Structure Function Relationship of the Hippocampal Memory System in Patients with an Amnestic Syndrome

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Meinen lieben Großeltern

Jutta und Werner Döhring

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DECLARATIVE MEMORY CONSOLIDATION

PROCEDURAL MEMORY AND THE HIPPOCAMPUS

Abbreviations

ADC:	apparent diffusion coefficient
ATP:	adenosine triphosphate
CA:	cornu ammonis
cAMP:	cyclic adenosine monophosphat
DW MRI:	diffusion-weighted magnetic resonance imaging
GABA:	gamma-aminobutyric acid
HADS-D:	hospital anxiety and depression scale
HPA:	hypothalamo- pituitary- adrenal (axis)
LTD:	long-term depression
LTM:	long-term memory
LTP:	long-term potentiation
MRI:	magnetic resonance imaging
MTL:	medial temporal lobe
MTT:	multiple trace theory
NMDA:	N-methyl-D-aspartate receptor
PET:	positron emission tomography
PFC:	prefrontal lobe
PreSMA:	presupplementary motor area
PSS:	perceived stress scale
RAVLT:	Rey Auditory Verbal Learning Test
ROCF:	Rey-Osterrieth Complex Figure
SAE:	subcortical artheriosclerotic encephalopathies
SMA:	supplementary motor area
SMC:	standard model of memory consolidation
SPECT:	single photon emission computed tomography
SRRS:	Social Readjustment Rating Scale
STM:	short-term memory
SVF:	Stressverarbeitungsfragebogen
TGA:	transient global amnesia

Preface

This cumulative thesis incorporates two papers, one manuscript and a presentation abstract whose topics are closely connected to the role of the hippocampus in memory processing. The hippocampus is a phylogenetically old structure in the medial temporal lobe (MTL). Here, information from various cortical areas converges. Binding this information, it generates integrated and coherent representations that constitute our inner world of thoughts and memory. This mainly applies to objects and situations that are available to our consciousness; more precisely: contents that can be declared. For this reason, it can be stated that the hippocampus stands at the top of the declarative memory processing hierarchy.

I will put special emphasis on the hippocampal subregion CA1- the "section one of the cornu ammonis", also designated as "Sommer sector". The Sommer sector is set apart by some outstanding characteristics. It plays a crucial role in memory formation and can be considered as the "output area of the hippocampus", because its neurons constitute the main hippocampal efferent pathways.

Due to its anatomical position it is evident that CA1 damage implies an extensive functional disconnection of the hippocampus. CA1 is highly vulnerable to oxidative and metabolic stress, basically because of its specific receptor assembly and blood supply. This vulnerability can be observed in various neurological conditions, inter alia the transient global amnesia (TGA). TGA is one core topic of this work. This enigmatic and rare syndrome serves as a natural lesion model that is well suited to investigate the functional anatomy of the declarative, episodic memory system as well as the hippocampal contribution to procedural memory formation. The subjects mentioned are closely linked to each other at various points. Hence, I have sought to address the interconnection of topics by a comprehensive introduction. Thereby, the separation of the single manuscripts recedes into the background for the benefit of a more clearly arranged theoretical substructure.

However, in the last part I gave particular attention to the individual manuscripts and their results, so the three principal parts of this work can also be read as separate sections. I will start with some significant ideas regarding the nature of memory throughout history. These ancient ideas remind us of how long the path to our current level of knowledge has been, how many detailed insights were gained over time and they foreshadow the true dimension of the depth in which this phenomenon has to be dealt with.

PART 1

1.1 Considerations about the Nature of Memory - a Short Historical Overview

Already in the ancient world keen thinkers wondered about the functionality of memory. In that age it was common practice to hold information by carving letters into a tablet with a surface of wax. By employing this method, information is preserved until the waxen surface is brought to level and becomes irretrievably extinguished. Over the centuries, these ancient writing methods were used as a metaphor of memory as a waxen tablet. Plato assumed that the human mind has similar properties. He thought that all things that leave an imprint in our mind can be memorized. If these contents were deleted or not even imprinted, we would forget the fact that we were ever confronted with them (Apelt, 2004). Interestingly, he did not imagine the mind as a "tabula rasa", comparable to an empty jar, but instead as a previously imprinted template. This template includes "world- knowledge" which had already possessed a particular structure before the physical body was materialized.

According to the wax-metaphor, Plato considered memory as static in nature: "mental imprints" remain in their shape and if they are erased, they disappear completely. Furthermore, old memories do not differ in quality from more recent ones. Etymologically, the term "impression" is rooted in ancient inscription techniques and means in the literal interpretation "to press/ scratch into". Therefore, even nowadays in our modern linguistic usage the idea of the mind as a waxen tablet still exists.

