbal than visual memory in the WMS-R, whereas G.H. and I.J. showed a preference of visual over verbal memory tests. Patient A.B.'s preference of verbal materials was inconsistent with other test results. For instance, she achieved a high average score in delayed recall of the Rey Osterrieth CFT and her nonverbal IQ in the WAIS-R (performance IQ) was even higher than her verbal IQ. Though the identical analysis could not be carried out with patient E.F. since some of the tests were not administered to him (see Table 5), below average verbal learning abilities were observed in the CVLT. This generally casts doubt on a consistent preponderance of verbal memory capacities in patient E.F. In patient C.D., the preference of verbal over visual materials in the WMS-R was not clearly paralleled by other memory tests since he showed impaired acquisition of words in the CVLT and average, though low average, performance in the delayed recall of the Rex Osterrieth CFT. Moreover, his IQ profile in the WAIS-R indicated better nonverbal performance than verbal abilities. In the WMS-R, patient G.H.'s visual memory was considerably better than verbal memory. Similarly, she exhibited above average performance in delayed recall of the Rey Osterrieth CFT and only average to low average verbal learning in the CVLT. However, the pattern was not paralleled by verbal and nonverbal IQ test results in the WAIS-R in which she showed above average verbal but only average nonverbal results. Taken together, as can be said from the applied tests, there was no consistent evidence for clearly lateralised functions in the investigated patients. At most, there was a tendency to achieve better results in verbal compared to visual short-term and working memory in all but patient E.F., who exhibited the opposite pattern (see Table 9). The current patients can therefore only be seen as partly comparable to previous organic cases of focal retrograde amnesia most of them showing more impairment of visual than verbal functions (e.g. Hunkin et al., 1995; O'Connor et al., 1992)

1.1.5 Recent memory is more severely affected than remote memory

Similar to organic retrograde amnesia patients, E.F. and G.H. showed a temporally graded retrograde amnesia with severely impaired recent memories and spared childhood memories. This temporally graded memory loss did not only comprise autobiographical but also semantic remote memory, which was strikingly clear in patient E.F. (cf. Famous Faces Test). These kinds of temporal gradients are usually seen in organic forms of amnesia (cf. comparison between TGA patients and functional retrograde amnesia patients in Kritchevsky et al., 1997). However, in all other patients, the retrograde memory loss was not temporally graded and remote memory was similarly affected as were more recent memories.

1.1.6 Functional recovery is partial rather than complete

As can be inferred from the case histories concerning initial stages of the remote memory loss, there may have been a partial recovery of memory functions in most patients. It is reported that patient A.B. was initially confused about her personal semantics which quickly recovered but did not include recovery from episodic memory loss. Similarly, loss of knowledge for common devices and actions, which can be interpreted as procedural memory (cf. De Renzi et al., 1997), is reported of patients C.D. and E.F. In the beginning they were unable to perform everyday routines (shaving, riding on a tram etc.), but later on regained this knowledge. Nevertheless, it was impossible to clarify by the time of testing, whether and to what extend such information was regained by intentional learning or spontaneous recovery. It is reported that E.F. was initially amnesic for his entire life but after a few days spontaneously retrieved memories of his childhood and early adulthood. Patients E.F. and G.H. reported spontaneous retrieval of memory fragments or isolated episodes, a fact that resembles I.J.'s autobiographical dream (see **section V-1.5**). The latter instances can be interpreted as partial rather than complete recovery. Given the general course of the amnesia, however, in all but patient A.B. the amnesic symptoms mostly remained unchanged in terms of vivid retrieval of most autobiographical episodic information and in A.B., the recovery was complete rather than partial. To conclude, though partial recovery is likely in the majority of the patients, it cannot be determined whether re-learning accounts for most of the regained information. At least in patient A.B. a complete rather than partial recovery can be concluded.

1.1.7 Patients do not have a significant psychiatric background

No significant psychiatric background was documented in patients E.F. and I.J. In contrast, patient A.B. suffered from Major Depression and patients C.D. and G.H. had previously reported psychiatric symptoms potentially related to the current condition (cf. **section III-1**). It should be mentioned at this point that – comparable to the risk of undetected or undetectable functional metabolic disturbances in memory relevant brain regions (cf. De Renzi, 2002) – a probable psychiatric background can likewise be overlooked (Kopelman, 2000). Though in patient A.B. the diagnosis of depression was apparent, neither in patient C.D. nor in G.H., detection of previous psychiatric symptoms was straightforward. Search of extensive medical records of patient C.D. uncovered his previous conversion-like symptoms which were negated by himself as well as by his wife. Likewise, conversations with G.H.'s husband had to be continued over several days unless previous instances of conversion paralysis and altered states of consciousness were reported. Therefore, the risk of underdiagnosed psychiatric precursors has to be born in mind in all patients with functional retrograde amnesia as well as in the cases here.

1.1.8 There is no immediately preceding stressful life event

There was no clear evidence of stress that immediately preceded the onset of amnesia in patient E.F. and potential signs of previous stress were weak in patient I.J. (cf. **section III-5**). The definition of preceding stress is particularly difficult given the fact that a) the patients were only seen after the onset of their amnesia and b) the trigger of the amnesia may itself be a stressful life event. On this note, reconstruction of immediately preceding life events is dependent on information given by patients' relatives, who, however, may also have been part of the stress and probably underestimate the personal relevance of such events for the patients. Because of this, it was impossible to identify potential immediately preceding stressors in most patients (but see **section VI-1.2.1**). Experience of head trauma, whether it results in structural brain damage or not, can be understood as a major stressful life event. This issue will be discussed in **section VI-1.2.1**.

1.1.9 There is no evidence of secondary gain from the symptoms

Judgement of existence or non-existence of secondary gain is intricate, prone to biases by the experimenter and therefore should be made cautiously (cf. Lucchelli & Spinnler, 2002). Nevertheless, no evidence of secondary gain was observable in patient E.F., and also G.H. and I.J. repeatedly stated their desire to recover from their amnesia. However – to a greater or lesser extent – benefit from amnesic symptoms was at least possible in almost all patients. Reasons for this assumption are given in **section VI-1.2.3**.

1.1.10 Theory of Mind

Strikingly impaired Theory of Mind (ToM) abilities were observed in three of the four patients (C.D., E.F., G.H.) in whom the ToM test was applied. In a recent study by Corcoran and Frith (2003), schizophrenic patients were investigated with the Autobiographical Memory Interview (Kopelman, 1990) and two ToM tests. Compared to controls, both domains were impaired in schizophrenics and furthermore, a high correlation was found between autobiographical event recollection and the ToM hinting task. According to Abu-Akel (2003), the representation of one's own and others' mental states can be ascribed to separate brain regions in either the right parietal operculum or the superior temporal lobes, respectively. Moreover, brain regions commonly involved in representation of self and others' mental states may be the ventral medial prefrontal/orbitofrontal brain regions as well as anterior cingulate gyrus and amygdala. He argues that Theory of Mind abilities are accomplished by intact neural transmission between posterior parieto-temporal brain regions and prefrontal cortex mediated by limbic/paralimbic brain structures. Since in schizophrenia dysfunctions in temporo-limbic-prefrontal transmission can be seen (cf. Heinz, Romero, Gallinat, Juckel, & Weinberger, 2003), it is possible that the Theory of Mind deficits observed by Corcoran and Frith (2003) are due to these dysfunctions. The Reading the Mind in the Eyes Test, which was applied in the current study, resembles the ToM hinting task employed by Corcoran and Frith (2003). In both tests, ambiguous or fragmented information is given from which subjects have to infer social meaning such as mental states or intentions of others. The tasks require executive control (e.g. search strategies, monitoring) which is also involved in autobiographical episodic retrieval, as well as re-experience of former situations, feelings, or social interactions. Both functions might be impaired in patients with retrograde amnesia. The relationship between impairment in ToM abilities and autobiographical episodic retrieval deficits as observed in Corcoran and Frith (2003) can therefore reflect a general inability of patients with autobiographical retrieval disturbances to resort to contextual knowledge such as one's own previous feelings, intentions and thoughts. This may be necessary for the retrieval of specific social information, be it autobiographical (personal events) or not (ToM tests). In this regard, it may be of interest that patients C.D., E.F. and G.H. were reported to have considerable difficulties in inferring mental states of others also in their everyday life. For example, G.H. herself explained new strategies how she tried to understand contingencies between facial expressions and feelings of others; she reported that she had to fragment single aspects of an expression such as the form of the eyebrows, direction of the corner of the mouth etc. and then reassemble these aspects. This approach had led to several judgement errors in her environment and caused considerable disagreements within family and circle of friends and neighbours.