The most popular disciple of Plato, Aristotle, made further considerations on the nature of memory in his treatise "De memoria et reminiscentia" (Bloch, 2007). He regarded objects as truths coming into the mind via sensory impressions that will be transformed into images in one´s memory. These images can be stored and deliberately retrieved. They exist as a "sensory vestige" in the human mind. According to Aristotle's perspective, memory can be interpreted as graded in quantity, i.e. sensory perceptions can leave a stronger or weaker imprint in the human mind. Aristotle writes of a "physical starting point" that is required for retrieval. It requires an effort to recover a certain memory by paving the way through contents of memory by means of ordered associations. His assumption can be considered as an ancient model of information retrieval mechanisms. He postulated that the processes of thinking as well as remembering rely exclusively on physical matter and therefore he can be regarded as a representative of the materialistic theory. Nowadays, this theory is still valid. However, it must

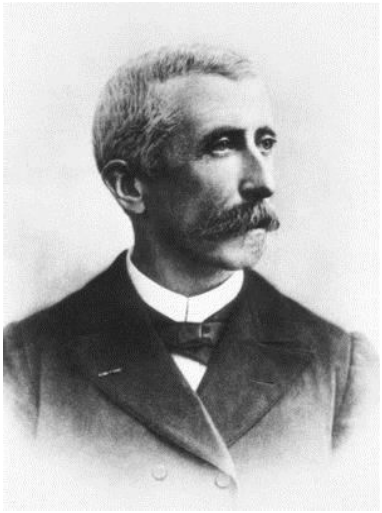
not be forgotten that Aristotle, like most of his contemporaries, thought that the human soul resides not in the brain but in the heart.

Plato's and Aristotle's ideas of memory also inspired the stoic teachings. The stoics compared memory to a waxen tablet as well. Augustine, a Latin Doctor of the Church in the late antique period postulated the co-existence of several memory systems, among others an emotional and an intellectual type of memory (Zimmermann, 1988). More than thousand years passed until Augustine's hypothesis could be supported in essence by modern empirical investigations.

The wax-metaphor was employed until the dawn of the philosophy of the middle ages. Thomas Aquinas, one of the most popular philosophers and theologians of his time, shared Aristotle's view of memory as a "tabula rasa". He distinguished between different types of memory (similarly to Augustine), but he applied other differentiation criteria. Thomas Aquinas postulated an implicit "basic memory- system", inherent in all higher animals and therefore also in humans, called "memoria". Memoria designates the "pure imprint", a reactivation of sensory stimuli without conscious reflection. In contrast to *memoria, reminiscentia* refers to the reasoned capability of memory, which is based on the rules of syllogistic conclusions (Tellkamp, 1999). This ability is a unique quality of human beings. Only humans are able to memorize experiences, feelings or objects through an aware and partially self-controlled recollection. They are capable of employing the intellect to reconstruct the past in the light of current, rational insights. Thomas Aquinas terms this exclusively human ability as "inquisition". His considerations allow an interesting conclusion regarding the nature of memory: if a memory trace is interpreted against the backdrop of current intellectual considerations it becomes deformed and no longer persists in its original configuration. It is "intellectually contaminated". Nowadays we would say that this specific feature is a property of mental categorization in the human mind (Zelinsky- Wibbelt, 2000).

Thomas Aquinas assumed a further quality of human memory organization: an object which is perceived is stored without individually characteristic features, but in universal forms that can also be applied to other entities which stem from the same category. This presumption includes further qualities of memory: Conversely, a perception of an object leads to recognition by matching stored universal schemes (today we would probably use the term "prototypes"). According to this point of view, memory works on the basis of interpolation, categorizing objects as either "typical" or "not typical". Therefore, memory operates by constructing as well as reconstructing, which is a central characteristic of the "semantic memory". Consequently, there must be a process occurring before, during which certain (irrelevant) information is filtered out on a subjective base. This is an active mechanism resulting in a subjective individual

memory representation. In current neuroscience, hardly anyone doubts the correctness of this theory. It contrasts Aristotle's assumption of a passive storage and memory representation as a fading sensory vestige.



In 1881 the French scientist Theodule Ribot described regular memory loss as a result of normal aging processes or brain damages, respectively: he emphasized that memory loss follows a gradient that is characterized by instability of more recent memories and stability of older memories. Therefore, the latter are more resistant to detrimental influences. This phenomenon was termed as Ribot´s law. Ribot knew that this gradient derives from related neuroanatomical processes, but in his time there were no methods available to investigate them (Ribot, 1881).

Fig.2 Theodule Ribot, retrieved January 10, 2015 from http://ebook.lib.sjtu.edu.cn/iupsys/Hist/HBch03.htm), public domain

Many of these ideas occupy us until now. How does memory work? What structures contribute to memory formation? What are the underlying mechanisms of the remote memory gradient as described by Ribot?

1.2 Memory Systems

Examined in detail, memory is a highly heterogeneous concept and various theories of memory coexist. Three different established approaches will be described in the following section, which classify memory in various dimensions: time-based, content-based and process-based. The reader will recognize some approaches that have been formulated by the ancient thinkers mentioned above. These modern theories are well suited for a description of a complex of issues that will be raised in this work.

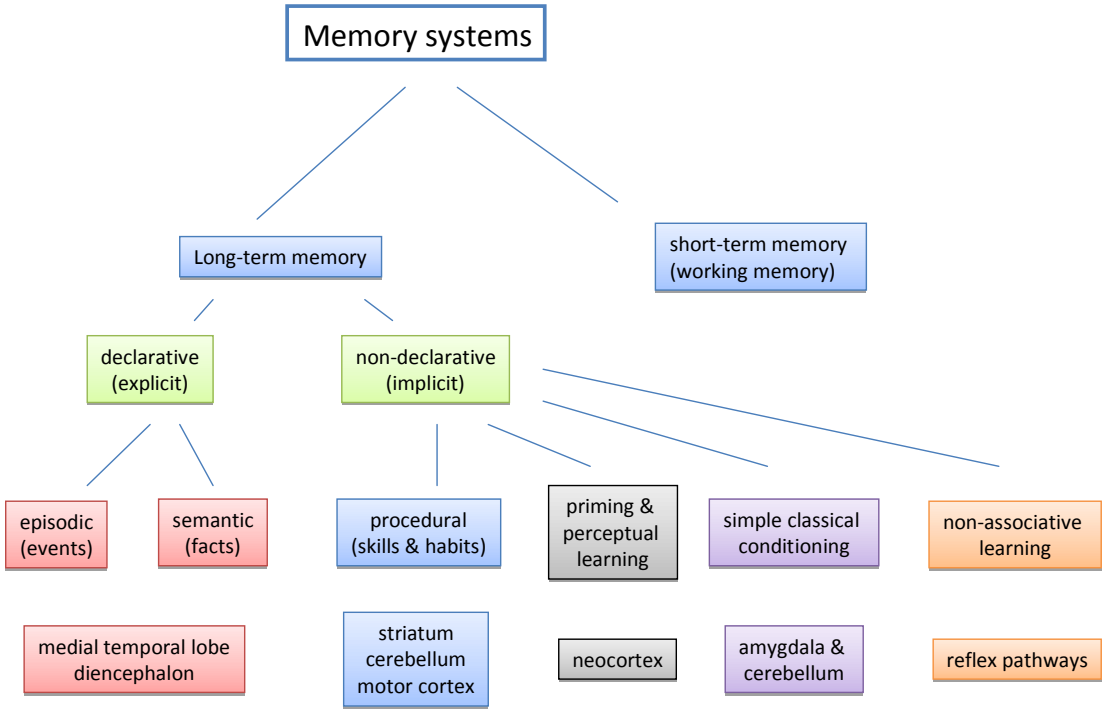


Fig. 3 Memory systems including the time-based as well as the content- based approach and associated brain structures (Image courtesy of Prof. Thorsten Bartsch, Dept. of Neurology, University of Kiel)

1.2.1 The Time-based Approach

The time-based classification includes three memory-dimensions. Sensory memory contains pure sensory perceptions. It can be understood as an internal reverberation or an echo of sensory stimuli that are perceived for milliseconds. In 1960 Sperling found evidence for a very high storage capacity of the sensory memory. At this preconscious level, the incoming stimuli are processed and categorized according to their relevant properties (rewarding, dangerous etc.), but no comparison to contents stored in long-term memory takes place. Preconscious selective attention-mechanisms are stimulated in order to extract relevant features. Disregarded information decays while the remaining information is transferred to the short-term memory (STM).

STM is defined as a repository for information lasting seconds up to a few minutes: the material is reshaped and encrypted in temporal and local sequences or semantic relations. Its capacity is limited to 7± 2 units of meaning (=chunks). Long-term memory (LTM), however, refers to the stable storage system of the brain. The LTM has a theoretically unlimited capacity ranging from about 30 minutes up to an individual´s entire life span. Material in the STM which is identified as sufficiently important is stored in the LTM. William James was the first philosopher and psychologist who made a distinction between STM and LTM, though he used the terms “primary memory” and “secondary memory” (James, 1890).

1.2.2 The Process-based Approach

Memory is composed of three main-processes: encoding, consolidation and retrieval. As described above, the incoming information is already filtered on the level of sensory perception according to relevance and novelty. This classification is controlled by prior experience and genetic behavioral disposition, leading to an appraisal of the affective valence and resulting in attention-focusing. It takes places within fractions of a second in the sensory memory. The selected information is maintained in the STM and part of it is embedded in the existing cognitive structure (encoding). By forming associations, deep elaboration is enabled which leads to long term storage. Initially, the new memory trace is fragile. It is converted into a more stable state through consolidation. This strengthening of the memory trace is supported by

sleep. Retrieval requires a transient transfer from LTM to the working memory where it is reprocessed and restored.

The attentive reader has probably recognized that the time- and the process-based approach are closely linked to each other: the mentioned processes are equivalent to transitions between the time-based classifications of memory.