1.1.11 Summary

Organic factors contributing to the onset of the retrograde amnesia were unevenly distributed across patients. The most definite evidence could be gathered in patient E.F. who exhibited hypometabolism of brain glucose, enduring and temporally graded episodic and semantic retrograde amnesia without additional psychiatric background, preceding stressful event, or obvious secondary gain. In patient A.B., except for the head trauma as a trigger of the amnesia and some equivocal paroxysmal incidents following the onset of amnesia, no definite signs of organic aetiology were detected. In the three remaining patients (C.D., G.H., I.J.) enduring semantic and episodic retrograde amnesia can be interpreted as signs of organic causation. However, since there are exceptions of psychogenic retrograde amnesia with these characteristics, this interpretation should be taken with caution. Furthermore, in patient C.D. a diversity of neuropsychological deficits beyond remote memory deficits was observed, potentially indicative of organic factors. The temporal gradient of remote memory loss observed in patient G.H. was somewhat different from that of patient E.F. and may be more indicative of psychological factors (see below). The psychiatric background in patient I.J. did not show any pathology which may point to organic causation of the amnesia in his case.

1.2 Factors in favour of a psychological causation

Psychological factors contributing to the onset and the maintenance of the retrograde amnesia were present in the majority of the patients. To follow Lezak (1995), a psychological aetiology of cognitive deficits is likely if:

1. The onset of the cognitive impairment is preceded by emotional stress
2. Patients are currently emotionally distressed and/or exhibit a psychiatric background
3. There is evidence of secondary gain
4. Organic pathology which might account for the level of cognitive impairment cannot be demonstrated and symptoms exceed what an injury/illness would be expected to cause
5. Patients exhibit ‘la belle indifférence’ or other unusual behaviour with respect to their symptoms
6. Patients’ performance is inconsistent between tasks and/or over time

Three further important characteristics are added concerning psychogenic factors in functional retrograde amnesia. These include:

7. Specific symptoms of remote memory deficit

8. Characteristics of the neuropsychological profile
9. Personality and the issue of repression

In the following sections, all ten characteristics are addressed.

1.2.1 The onset of the cognitive impairment is preceded by emotional stress

Most definite evidence of preceding stress was revealed in patient A.B. On the one hand, she was previously depressed and on the other hand, four suicides in her circle of friends were reported. Both circumstances exerted major stress on her as was emphasised by her relatives and her friend. In patient C.D., no precursory emotional stressors were reported by his wife. However, at least the car accident that ultimately triggered the amnesia, can be seen as a stressful life event. If consciousness in traumatic brain injury is maintained during the incident the probability of the development of PTSD is heightened (Harvey, Brewin, Jones, & Kopelman, 2003). This was the case in patient C.D., who reported that initially he was aware of the course of events during his car accident, but only later on lost consciousness (cf. section III-2.). Though PTSD was not clinically diagnosed in C.D., some of the cognitive and behavioural symptoms reported by himself and his wife can be seen in light of PTSD (e.g. mental slowing, distractibility, irritability, social withdrawal, sleep disturbances; Ehlers & Clark, 2000). As aforementioned, there was no obvious evidence of preceding emotional stress in patient E.F. In patient G.H., several stressful life events were identified and included a traumatic childhood and a series of surgeries during the years preceding the onset of amnesia. Though not all of these incidents immediately preceded the amnesia, it is likely that they contributed to the disturbance. In this vein, one may think of the specific vulnerability of right hemispheric brain functions (e.g. emotion regulation, coping with stress, episodic memory retrieval) by stressful attachment in childhood as proposed by Schore (2002). Moreover, the personal emotional relevance of the past surgeries became obvious by her denial of her sterility after the onset of amnesia (cf. section V-1.4). Concerning patient I.J., the onset of his amnesia requires specific attention. He was found disoriented and amnesic three weeks after he disappeared from home and these symptoms are commonly labelled as fugues, one of the most prominent syndromes of psychogenic retrograde amnesia (cf. section I-2.3). However, the exact circumstances of his disappearance remained unclear. Though his wife did not report any preceding stressful event or life situation, the possibility that he experienced a precursory psychological or organic trauma has to be considered for several reasons. First, he was diagnosed suffering from symptoms of PTSD during his initial stay in Russia. Secondly, when he was found in the train, he was not in possession of a large amount of money he had intended to receive from his former business partner. Instead, he carried a bag of clothes which were not even approximately his size. It can be hypothesised that he did not buy these clothes himself – though this possibility cannot be completely excluded – but rather was given the bag by a potential assaulter. Unfortunately, it was impossible to identify the former business partner's name or address since I.J. himself did not remember either and I.J.'s wife reported not to have known him. From this course of events, it seems reasonable that there was an immediately preceding stressful life event, be it psychological or somatic.

1.2.2 Patients are currently emotionally distressed and/or exhibit a psychiatric background

Current emotional and psychological stress was clearly observed in patients C.D. and G.H. In both patients' current life situation their amnesic condition caused major problems with their relatives leading both patients to initiate psychotherapy. This behavioural pattern was confirmed by psychological screenings pointing to significant emotional-psychiatric aberrations in both patients. Moreover, both patients exhibited a psychiatric background of conversion-like symptoms giving evidence for Oakley's model (Oakley, 1999) of similarities across different autosuggestive disorders (cf. **section I-2.3**). While no definite evidence of previous dissociative episodes was observed, G.H.'s highly pathological profile in the Dissociative Experience Scale can be seen in the same vein. Furthermore, both patients exhibited previous episodes of transient memory loss which is considered a crucial precursor of psychogenic amnesia (Kopelman, 2002b). A similarly clear psychiatric background was observed in patient A.B. previously suffering from Major Depression. This resembles previous retrograde amnesia cases of psychiatric origin such as the case of Yasuno et al. (2000) who became amnesic after a suicide attempt. No indication of current stress or psychiatric pathology was observed in patients E.F. and I.J.

1.2.3 There is evidence of secondary gain

Benefit from the retrograde amnesia was obvious in A.B. who, as an immediate consequence of her retrograde amnesia, lost her depressive symptoms. Accordingly, she was reported to have extensively changed her everyday mood and she herself described her situation as being very satisfying now. Several instances following examination of patient C.D., point to a personal benefit from his current state. Litigation with his former employer to receive compensation can be stated. Furthermore, C.D. was interviewed by several news magazines and TV stations, which could be seen as beneficial in terms of receiving increased attention.

A similar trend for secondary gain was obvious for G.H.. Her reported childish and egocentric behaviour after the onset of amnesia let her initially avoid most of her daily duties such as shopping and cooking. Moreover, the time period for G.H. amnesic became, contained numerous gynaecological surgeries which left her unable to conceive children. It can be inferred from her reported denial of her sterility that the amnesia and also the time range of the amnesia may have born a secondary gain consisting of forgetting a currently stressful autobiographical actuality. The restrained and evasive reactions of I.J. and his wife concerning the regaining of their money may be seen as forgetting a potentially threatening event. However, this could not ultimately be tested and might rather simply reflect their general wish to forget the emotionally stressful time period (or cause) of their separation. It was impossible to observe any secondary gain from the symptoms in patient E.F.

1.2.4 Organic pathology which might account for the level of cognitive impairment cannot be demonstrated and symptoms exceed what an injury/illness would be expected to cause

Per definition, organic pathology was absent in the patients and therefore their comprehensive retrograde memory loss largely exceeds what their injuries or triggers of the amnesia would be expected to cause. Patient E.F. might be the exception (see **section VI-1.1.1**). Since G.H. and I.J. could not undergo magnetic resonance imaging, undetected minimal structural brain damage may still have been present. In patient G.H., the amnesia started after general anaesthesia pointing to a probable organic causation. However, several previous cases were reported who started to suffer from psychogenic syndromes following general anaesthesia (e.g. Adams & Goroszeniuk, 1991; Meyers, Jafek, & Meyers, 1999; Reuber, Enright, & Goulding, 2000). In the context of gynaecological surgery, these syndromes comprised prolonged periods of unconsciousness (Albrecht, Wagner, Leicht, & Lanier, 1995; Pertek, Omar-Amrani, Artis, Vignal, & Chelias, 2000), dissociative retrograde amnesia (Chang, Huang, Wen, Chen, & Wu, 2003), which was accompanied by conversion-like symptoms in the case of Hwang et al. (2002). In these cases, psychogenic causation was suspected by excluding all likely organic causes. Similarly, since in G.H. the course of the anaesthesia and the surgery were reported to have been unproblematic and no additional somatic symptoms were seen, it is very unlikely that the administered anaesthetics caused the retrograde amnesia.

1.2.5 Patients exhibit 'la belle indifférence' or other unusual behaviour with respect to their symptoms

A lack of concern for one's own symptoms was clearly observed during examination of A.B. In detail, she continuously and explicitly mentioned her unconcern stating that 'she is now simply and finally herself' and that 'the others may or may not accept her change'. This behaviour, together with several other characteristics highly resembles case R.F.[14] reported by Dalla Barba et al. (1997). Though the authors did not propose psychogenic causation in their patient, the apparent lack of concern may be interpreted as evidence of functional diseases (cf. Lezak, 1995). To a lesser extent, these kinds of statements were also given by patient C.D., who reported he 'had arranged his new life very well' and generally was afraid to 'get his memory back'. All other patients exhibited the opposite attitude of severe concern about their retrograde amnesia symptoms and they frequently expressed their desire to recover (e.g. patient I.J. who was unable to continue his autobiographical interview since he was emotionally upset by his apparently massive remote memory loss). Further unusual behaviour with respect to the symptoms was obvious in patient C.D., who was so upset by his normal resting state PET results that he stopped talking to the Psychology Department for some time. This behaviour can be considered unusual if his retrograde amnesia was solely caused by an organic aetiology. Instead, if the amnesia did not have any psychiatric components, he may rather have been relieved to hear about his normal brain functioning. In contrast, his reaction may be reasonable when seen in light of potential secondary gain, e.g., concerning compensation from litigation.

1.2.6 Patients' performance is inconsistent between tasks and/or over time

The issue of implicit access to explicitly inaccessible memories can be viewed as inconsistent test performance between or within tasks. Though not tested systematically, there were hints for such implicit use of 'forgotten' information in patients A.B. and G.H. By direct questioning – as in the autobiographical interview – A.B. was almost unable to retrieve episodic information. However, during semantic remote memory testing, she involuntarily recalled fragments and details of former autobiographical events, a condition which was – by observation – threatening to her when she became aware of her performance. Comparably, during semantic remote memory testing with the Famous Events Test, G.H. misunderstood a question as if it was referring to an incident that had happened in 1988 (before her amnesic time), but in fact it had happened in 1990 (within her amnesic time). She performed perfectly on this item and could even provide considerable details on the public event in question. When she noticed her misunderstanding, she instantly refused to answer the next questions and thus, the test had to be interrupted and continued later. This can be seen as implicit access or unconscious memory as well as an indicator for malingering (cf. **section VI-1.3**). Furthermore, generally regarding the neuropsychological and psychological profiles of the patients, several inconsistencies were observed (cf. **section VI-1.1.3**). These were particularly obvious in patient C.D. For instance, his

[14] Age, sex and family situation were highly similar and their neuropsychological profile showed striking similarities (e.g. above average WAIS-R-IQ and WMS-R performance with the same dissociations between verbal and visual subscores).

pattern of slightly impaired immediate but entirely normal delayed anterograde learning in the WMS-R is unusual. His results in the span tasks were clearly disparate with average or above average performance in Digit Spans but clearly deficient Block Span reversed which can be seen as evidence for functional rather than organic diseases (Bernard, McGrath, & Houston, 1993). The SCL-90-R showed a pattern of probably exaggerated psychological-psychiatric complaints in patients C.D. and G.H. Though the overall severity of the symptoms was only slightly elevated, the sheer quantity of the symptoms may indicate a functional rather than organic condition (cf. Lezak, 1995). Since no repeated testing was conducted, evaluation of inconsistencies over time is not possible in the current study.

1.2.7 Specific symptoms of remote memory deficit

Concerning specific characteristics of retrograde amnesia, the aforementioned temporal gradient of the amnesia in G.H. can be considered unusual and casts doubt on an organic causation since the beginning of her amnesia was exactly pinpointed to a day in May 1989. Though steep temporal gradients can also occur in organic retrograde amnesia (e.g. Albert, Butters, & Brandt, 1981), it is unusual that a single day can be specified as the onset. Interestingly, Kapur (1996) found a strikingly similar temporal gradient of 14 years in a patient with psychogenic retrograde amnesia (cf. Table 3). as was seen in E.F. and G.H. These kinds of temporal gradients were also reported in psychogenic amnesia patient A.M.N. studied by Markowitsch et al. (1998) as well as in patient P.N. (Costello et al., 1998) in whom organic and psychological factors co-occurred.

1.2.8 Neuropsychological profile

Though frontal lobe dysfunction generally points to organic aetiology, the observed deficits may also be related to previous or current psychological stress. In all patients, neuropsychological test results pointed to frontal lobe dysfunction. Deficits were consistently observed in attention, and/or executive functions. Severe attentional problems were seen in patients E.F. and G.H. who were, however, additionally tested with more challenging tasks of the Test Battery for the Assessment of Attention. On the other hand, also the more basic Concentration Endurance Test d2 revealed relatively low percentiles in A.B. (33^{rd} percentile), C.D. (16^{th} percentile) and G.H. (21^{st} percentile). Thus, attentional difficulties were present in more than half of the patients (C.D., E.F., G.H.). Moreover, in patients (A.B., C.D., I.J.), in whom the retrograde amnesia was not temporally graded and covered the entire life, frontal lobe associated functions working memory and cognitive flexibility were deficient. Furthermore, executive functions such as the ability to form abstract concepts, to shift and maintain set, and mental flexibility were deteriorated in C.D., and both C.D. and G.H. had deficient inhibition of interference. This raises to the question whether frontal lobe associated functions of attention and executive control may have had a major impact on the remote memory retrieval failure. According to Kopelman (2000) and his model of psychogenic amnesia, stress can affect frontal executive control and therefore potentially contributes to an inhibition of autobiographical retrieval. In this regard, some previous neuroimaging studies of psychogenic/functional retrograde amnesia have revealed frontal lobe dysfunctions or irregularities corresponding to a remote memory retrieval deficit (Costello et al., 1998; Glisky et al., in press; Markowitsch, Calabrese, et al., 1997; Markowitsch, Fink et al., 1997). Even in the absence of obvious psychological stressors as aetiological factors (i.e. in patient E.F.), it is plausible that the current situation exerts considerable everyday stress for the patients. This ongoing or current stress situation is also likely to be reflected in attentional/executive dysfunctions and in turn may promote maintenance of the retrograde amnesia.