1.2.3 The Content-based Approach

The content-based approach distinguishes two main categories of memory: the declarative (explicit) and the non-declarative (implicit) memory system. The declarative memory system contains learned information that can be verbally described (=declared) and is accessible to conscious awareness. It is bisected into the episodic and the semantic memory system.

1.2.3.1 Episodic Memory

Episodic memory (Tulving, 1972) enables us to vividly recollect situations that we experienced in the past. During this mental recollection we can actually locate ourselves in time and space. For example, when we remember an exciting journey, it is easy to reconstruct the temporal order of significant incidences, our personal emotions in certain situations and other important circumstances. The episodic memory system in the described form seems to be unique to human beings and constitutes the base of our identity. In that context two related terms are to be mentioned: autonoesis corresponds to the neurocognitive ability to experience the self as a continuous entity within a succession of subjective episodes (Tulving, 2005). This concept comprises both imagining the future and recalling the past. For the imagination of future events the term “prospective memory” was introduced. As a part of autonoesis, it is also based on episodic memory functioning. The autobiographical memory system is often used as a synonym for episodic memory, but some authors interpret it in a broader sense, comprising episodic and semantic contents within the subjective past.

1.2.3.2 Semantic Memory

Semantic memory, however, encompasses one’s general knowledge about the world. Usually, we do not remember when and where these facts were encoded. This concept also includes self-experienced events that cannot be vividly recollected, but the individual knows that they took

place (noesis). They exist independently from a temporal and local source of encoding in our mind.

Therefore, the distinction between episodic and semantic memory can be summarized under remembering personally experienced sequences (in my early childhood uncle G. dipped me into the rain barrel because I hid his shoes) versus knowing facts (billions of years ago there was a primary supercontinent named Pangaea).

1.2.3.3 Implicit Memory

The other big subfield of memory contents is implicit, sometimes termed as "tacit knowledge" (Reber, 1993), which is not accessible to a verbal description. We simply "know" how to swim, cycle or tie our shoes. These examples are learned procedural skills, an important subfield of non-declarative knowledge. Implicit memory is a rather theoretical construct like an overarching category because it encompasses highly heterogeneous types of memory, fulfilling a great number of functions. Some of them are phylogenetically quite old and simple such as habituation (an individual is repeatedly exposed to a stimulus, which proves to be negligible. The reaction to it weakens in succession or disappears completely). In contrast, sensitization is less specific to a stimulus. If a sudden or harmful stimulus appears, the organism reacts with an increased arousal (also to another stimulus) in general. Habituation and sensitization can be even found in protozoa or primitive metazoa and are termed "non-associative". The associative form of memory refers to conditioning, which can be subdivided into classical (also: Pavlovian) conditioning (an association between two (or more) stimuli is learned by temporal linkage) and operant conditioning (behavior is modified by reward or punishment). Priming is also based on the propagation of associations.

Regarding the three introduced approaches, I will mainly focus on the on the declarative, especially the episodic memory system. What neuroanatomical structures support episodic memory processing? Do the memory systems work independently?

1.3 On the Trail of Episodic Memory

The case study of the famous patient Henry Molaison (H.M.) is an important milestone in memory research (Scoville & Milner, 1957). Because of his epilepsy a bilateral resection of

large parts of his medial temporal lobe (MTL) was conducted. Though his epileptic seizures were significantly mitigated, a severe anterograde amnesia remained: he was unable to store episodic contents for longer than a few minutes. Episodic memories that were encoded before

the surgery could be retrieved easily. His condition suggested that the medial temporal lobe is an essential component in encoding new episodic memories. Furthermore, H.M.'s case offered even more insights into the neurobiological base of memory. His performance in implicit learning tasks was comparable to healthy controls. This dissociation underpins the existence of different memory systems and the temporal lobe being essential for just one kind of them. It was an initial anatomical indication of dissociated memory systems as Thomas Aquinas postulated. The rapid decay of information suggested a second (transient) storage mechanism that is independent from the medial temporal lobe system, concerning the substrate of the STM (Pritzel et al., 2003). Today it is assumed that the underlying mechanisms of STM processing depend on temporary changes of the synaptic efficiency (will be specified in the section "synaptic consolidation").

H.M.'s example was followed by the examination of other patients who suffered from damage to medial temporal lobe structures. There is a broad spectrum of clinical conditions causing amnesia, which elucidated the role of the MTL-system and especially the hippocampus in learning and (declarative) memory. In this respect the transient global amnesia is particularly well suited to study this topic because of its focal confinement and complete remission.

Further evidence of the hippocampal contribution to episodic memory stems from lesion studies in animals. The lesion approach is a common method to draw conclusions from damaged tissue to its physiological function, but it is important to keep a general theoretical consideration in mind: functional deficits can also affect more distant brain areas. Von Monakow referred to this phenomenon as "diaschisis": a sudden loss of function of a brain area that is located outside the originally injured tissue (Finger, Koehler, & Jagella, 2004).