1.2.9 Personality and the issue of repression

Three of the patients (C.D., E.F., I.J.) exhibited low scores in a measure of social desirability (FPI-R openness scale) indicating problems in admitting minor weaknesses and violations of everyday conventions. Though the FPI-R openness scale is not in itself valid for assessing repressive tendencies, the concept of repression is related to limited openness. According to Singer (1990), repression is the most general form of avoidance of conscious representation of frightening memories, wishes, fantasies, or unwanted emotions. In psychodynamic terms, defence mechanisms such as isolation, denial, or rationalisation serve to repress thought or affect. A repressive coping style (e.g. with regard to stress) is usually assessed by the Marlow-Crowne Social Desirability Scale (Crowne & Marlowe, 1960) and self reports of anxiety as with the State-Trait-Anxiety Questionnaire (Spielberger et al., 1977). Individuals exhibiting high social desirability/defensiveness and report low levels of state anxiety are classified as repressors (Weinberger, 1990). According to Weinberger (1990), repressors usually claim little experience of negative affect (e.g. distress, anxiety), whereas their psychophysiological stress reactivity as well as vocal, facial, and paralinguistic performance measures suggest that they are as anxious or even more anxious than individuals who report chronic stress (Barger, Kircher, & Croyle, 1997; Pauls & Stemmler, 2003). These kinds of idealised self-reports are further related to memory retrieval. In a series of studies, Davis (1990) reported that repressors had difficulties in retrieving specific emotional memories, even if explicitly encouraged to search for such memories. Similarly, the age of the first autobiographical memory was found to be related to repressive coping style, pointing to a higher age for earliest reported memories in repressors (7 years and older) than in non-repressors individuals (Spirrison & McCarley, 2001). It can be hypothesised in the patients investigated in the current study that a repressive coping style contributed to the retrieval deficit in some of them (C.D., E.F., I.J.), especially given that the forgotten remote time periods may have possessed an emotional meaning for them. At least in patient C.D. who received the State-Trait-Anxiety questionnaire and reported low – though not pathologically reduced – levels of state and trait anxiety (cf. Tab. 10), a (current) repressive coping style is likely.

1.2.10 Summary

Psychological factors contributing to onset and maintenance of the retrograde amnesia were present in the majority of the patients. The most obvious indicators were fugue-like state (I.J.), immediately preceding depression (A.B.), stressful current life events (A.B., G.H.) or childhood trauma (G.H.), previous experiences of transient memory loss (C.D., G.H.), previous psychiatric background such as conversion symptoms (C.D., G.H.) and current somatic complaints of probable psychogenic origin (A.B.).

1.3 Malingering

As is almost always the case in functional or psychogenic retrograde amnesia, it was particularly difficult to specify whether and to what extent the patients deliberately aggravated their symptoms. Even when comparing patients' performance with that of normal subjects, who were instructed to simulate amnesia (Glisky et al., in press), the psychological motivation of – deliberate or involuntary – simulation still has to be considered critically different between patients and controls. Therefore, intentionally simulators' performance cannot without restriction be used to definitely exclude malingering in retrograde amnesia patients. Moreover, most standardised neuropsychological tests for malingering assess anterograde memory (e.g. Rey Fifteen Item Memory Test [Rey, 1964], Test of Memory Malingering [Tombaugh, 1996]). Therefore, they are inappropriate measures for simulation of retrograde memory loss. Due to these methodological difficulties, the issue of malingering was not explicitly addressed here. However, in clinical observation some of the aforementioned characteristics of psychogenic causation could suggest simulation. These include patient A.B.'s apparent lack of concern about her symptoms, her behaviour in semantic remote memory evaluation, C.D.'s current legal situation, behavioural characteristics and neuropsychological irregularities and G.H.'s atypical temporal retrograde amnesia gradient, the benefit from her current situation and her unusual behaviour in the Famous Events Test (cf **sections V-1.4** and **VI-1.2.6**). Furthermore, the evasive reactions of patient I.J. and his wife concerning legal actions to regain the lost money, could also reflect that they might have consciously withheld crucial information. This may point to malingering also in I.J. One can speculate that malingering occurs in a state of self-suggestibility (cf. **section I-2.3**): Patients start to believe in their initial lies and later on construct a plausible world for themselves on the basis of their inventions or creations (cf. Barbarotto et al., 1996). Thus, initially conscious and deliberate aggravation may change to unconscious and involuntary or uncontrollable reactions. The results of Barnier (2002) showing hypnotic induction of explicit autobiographical amnesia in high- but not low-hypnotisable subjects (cf. **section I-2.3**) also suggest that in probably all humans a tendency for (auto-)suggestion of amnesia is present to a greater or lesser degree. This tendency may be heightened in patients with functional retrograde amnesia. Whether it is triggered and maintained by external sources or internal states, and whether it occurs deliberately or not-so-deliberately is indiscernible to standard neuropsychological evaluation. Therefore, it is particularly difficult, if not impossible, to draw an ultimate distinction between conscious and unconscious processes of retrieval deficits in these patients.

2. Neuroimaging results

Before turning to the discussion of the neuroimaging results and how they relate to the neuropsychological and behavioural results, some theoretical aspects have to be elaborated.

2.1 Theoretical considerations

Neuroimaging studies on autobiographical episodic memory demonstrated activations in a distributed network of brain regions (cf. **section I-1.4.3**). In most of these studies, stimuli were acquired prior to the scanning sessions by interviewing the subjects. In contrast, in the current study autobiographical information about the patients was received by their relatives. Though one previous autobiographical memory study on normal subjects employed a comparable method leading to similar as the aforementioned activations (Ryan et al., 2001), this approach is critically different from that of the current study. The retrograde amnesia in the patients investigated in the current study was partially caused by previous or current psychological mechanisms. These, however, necessarily arose or subsisted within the context of the patients' domestic environment. Thus, it is likely that the received autobiographical information was neither comparable to stimuli employed in previous studies nor across patients. In particular, though it was aimed to account for comparability of stimuli across time periods and patients, it cannot be ultimately ruled out that the information contained aspects of the patients' previous lives which were parts of their 'motivation' to forget their autobiography. In other words, the current study had to handle a situation wherein autobiographical episodic retrieval had to be tested in patients with retrograde amnesia accompanied by psychogenic components. For this purpose, test stimuli had to be applied that originated from an environment that might have caused or perpetuated the symptoms. Therefore, interpretation of a general autobiographical retrieval network and its disturbance in the single patients is impossible. Instead, the patients' activations can only be considered individually by comparisons with themselves across the different memory conditions and their results can then be interpreted in light of previous functional neuroimaging studies. Furthermore, there were no control subjects in the neuroimaging experiments. However, if controls had been included, additional theoretical problems might have arisen. For instance, it is not clear how to design a comparable temporal distinction between old and new memories in controls. Though an arbitrary time marker (e.g. 6 months prior to investigation) could have been thought of in designing control subjects' stimuli, it is apparent that the personal relevance of such a distinction would have been entirely different from that of the patients. Thus, further comparisons to healthy subjects would have additionally confounded the picture in the sense of underlying psychological factors and their probable neural correlates.

Concerning the PET experiment, exact localisation of activations was impeded by the fact that it was impossible to receive static anatomical images from the two investigated patients (see **section IV-6**). Therefore, reported activations are based on standard Talairach and Tournoux coordinates (Talairach & Tournoux, 1988). To partly account for the spatial uncertainty, only the largest activated clusters were analysed. Furthermore, though experimental stimuli in the PET experiment were constructed similarly to those of the two true memory conditions in the fMRI experiment, results across both tasks may not be entirely comparable for several reasons. Firstly, the amount of to be retrieved information differed between the experiments. While in the fMRI experiment patients were supposed to remember ten single events per condition described by six sentences each, in the PET experiment only four episodes had to be retrieved described by four sentences each. Though potential erroneous or irrelevant information was carefully controlled by interviews with the relatives, the relative likelihood of such errors must be considered higher in the PET experiment given the smaller total number of stimuli. Secondly, stimulus presentation time differed between the experiments (see **sections IV-5.2** and **IV-6.3**) and therefore, the attentional demand during the fMRI experiment might have been considerably higher than during the PET scan. Finally, due to the fact that fMRI and PET measure different physiological parameters (regional cerebral blood flow and deoxyhaemoglobin concentration) that do not share a common stimulus-rate dependency, discrepancies in results are possible (cf. Mechelli, Friston, & Price, 2000). However, despite these constraints, results from all patients indicated differential brain activation patterns associated with at least some of the experimental memory conditions.

In the following, an interpretation of all patients' results is given with regard to differential activations between the two memory conditions tested in both paradigms (true episodes from the amnesic contrasting the non-amnesic time period). Then, contrasts of additional memory conditions of the fMRI experiment are discussed across patients as well as individually. Since results of the post-scanning debriefing are related to the neuroimaging experiments, they are added at the respective passages.

2.2 Old versus new events

Regarding true memory conditions across the two time periods, processing of old in contrast to new episodes revealed enhanced activation in right prefrontal brain regions in patients E.F. and I.J. In contrast, patient A.B. showed a largely left lateralised activation pattern of lateral superior temporal/inferior parietal brain regions. I.J. further exhibited superior parietal activity, which was, however, also seen and extended in the reverse contrast and therefore will be discussed in the subsequent section. Patients C.D. and G.H. did not show enhanced significant differential activity during retrieval attempt of true old in contrast to new events.

It can be inferred that, given the clear dissociation between both conditions in post-scanning debriefing in E.F. and I.J. (see **sections V-3.1.3** and **V-3.2.2**), the attempts to retrieve inaccessible episodes required greater effort for events of the time period covered by amnesia compared to episodes outside the amnesic time. This is reflected in enhanced prefrontal lobe involvement (Fletcher & Henson, 2001). This is especially likely in patient I.J., since his enhanced activity was seen in right frontal pole possibly indicating sustained retrieval control processes under high task demands (cf. Velanova et al., 2003). According to Fletcher and Henson (2001), these control processes during memory retrieval can concern meta-memory (Kikyo, Ohki, & Miyashita, 2002), coordination of search and monitoring retrieval processes (Sakai, 2003). Furthermore, right anterior prefrontal lobe may be specifically involved in intentional compared to incidental retrieval (Fletcher & Henson, 2001). In both patients, lateralisation of activations to the right hemisphere could reflect episodic retrieval mode (Lepage et al., 2000). Also, right hemisphere mid-ventrolateral prefrontal activity (as seen in E.F.) was reported in an fMRI study when subjects were actively engaged in episodic memory recollection versus automatic recall (Kostopoulos & Petrides, 2003). Medial prefrontal activity - as seen in E.F. within the gyrus rectus - was previously implicated in autobiographical retrieval in healthy subjects (e.g. Maguire, Henson et al., 2001; Maguire et al., 2000). Specifically, medial prefrontal cortex may be engaged in taking a emotional self-perspective during autobiographical episodic retrieval. The exact contribution of this area may lie in processing emotional and social aspects of autobiographical information. Previous neuroimaging experiments revealed activation in this area in fear extinction (Milad & Quirk, 2002), reward learning and addiction (cf. Robbins & Everitt, 2002), as well as social-cognitive tasks such as retrieval of person-knowledge compared to object-knowledge (Mitchell, Heatherton, & Macrae, 2002) and self-referential cognition (Kelley et al., 2002; Johnson et al., 2002). Taken together, previous functional neuroimaging studies suggest that retrieval of information from the amnesic time period (compared to the non-amnesic time) was more effortful for patients E.F. and I.J. In particular, there may have been either enhanced processing of emotionally relevant self-referential information from the amnesic time (E.F.) or experience of demanding memory retrieval control processes (I.J.) and both patients may have been in an episodic retrieval mode.

In contrast, post-scanning debriefing of patient A.B. indicated less clear dissociations between true episodes from amnesic and non-amnesic time periods. In this patient, activations comprised a left cerebellar and a left lateralised lateral activation pattern in superior temporal and inferior parietal cortex in the region of the supramarginal and angular gyrus. The latter regions are frequently described in the context of language comprehension (e.g. van Buren, Fedio, & Frederick, 1978) and were previously found to be involved in semantic comprehension of words (Démonet et al., 1992; Démonet, Price, Wise, & Frackowiak, 1994) and sentences (Sakai, Hashimoto, & Homae, 2001), visual word recognition (Hart, Kraut, Kremen, Soher, & Gordon, 2000), cross-modal conversion of visual/auditory words (Booth et al., 2003), as well as verbal working memory (Clark et al., 2000; Paulesu, Frith, & Frackowiak, 1993). Accordingly, in the context of memory retrieval these areas were associated with retrieval of semantic and language-related information (Kircher, Brammer, Williams, & McGuire, 2000; Lee et al., 2002). Several PET-studies of episodic memory for spatial locations and object identity revealed right supramarginal/inferior parietal activations in the retrieval of spatial locations only (Köhler, McIntosh, Moscovitch, & Winocur, 1998; Köhler, Moscovitch, Winocur, Houle, & McIntosh, 1998; Moscovitch, Kapur, Köhler, & Houle, 1995). Furthermore, Russ, Mack, Grama, Lanfermann and Knopf (2003) found predominantly right hemispheric supramarginal activity associated with recognition of actions that were previously encoded by motor performance in contrast to verbally encoded actions. However, the clear left hemisphere lateralisation of activations in A.B. strongly suggests that language-associated processes played a major role during her retrieval attempt. In particular, she may have processed episodes from the amnesic time compared to new events in a more language-dependent and semantic way and could have engaged more intensely in comprehending and analysing the meaning of events which occurred within this time. Also verbal working memory processes such as actively holding sentences in mind are likely to have contributed to the activations observed. Moreover, a strikingly similar activation of left supramarginal gyrus was observed during retrieval attempt of fictitious in contrast to true events from the non-amnesic time. This pattern provides evidence for the assumption that A.B. treated her true episodes from the amnesic time in a similarly semantic and language-related manner as if they were descriptions of fictitious events and not like events she could easily remember.

The lack of differential activation seen in patients C.D. and G.H. when retrieving true old in contrast to true new events could have resulted from various reasons. Old events may have been already rehearsed prior to scanning, rendering them indistinguishable from new events. It may have happened in these patients that they retrieved their re-encoding experiences rather than the actual episodes themselves. Furthermore, across all patients, C.D. and G.H. showed the most definite characteristics of precursory psychiatric history combined with current psychological problems and they both showed more probable signs of malingering than the other patients. On this basis, C.D. and G.H. may not have engaged to the same degree in retrieval attempt of old episodes, originating from stressful life periods, compared to their new experiences.

2.3 New versus old events

The reverse contrast, processing of true new in contrast to true old episodes, revealed differential activation in posterior association cortex in patients E.F., G.H. and I.J., temporal lobe areas in patients G.H. and I.J., as well as inferior frontal and superior parietal regions in I.J. Patients A.B. and C.D. did not show enhanced significant activity in this contrast.

The fusiform activity in patient E.F., may reflect greater imagery of newly experienced and retrievable events (cf. Vaidya, Zhao, Desmond, & Gabrieli, 2002). However, exactly the same activation was found when contrasting fictitious new with fictitious old events while there was differential left inferior temporal activity at the boundaries of the occipital lobe for the reverse contrast (fictitious old vs. fictitious new; **see section VI-2.5**). Importantly, the occipital activation covaried with time period, regardless of whether the stimulus material depicted a true or fictitious event. Thus, E.F. may have differentially processed the visual characteristics of information relating to old and new time periods (Kellenbach, Brett, & Patterson, 2003; Wheeler & Buckner, 2003).

Similarly, precuneus activity as seen in patient G.H., has repeatedly been associated with retrieval of episodic information (Cabeza & Nyberg, 2000) and may particularly indicate retrieval of imageable information, though this is controversial. Classically, mental imagery during retrieval of visual information has been associated with precuneus activity (Fletcher et al., 1995; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1996), while more recent experiments also pointed to precuneus involvement in mental imagery of motor actions (Hanakawa et al., 2003) and auditory information (Yoo, Lee, & Choi, 2001). Activation of this region was also seen in studies of autobiographical memory retrieval (e.g. Maddock et al., 2001; Piefke et al., 2003). Maddock et al. (2001) suggested that precuneus functions are not restricted to the retrieval of visual information.

Rather, this brain area is likely to be implicated in polymodal imagery associated with successful retrieval, as well. According to this hypothesis, processing of the visual/sensory characteristics of accessible compared to inaccessible events may have been enhanced in G.H. such that she was able to re-experience these features of visually detailed memories only within the non-amnesic time. The fusiform activation seen in E.F. during the processing of new (versus true old) episodes may reflect a similar mechanism (see above). Temporal pole activation as seen in patient G.H. was also implicated in autobiographical memory retrieval in previous PET studies with healthy subjects (Fink et al., 1996; Maguire & Mummery, 1999; Markowitsch, Thiel et al., 2000). Furthermore, it is known that lesions to the right temporo-frontal junction can result in selective episodic retrograde amnesia (Levine et al., 1998; Calabrese et al., 1996; Kroll et al., 1997; Markowitsch, Calabrese, Liess et al., 1993). Markowitsch (1997, 2000c) proposed that the right ventral branch of the uncinate fascicle (interconnecting the temporo-polar and inferior prefrontal cortex) represents an important link to limbic structures (e.g. the amygdala) which in turn are specifically engaged in emotional aspects of episodic remote memory retrieval. Concordantly, some functional retrograde amnesia patients exhibited metabolic aberrations in this area during rest (Markowitsch, Calabrese, et al., 1997; Sellal, et al., 2002) and attempts to retrieve information from their amnesic time (Costello et al., 1998; Markowitsch, Fink et al., 1997; Markowitsch, Thiel et al., 1997; Yasuno et al., 2000). In the present study, patient G.H. did not activate temporo-polar areas when she attempted to retrieve information from the amnesic time period. In contrast, during the recollection of episodes from the non-amnesic time the temporal pole was more active, indicating that successful episodic memory retrieval proceeded via this crucial region.