The establishment of modern imaging- methods provided more fine-grained insights into our understanding of the organization of memory processing. In short, in the last decades a great number of converging evidence disclosed the important role of the medial temporal lobe and particularly the hippocampus in declarative memory.

1.3.1 Functional Anatomy of Episodic Memory

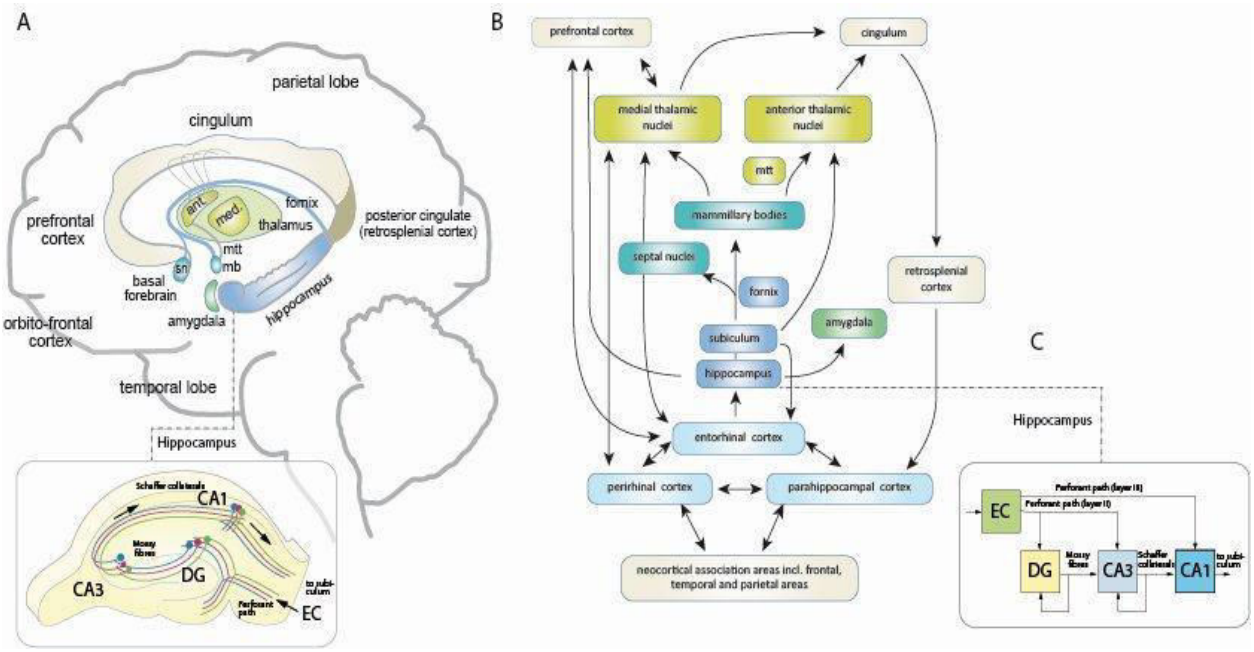


Fig. 4 A Schematic representation of brainstructures engaged in declarative memory processing and the hippocampal trisynaptic circuit

Fig. 4 B Information flow of declarative memory processing (Image courtesy of Prof. Thorsten Bartsch, Dept. of Neurology, University of Kiel)

1.3.1.1. The Temporal Lobe

At the beginning of information processing and storage stands the mere sensory perception that projects via thalamus into primary sensory areas. The information flow passes from there to unimodal and polymodal associative areas and is thus distributed over the cortex from which it is transferred to neocortical structures surrounding the hippocampus within the medial temporal lobe. The temporal lobe is one of the four lobes of the cerebrum and contains - beside relevant memory structures – the primary auditory cortex and the Wernicke area. The medial temporal lobe incorporates the hippocampus, the entorhinal cortex, the perirhinal cortex as well as the parahippocampal cortex. These heterogeneous subregions make different contributions to declarative memory (Ranganath, 2010).

The perirhinal cortex receives topographically organized projections from associative areas of the neocortex. The processed information is transferred mainly to the lateral entorhinal area, which is considered as the main interface between the hippocampus and other areas (Martina, Royer, & Pare, 2001). The associative areas interconnect primary unimodal cortical areas of the brain (therefore “non- specific”) and generate integrated representations about the quality of an object. The parahippocampal cortex, however, receives input from areas, which process polymodal spatial information, and projects to the medial entorhinal area (Eichenbaum,

Yonelinas, & Ranganath, 2007). Between the subareas of the medial temporal lobe, the perirhinal, parahippocampal as well as the entorhinal cortices there are few interconnections.
The essential part of information flow converges in the hippocampus, at the top of the processing hierarchy within the MTL. Examined on the basis of anatomy, it can be concluded that the hippocampus combines and extends functions arising from structures which project to it. The information about the quality and location of an object is assembled in the hippocampus and, accordingly, a broader context of the memory content is generated. The anatomy and pivotal role of the hippocampus in declarative memory processing will be the subject of the next section. For the sake of completeness, I will previously give a short insight into the integral role of the prefrontal cortex (PFC) and the amygdala in the formation of episodic memory.