In contrast to G.H., patient I.J. showed enhanced left-lateralised activity in the anterior temporal/inferior frontal junction during retrieval of new versus old episodes. This is consistent with most neuroimaging studies of autobiographical memory retrieval in healthy human subjects which demonstrated predominantly left lateralised activation of this area (cf. Maguire, 2001; Piefke et al., 2003; but see Fink et al., 1996). In I.J., left hemisphere prefrontal activity during the retrieval of new (relative to old) events may reflect enhanced engagement of common memory-related areas subserving higher-level control processes. A psychogenic fugue patient, however, who closely resembled I.J. on the behavioural level (Markowitsch, Fink et al., 1997), exhibited brain activity in this area not only during the retrieval of episodes covered by amnesia but also while he remembered post-amnesic and memorisable episodes. This finding was in contrast with the preponderantly right hemisphere activation pattern associated with autobiographical memory retrieval but left hemisphere involvement in the processing of impersonal information (Fink et al., 1996) in their PET study with healthy subjects. Therefore, Markowitsch, Fink et al. (1997), concluded that their patient may have processed his autobiography in an emotionally detached, semantic way. Patient I.J. may suffer from a similar deficit, given that he judged only two of the four episodes presented to him from his non-amnesic time to have a significant emotional impact. Taken together, it can be suggested that the lateralisation of prefrontal activations to the left hemisphere indicate an enhanced engagement of control processes during retrieval combined with a semantic, but rather unemotional processing of events from the non-amnesic time period.

I.J. further exhibited left posterior superior parietal activations during retrieval of new (relative to old) episodes as well as in the reverse contrast, extending also into inferior parietal regions during the retrieval of new episodes. Left parietal activity was reported from some previous autobiographical memory retrieval studies (Andreasen et al., 1999; Conway et al., 1999; Piefke et al., 2003; Ryan et al., 2001), as well as investigations on non-autobiographical episodic retrieval (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Henson, Rugg, Shallice, Josephs, & Dolan, 1999). Although lateral parietal cortex has been implicated in successful episodic retrieval (Andreasen et al., 1999; Konishi et al., 2000), it may also reflect visual attention (Kastner & Ungerleider, 2000). Successful episodic retrieval may lead to an attention shift from the retrieval cue to the retrieved information corresponding to lateral parietal activation (Cabeza et al., 2003). Since I.J. showed comparable parietal activations for both contrasts (new versus old memories, and vice versa), a more general occurrence of attention shifts from the external retrieval cue to internal information processing has to be taken into consideration. Given his disparate results across retrieval conditions in the post-scanning debriefing (see **section V-3.2.2**), however, it cannot be inferred that these attentional shifts were associated with retrieval success. In addition to the parietal activity, posterior cingulate gyrus activity was revealed during retrieval of new in contrast to old episodes. Posterior cingulate/retrosplenial cortex involvement has been consistently observed in autobiographical memory retrieval (e.g. Andreasen et al., 1999; Fink et al., 1996; Maddock et al., 2001; Maguire & Mummery, 1999; Piefke et al., 2003; Ryan et al., 2001) as well as in self-related cognition (Johnson et al., 2002; Kelley et al., 2002). Therefore, it is probable that this activity during processing of episodes from the non-amnesic time reflects enhanced self-related cognition in successful autobiographical retrieval.

Generally, the enhanced activity in posterior sensory-perceptual brain regions in three of the investigated patients was restricted to the accessible time period. This may be interpreted as evidence for Conway's approach to episodic memory (cf. **section I-1.4.3**; Conway, 2001b; Conway & Pleydell-Pearce, 2000). Given his assumption that episodic memories are specific and distinct from other memories by their sensory-perceptual nature. Since posterior association cortex in the three patients here, was engaged to a higher degree within a time period that can be overtly remembered, it may be suspected that exactly these sensory-perceptual details distinguished accessible and inaccessible episodic memories.

Patients A.B. and C.D. did not show enhanced activity during retrieval of new in contrast to old episodes. Different mechanisms for this lack of differentiation can be assumed in both patients. Given post-scanning debriefing, A.B. was able to access parts of her amnesic time period due to her gradual recovery. Thus, it is possible that episodic retrieval-related activations across both time periods were similar and therefore eliminated in contrasting new and old episodes. As was outlined above, processing of old episodes may have been characterised by selective involvement of language-related brain areas (cf. **section VI-2.2**). In C.D. neither contrast (old versus new and new versus old episodes) yielded significant differential activations. This may reflect memorisation of re-learning processes that eliminated any differences between events from the amnesic and the post-amnesic time period (see above). Since this result is clearly contrary to his responses in the post-scanning debriefing (see **section V-3.1.3**), the identical processing of all autobiographical episodes on the brain level, could also be seen as malingered retrograde amnesia, especially given his psychological background (see **sections VI-1.2** and **VI-1.3**).

2.4 Distinguishing true from fictitious memories

In the fMRI experiment, differential activations associated with true in contrast to fictitious episodes were observed only within the non-amnesic time period. In particular, left temporal and parahippocampal activity showed this effect in A.B., whereas right insular activation showed this effect in C.D. In the same contrast, increased anterior cingulate gyrus activity in patient E.F. did not reach statistical significance.

Previous neuroimaging research related activation of the hippocampal and parahippocampal regions during memory tasks to mechanisms of memory consolidation (Haist et al., 2001; Piefke et al., 2003; Niki and Luo, 2002) and to retrieval success (Maguire et al., 2000; Maguire, Vargha-Khadem et al., 2001). For example, in line with the 'classic' consolidation theory (Squire, 1992), the fMRI studies on autobiographical memory retrieval by Piefke et al. (2003) and Niki and Luo (2002) reported activity in the hippocampal/parahippocampal complex during the retrieval of recent (relative to remote) memories, suggesting that this brain area plays a time-dependent role in declarative memory processing. Parahippocampal activity differentiating true from fictive episodes in the non-amnesic time in A.B. was not detected in the same contrast within the amnesic time and may thus be attributable to the recency of new autobiographical episodes. However, given the minimal temporal separation between time periods in the current study, it is more likely that the observed parahippocampal involvement is unrelated to the recency of true new episodes but instead points to successful autobiographical memory retrieval (in contrast to processing of fictitious episodes) only within the non-amnesic time (cf. Maguire et al., 2000; Maguire, Vargha-Khadem et al., 2001).

During the retrieval of autobiographical memories, the insular cortex is likely to predominantly contribute to the processing of emotional aspects of autobiographical memory formation and/or sensory-emotional integration (Markowitsch, 2000c). This brain structure represents a critical component in regulation of autonomic emotional responses through its interconnections with hypothalamic regions. Selective lesions or electrical stimulation of the insula produces changes in autonomic parameters (Cereda, Ghika, Maeder, & Bogousslavsky, 2002; Oppenheimer, Saleh, & Cechetto, 1992). Accordingly, activation of the insular cortex was observed in a number of studies of emotional/vegetative processes (Aziz et al., 1997; Oshiro et al., 1998) as well as in more cognitive tasks of emotional processing (e.g. evaluative judgements of emotional faces [Gorno-Tempini et al., 2001]; processing of disgusted faces [Phillips et al., 1997]). The strength of insular activation may further vary with levels of attention to the emotional stimuli (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Krolak-Salmon et al., 2003). In a meta-analysis of functional neuroimaging experiments of emotion processing, Phan, Wager, Taylor, and Liberzon (2002) revealed a particular and consistent involvement of the insular (and anterior cingulate) cortex in emotional recall and imagery as well as effortful emotional task performance. With regard to the current data, it is likely that C.D. (and probably also E.F. who exhibited non-significant anterior cingulate gyrus activity) was emotionally more engaged in recall of true events from the non-amnesic time than in processing of fictitious events. Activation of the insular cortex may thus indicate that C.D. evaluated emotional aspects of his newly acquired autobiographical in contrast to fictitious memories during the fMRI measurement.

2.5 Distinguishing fictitious from true events

Differential activations associated with fictitious in contrast to true episodes were observed in the non-amnesic time period and were seen in left supramarginal gyrus and cerebellum in patient A.B. as well as in left medial and inferior prefrontal gyrus in patient C.D. Patient E.F. did not show significant differential activity in this contrast.

As mentioned, left supramarginal gyrus activity observed in A.B. may reflect language-associated processing of the fictitious events (see **section VI-2.2**). In patient C.D., activation of the medial, subgenual area and left ventrolateral prefrontal region may be seen related to retrieval effort and emotional aspects of the task. Subgenual activity was associated with emotional processing as in retrieval of sad autobiographical episodes (Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002), or in evaluating the valence of emotional words (Maddock, Garrett, &

Buonocore, 2003). This region may be involved in inhibition of adverse emotional reactions (Pochon et al., 2002) and structural brain abnormality in this area was seen in patients with mood disorders (e.g. Botteron, Raichle, Drevets, Heath, & Todd, 2002; Brambilla et al., 2002). As aforementioned, ventrolateral prefrontal cortex may be particularly involved in retrieval effort such as specification of search parameters and activation strength may vary with increasing task demand (Fletcher & Henson, 2001; Rugg, Otten, & Henson, 2002, but see also Pochon et al., 2002). The lateralisation to the left hemisphere may indicate an evaluative component. In this regard, Zysset et al. (2002) found left hemispheric ventrolateral prefrontal regions to be more active during the processing of evaluative judgements compared to episodic and semantic remote memory retrieval. The authors suggest this brain region to be particularly involved in tasks that require response selection on the basis of a continuum of responses rather than simple yes/no decisions. Thus, within the non-amnesic time only, C.D. may have processed emotional connotations of fictitious events in a different way than that of true events. He might have experienced difficulties in deciding whether the depicted events were true or not, rendering this task and memory retrieval particularly demanding for him. This difficulty may party have been caused by the high similarity between true and fictitious events. Given C.D.'s attentional difficulties which were also reflected by his longer reaction times to the stimuli in the scanner, it is questionable whether these differences may have arisen from stimulus features. Probably, events from the non-amnesic time were more emotional than events from the non-amnesic time and that this difference was reflected in both contrasts of true and fictitious events from the non-amnesic time. Also, the results in the post-scanning debriefing point to enhanced emotional relevance of the stimuli within this accessible time period (see Figures 21 and 22). However, C.D. himself pointed out that he could not judge the emotionality of true old events, and it was impossible to verify a significant emotional difference in the stimulus materials by interviewing his wife. Thus, it can be concluded that emotion-related activity in both contrasts were not caused by features of the presented material but rather by a selectively enhanced emotional engagement within this time. This in turn may have arisen either from heightened motivation within the accessible time period or by actual (enhanced) memory retrieval of former emotional states.

2.6 Fictitious events across both time periods

In patient E.F. only, processing of fictitious events differed across time periods. Retrieval of old in contrast to new fictitious events revealed left inferior and middle temporal gyrus activation whereas the reverse contrast showed left fusiform gyrus activity.

As previously mentioned, E.F. may have differentially processed the visual characteristics of information related to old and new time periods regardless whether this information was fictitious or not (see **section VI-2.3**). This is probably reflected in the fusiform activity. Differential brain activation within the amnesic time was seen in posterior inferior temporal regions at the boundaries of the occipital lobe. Also here, it can be hypothesised that integration of memory contents and visual components was specific to the described time period as Vaidya et al. (2002) observed fusiform activity not only within occipital lobe but also in the occipito-temporal junction area. An alternative hypothesis is that patient E.F. showed enhanced processing of semantic features of the stimuli only within this time period, since a highly similar activation was observed during a semantic versus phonological encoding task by McDermott, Petersen, Watson, and Ojemann (2003).

2.7 Summary

Comparison of the true memory conditions across all patients revealed that retrieval of episodes from the amnesic time period was associated with enhanced activation in right prefrontal brain regions in patients E.F. and I.J. This was interpreted as enhanced retrieval effort or episodic retrieval mode within this time period. Patient A.B. showed a left lateralised activation pattern of lateral superior temporal/inferior parietal brain regions which points to enhanced processing of language-related features. The reverse contrast, processing of new in contrast to old episodes, revealed activation in posterior association cortex in three patients (E.F., G.H., I.J.). This may indicate higher activation of sensory-perceptual features of to-be-retrieved memories in the non-amnesic time. Furthermore, in contrasting processing of true and fictitious episodes within both time periods, BOLD responses did not differ between attempts to retrieve true compared to fictitious episodes in the amnesic time period in the three patients investigated with fMRI. Concerning the non-amnesic time, however, significant differential activations associated with true relative to fictitious episodes were seen in A.B. and C.D., as well as a non-significant trend in the same direction in patient E.F. Therefore, even if behavioural differentiation between true and fictitious episodes was to some extent possible in the three patients (cf. post-scanning debriefing; **sections V-3.1.3** and **V-3.2.2**), this led to differential neural activity only within the accessible time period.

3. Categorisation of the patients

Given the multitude and complexity of behavioural and neuropsychological results per patient as well as their functional brain correlates during remote autobiographical retrieval, it may seem bold to categorise their amnesia according to underlying organic, psychological and malingering-related features as proposed by Kopelman (2000; 2002b). However, considering the outlined characteristics and their interpretation, it appears safe to apply the following summarising categorisation to each patient.

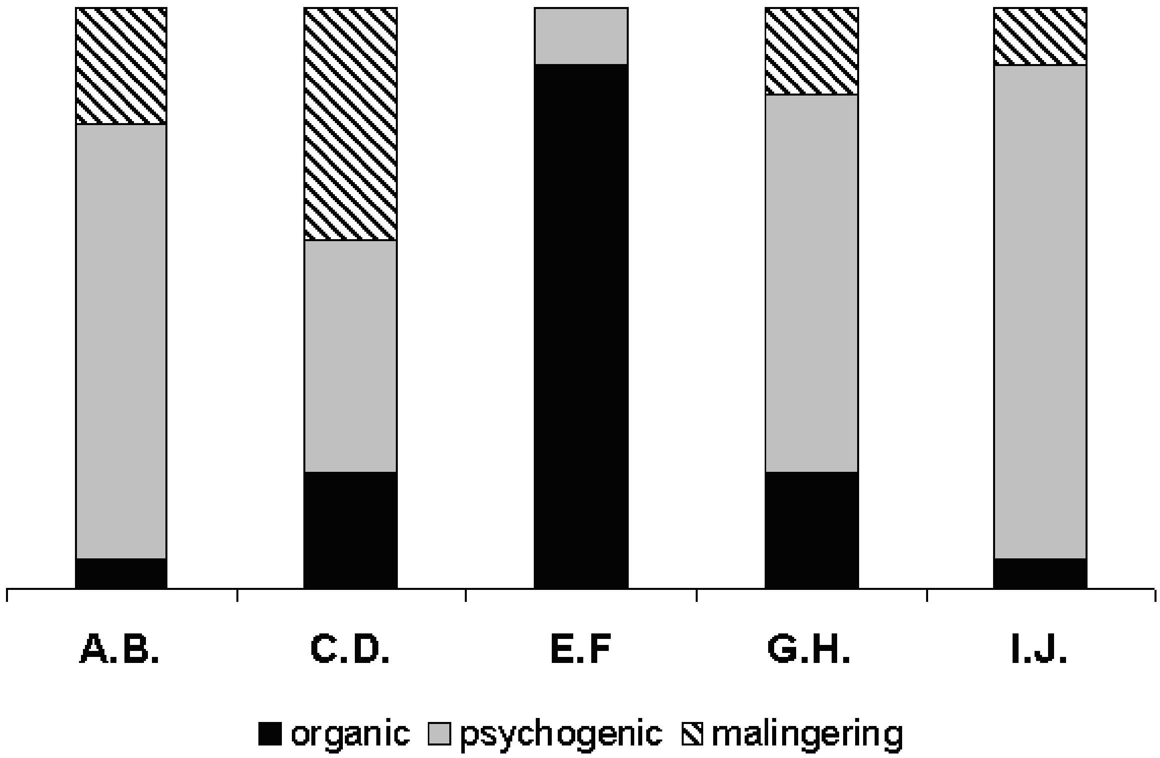

Figure 28: Features of malingering, psychogenic, and organic mechanisms contributing to the retrograde amnesia based on behavioural and neuropsychological results per patient.