1.3.1.2. The Prefrontal Cortex

The functions of the prefrontal cortex are highly diversified and some of them play an important role in episodic memory processing: The PFC is responsible for the interaction of emotions and for self-referenced and metacognitive processes (Bechara, Damasio, & Damasio, 2000). Some authors attribute PFC functions to certain temporal aspects of memory (McAndrews & Milner, 1991), personality (Berlin, Rolls, & Kischka, 2004), social cognition (Amodio & Frith, 2006) and empathy (Vogeley et al., 2001).
These functions are suspected to modulate episodic memories. A study conducted by Piolino et al. (2007) indicates a prefrontal involvement in the amount of memorized details. Furthermore, the PFC-amygdala connection plays an important role in episodic memory processing.

1.3.1.3. The Amygdala

The amygdala is a group of nuclei within the medial temporal lobe. As a part of the limbic system (like the hippocampus) it is involved in the interconnection of emotion and memory. The amygdaloid activity is particularly enhanced in memories that contain a high level of affective valence (Buchanan, Tranel, & Adolphs, 2005), especially in negative contents. McGaugh et al. (2002) concluded that the amygdala plays a pivotal role in the consolidation of personally significant long-term memories.

1.4 The Hippocampus- Anatomy and Nomenclature

The first written conveyed description stems from the Venetian anatomist Julius Caesar Aranzi who, in 1587, coined the Latin term “hippocampus” for a structure in the medial temporal lobe because of its superficial similarity to a seahorse. In the 18th century, the Parisian surgeon de Garengeot introduced the designation “cornu ammonis”, meaning “horn of Amun” (an ancient Egyptian deity).

The hippocampus as a part of the limbic system is symmetrically paired and one of the phylogenetically oldest structures within the telencephalon. It is the biggest part of the archicortex, that is itself a part of the allocortex. Embedded in the gyrus parahippocampalis, its anterior section borders on the amygdala and extends arc-shaped along the lateral ventricle to the corpus callosum. The hippocampus is constructed in three layers: a principle layer in the middle, embedded between two cell-sparse layers. Along the anterior-posterior axis it is divided into “head”, “body” and “tail” (Trepel, 2012).

The hippocampus proper is composed of the cornu ammonis and the gyrus dentatus (also: fascia dentata). In 1934 Lorente de Nó divided the cornu ammonis into four sections CA1-CA4.

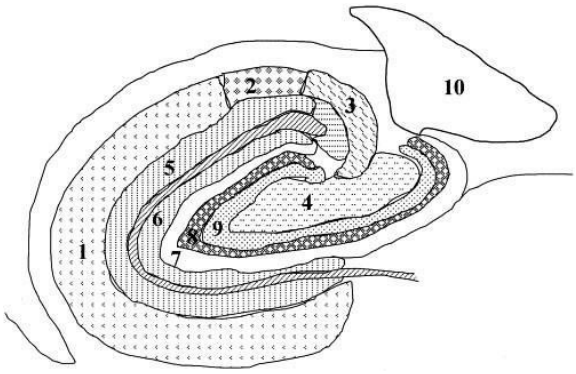


Fig. 5 the human hippocampus in coronal section. Number 1-4 correspond to CA1- CA4. From: Klimek et al. (1999)

This classification is based on morphological aspects- the CA1 region ("Sommer sector") is characterized by small, loosely packed pyramidal neurons, while the pyramidal neurons in the adjacent CA2 region have bigger nuclei and are more densely packed. CA3 and CA4 in contrast possess more loosely packed pyramidal neurons. The CA4 region is adjacent to the gyrus dentatus which represents the entrance to the hippocampus. It is a special area because of the life-long generation of new neurons (adult neurogenesis). The neurotransmission of the pyramidal cell layer is glutamatergic. There are various interneurons in the hippocampus proper for the regulation of local circuits that use GABA as a fast inhibitory neurotransmitter.
The hippocampal formation comprises the CA fields of the hippocampus, the gyrus dentatus, subiculum and the entorhinal cortex. Together with the adjacent perirhinal and parahippocampal cortices, the hippocampal formation encompasses the major components of the medial temporal lobe memory system.

1.5 Flow of Information within the Hippocampus: the Trisynaptic Circuit

The signal-transmission within the hippocampus is described under the concept of the "trisynaptic circuit" (Squire and Kandel, 2009), because the largest part of incoming signals is forwarded within a circuit of three glutamatergic synapses (see figure 4A).

The main afferences of the hippocampus originate in the entorhinal cortex, the starting point of a sequential signal transmission. Neurons from the entorhinal cortex project to the basket cells of the gyrus dentatus via the tractus perforans. From the gyrus dentatus the signal is transferred to the CA3 region by the mossy fibre synapses. Third, the Schaffer-collaterals of the pyramidal cells of CA3 project into the CA1 region. From there the information is transferred into the subiculum that completes the circle through projections to the entorhinal cortex.

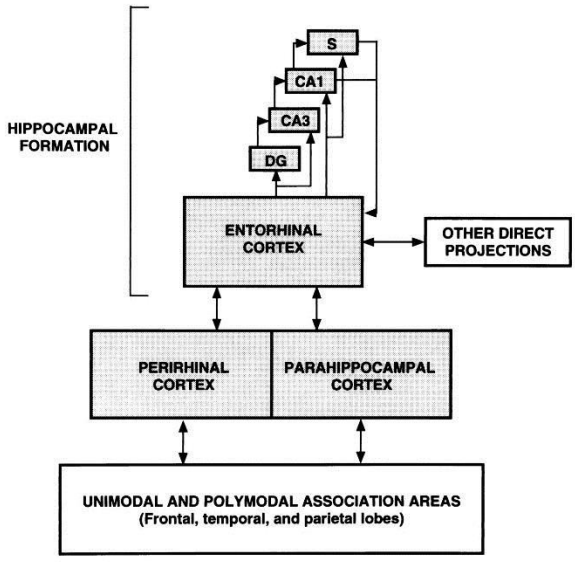


Fig. 6 Projections of the hippocampus retrieved January 15, 2015 from http://www.pnas.org/content/93/24/13515/F7.large.jpg

The trisynaptic circuit is a common, simplifying concept. In fact, there is a second path which directly connects the entorhinal cortex to the CA1 region (temporoammonic pathway). Scharfman (2007) points out that the area CA3 also receives direct input from various parts of the brain and can therefore be regarded as a second point of entry for hippocampal processing. Further, both hippocampi are closely linked by their commissure, suggesting a translateral information exchange. In addition to this, there are complex intrinsic circuitries and backprojections within the hippocampal subregions (Amaral & Lavenex, 2007). This is a decisive characteristic of an autoassociative system.

1.6 Vulnerability of the Hippocampus

The hippocampus and particularly the CA1 region is highly sensitive to oxidative and metabolic stress. This vulnerability can lead to a transient or permanent functional impairment or even deficiency of the hippocampus. Various properties including the composition of receptors, the vascular anatomy and psychological stress and arousal were identified as important causes of its high susceptibility.

Unlike CA3 and CA4 neurons, the CA1 neurons predominantly possess NMDA receptors, leading to a higher susceptibility to elevated glutamate concentrations. Therefore, the calcium level in CA1 is more increased than in the other sub-regions. If oxidative stress occurs, the neurotransmitter glutamate is released in a high concentration and elicits an overcharged calcium influx into the postsynaptic pyramidal cell which may cause detrimental effects on the cytoskeleton, dysregulation of electron transport of the mitochondrial membrane and subsequently a down regulation of adenosine triphosphate (ATP) synthesis (Ermak & Davies, 2002). ATP is required for the intracellular transport of chemical energy for cell metabolism. Moreover, it is a substrate in signal transduction pathways for the synthesis of the second messenger molecule cyclic AMP. The described process may elicit the programmed cell death (apoptosis), which takes place within a few days and can be detected by MRI.
A further reason for the CA1 vulnerability is the vascular anatomy. The blood supply in this area is especially endangered, because CA1 is located at the end of the capillary current. This phenomenon is called “last meadow”: in the entire affected area, the blood flow is reduced, but this effect is less pronounced in the “watershed areas”. The end of the current, the last meadow, receives the least amount of blood (Leestma, 2009).

The last category of causes refers to the influence of stress and emotional arousal. They are a clear example for the close relationship between psychological and physical processes:

receptors of stress- related hormones (glucocorticoids) are most frequently located in the hippocampus and the amygdala. In these areas episodic memory and emotions converge and are synchronised to an affective appraisal. If the subject experiences an external stressful event (stressor), an adaptive stress reaction will occur that is expressed on the psychological, physiological and behavioral level (Gadek-Michalska, Spyrka, Rachwalska, Tadeusz, & Bugajski, 2013). A release of hormones of the hypothalamo- pituitary- adrenal (HPA) axis, catecholamines and cytokines prepares the organism for an adequate short-term stress reaction. While mild stress improves hippocampal functioning, prolonged exposition to major psychological stress can elicit detriments, such as a reduction of hippocampal volume (Warner-Schmidt & Duman, 2006) and a disturbance concerning the balance of systems involved in the regulation of the stress response (*allostatic overload*) (McEwen & Seeman, 1999). Furthermore, subtle effects can occur with regard to a decrease in synaptic plasticity and deterioration of declarative memory. Here again, the CA1 region is particularly affected, as rodent studies show (Krugers, Goltstein, van der Linden, & Joels, 2006). Beyond hippocampal affection, adverse health effects such as a weakening of the immune system, slower wound healing and reduced muscle strength can be the consequence of stress exposure. In our own study we investigated the influence of psychological stress and stress- related factors on the etiology of transient global amnesia. Therefore, the next section is dedicated to this issue in general.