Though the exact extent to which the retrograde amnesia comprised malingering, psychogenic and organic factors could not – and probably can never in any case of functional retrograde amnesia – be ultimately resolved, it is proposed that in A.B., G.H. and I.J., psychogenic (unconscious) factors are predominant, while in C.D. malingering and in E.F. organic factors of the retrograde amnesia played a major role. Malingering was not detectable in E.F., while in C.D. and to a lesser extent also in A.B. and G.H. aspects of simulation cannot be denied. The co-contribution of organic factors could not be excluded in any of the patients.

This categorisation is mostly based on behavioural and neuropsychological results. This approach was chosen for several reasons. Firstly, the behaviour of these patients within test sessions as well as in everyday situations and interactions is just as or even more informative about the psychological co-contribution to the deficit as are memory scores or brain activity. Without such information, interpretation of differential brain activation in single subjects as with the five patients investigated here, is destined to fail and cannot be related to features specific to the individual. Secondly, even given brain dysfunction or functional aberrances either during rest or during remote memory retrieval, this is not by itself useful to determine potential organic co-contribution or rule out psychological factors. There is a continuum from overt lying over psychogenic to organic aspects of functional retrograde amnesia (e.g. Barbarotto et al., 1996) wherein a brain basis accompanies the deficit in a similar way as all behaviour has a neural correlate. Thirdly and related to this point, even if one could speculate that there is a common underlying brain dysfunction on the basis of similarity of the symptoms across different cases, the consistently affected behaviour in functional retrograde amnesia is by far one of the most complex emotional-cognitive functions, namely autobiographical memory retrieval. Therefore, and in contrast to patients with more circumscribed psychogenic deficits such as functional paralysis of a limb (e.g. Marshall et al., 1997), interindividual differences in brain activity during remote memory access are not only likely across cases but impossible to interpret without sufficient background information. Moreover, the significance of the social surroundings and day-to-day situation of patients with any disease will easily be underestimated in light of organic evidence. However, though in the case of functional retrograde amnesia the majority of affected individuals (overtly) appears less disturbed by their illness than their immediate life partners, these characteristics may lead to a prolonged disease state that can exert major stress. This in turn may again be reflected by functional brain disturbances (cf. Markowitsch et al., 1998; Markowitsch, Kessler et al., 2000). Therefore, the observed functional brain correlates of autobiographical memory retrieval in the five functional retrograde amnesia patients in the current study are to be understood as accompanying rather than causing the memory impairment.

VII. Conclusion

Functional retrograde amnesia is a rare pathology in neurological and psychiatric contexts. Previous neuropsychological studies were mostly single cases and investigation of brain correlates in this patient group is even more sparse. Therefore, the current study of five functional retrograde amnesia patients compared differences and commonalties in behaviour, neuropsychological performance and neural correlates during autobiographical memory retrieval across cases.

By neuropsychological examination and behavioural observation, it was shown that – in the absence of structural brain damage – all patients suffered from extensive retrograde amnesia for episodic remote memory either encompassing their entire life or the last 12-14 years. Parts of semantic remote memory were likewise impaired in most patients. The retrograde amnesia was accompanied by neuropsychological deficits beyond remote memory retrieval. These were most consistently seen in executive functions and attention strongly suggesting that these cognitive functions contribute to the retrieval deficit. However, compared to the extensive remote memory deficits, additional cognitive impairment was clearly disproportionate. Concerning emotional and interpersonal functions, it was revealed that some of the patients suffered from deficits in social cognition and at the time of test had additional psychiatric symptoms. Moreover, behavioural aberrances in social context were observed in a measure of social desirability.

Investigation of functional brain correlates during retrieval (attempt) of autobiographical episodes was conducted by fMRI in three patients or by $H_2^{15}O$-PET in two patients. Episodes were derived by interviews of the patients' relatives or friends and covered either the inaccessible time period before the onset of amnesia or the unaffected time period following the onset of amnesia. Contrasting true events from both time periods across all patients, two patients processed episodes from the amnesic time period with higher engagement of right prefrontal cortex, whereas another patient showed activations in left supramarginal and angular gyrus. These patterns may indicate retrieval effort and episodic retrieval mode in the two former patients and language-related processing in the latter. Processing of accessible episodes involved additional posterior association cortex activity in three patients pointing to enhanced retrieval of sensory-perceptual details of accessible episodic information. In the fMRI experiment, these conditions were further contrasted by retrieval attempt of fictitious episodes constructed as if they had happened within either of the time periods. Differential activations distinguishing true from fictitious episodes was confined to the non-amnesic time period. In this contrast, one patient showed parahippocampal activity and in another insular cortex activity was revealed. This suggests that only within the non-amnesic time, differentiation of true in contrast to fictitious events was accompanied by additional involvement of memory relevant brain structures or those involved in emotional processing.

Whereas a preponderance of psychological factors accompanying the memory disturbance was detected in most patients, clear causal inferences could not be drawn. Nevertheless, results indicate that the patients' current situation exerts a major everyday stress for themselves as well as for their social environment. In particular, they are amnesic for significant parts of their own past and identity, exhibit additional neuropsychological impairment in executive functions and attention as well as in some cases, psychiatric symptoms, emotional and social problems. Independent of aetiology, such patients' current emotional and additional neuropsychological disturbances can emerge from their amnesia, not only generate it. Likewise, functional brain correlates differentiating disturbed from unaffected time periods, have to be seen in terms of corresponding to the current behavioural aberrances. Taken together, the results allowed for a classification of each patient along the three axes of organic, psychogenic and malingering-related characteristics present in functional retrograde amnesia.

Several issues in the realm of functional retrograde amnesia are open to further investigation. For instance, it is of particular interest to test functional neural correlates of the retrieval deficit in acute phases of the amnesia. Since patients do not live in an isolated world and, fortunately, re-acquisition of previous knowledge in this disease is largely preserved, they quickly reconstruct their personal past, even if this is not accompanied by vivid and emotional re-experience of former events. This fact can be considered crucial for processing autobiographical events in functional brain imaging experiments, as it cannot be excluded that patients remember instances of re-learning instead of the actual episodes. Thus, construction of precisely demarcated retrieval conditions is per se intricate in functional retrograde amnesia but less likely to fail if patients are seen in more acute stages.

Furthermore, the relationship between altered states of consciousness and amnesic symptoms may be promising to investigate more systematically. In dissociative and conversion disorders, hypnotic procedures have long been (e.g. Janet, 1913) and are still one of the most common treatments (cf. Kihlstrom, 1997; Oakley, 2001) to unravel consciously inaccessible memories or emotions. A relation between amnesia and hypnotisability, autosuggestibility, or recovery from amnesia by hypnotic procedures is highly likely. However, there is by now no systematic evaluation of these associations in functional retrograde amnesia, e.g., comparable to that of Roelofs et al. (2002) who found enhanced hypnotisability in conversion disorder. Moreover, it would be particularly interesting to investigate functional brain correlates of hypnotically induced autobiographical amnesia in healthy subjects to clarify whether there may still be a common brain basis with repressing of one's own past.

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Declaration

I declare that the work presented in this thesis entitled

Brain and Behaviour in Functional Retrograde Amnesia

is my own work. None but the cited methods and materials were used. This work has not been submitted in this or another form at any other university or faculty.

Date

Signature