All above mentioned aspects of hippocampal, respectively CA1 vulnerability have a genetic component. Genetic conditions lead to individual properties of vessels, receptor density, hormone levels, rates of protein synthesis and other relevant qualities. In addition, experience influences the modifications of appraisal of the environment as well as hormone production and other factors.

Therefore, the increased susceptibility of the hippocampus and its CA1 region is based on a complex network of causes, which are reflected in various neurological conditions such as ischemia, postictal conditions, limbic encephalitis and transient global amnesia.

The majority of our research relies on the examination of TGA patients. It is a short-lasting and benign syndrome that almost exclusively affects persons in their late adulthood. Its etiopathogenesis is cryptic, but its functional correlate, punctuate lesions confined to the Sommer sector of the cornu ammonis, has recently been identified by high-resolution MRI. The lesions are supposed to produce a transient functional disconnection of the hippocampus. Therefore, TGA is a well suited natural lesion model which allows insights into the functional

anatomy of memory systems, especially the declarative memory system and the specific role of CA1 neurons in memory processing.

1.6.1 Psychological Stress and Stress-related Factors

Stress is categorized in (positive) eustress, which is related to processes of personal growth, learning and experience, leading to feelings of satisfaction, whereas (negative) distress is caused by mentally straining situations such as personally important life events or a cumulation of daily hassles. Beside objective, stress- inducing circumstances the according appraisal of the situation is required to elicit a stress reaction. This concept was formulated under the term "transactional model of stress" (Lazarus and Launier, 1981) and refers to a transactional process which is initiated by an interplay between environmental and internal requirements demanding an accomplishment (coping). Coping-strategies are manifold and vary in dependence of person and situation variables. Emotionally centred coping represents an intra-psychic examination with the objective of reducing the perceived thread. Problem- oriented coping comprises two options: facing the requirements and changing the situation or evasion. From an evolutionary perspective it is the preparation for a fight or flight reaction, which is mediated by the autonomic nervous system. Hence, stress is an essential psychological and physiological function of an organism for the purpose of handling threatening situations.

In this regard a biological concept of stress, the "general adaptation syndrome" was published by Selye (1976). He describes a physical, unspecific adaptation reaction to environmental pressure which elicits a disturbance of body homeostasis. This physiological reaction is three-fold and starts with the alarm phase causing a mobilisation of energy reserves, followed by the resistance phase. During the resistance phase the adaptation takes place by increasing the resilience against recurrent chronic stress. The exhaustion phase is characterised by regenerative processes. If this last phase does not suffice because of long-lasting stress a negative shift of the homeostasis can occur and lead to physical diseases and mental problems such as depression and anxiety.

Can TGA be caused by stress and related factors? What influence do stress-related factors have?

1.7 Declarative Memory Consolidation

Having dealt with pathological aspects I will dedicate the next section to the physiology of hippocampal functioning. After encoding, several alterations on the molecular, cellular and systems-level emerge. These unconscious and self-regulated processes are subsumed under

the term “memory consolidation” and result in a stabilization and enhancement of memory traces. Thereby an optimally integrated and long-lasting representation is created, which is resistant to interference (Stickgold, 2005). The fast mechanism of consolidation is denoted by the term “synaptic consolidation”. After passing the hippocampus, incoming information is distributed to an extensive neocortical network, representing the final long-term storage. This systems consolidation follows the synaptic consolidation and refers to a process extending over a longer period (Diekelmann & Born, 2010), which results in a gradual integration of memories into the already existing knowledge system within the neocortex.

1.7.1 Synaptic Consolidation

In the 1970s, Bliss and Lomo discovered a basic mechanism of memory processing that became generally known as “long-term potentiation, LTP” (Bliss & Lomo, 1973). They conducted an experiment in which they wanted to find out whether the synapses between hippocampal neurons possess the ability to store information. A hippocampal nerve pathway in rabbits was stimulated by a short sequence of high- frequency pulses. This stimulation strengthened the synaptic transmission for hours by repeating this procedure for days or even weeks.

LTP emerges at all synapses of the trisynaptic circuit (tractus perforans, mossy fibre synapses and Schaffer- collaterals) and is characterized by a rapid modification of the synaptic connection and long-term maintenance. At least two different mechanisms underlie the induction of LTP, coined as an associative and a non-associative type. I will now describe LTP using the example of Schaffer- collaterals, the pyramidal cells that originate in the CA3 region and project to CA1. A prerequisite for the induction of LTP is a sufficiently strong signal generated at the postsynaptic cell. Therefore, this type is named “associative”: coincident activity in the pre- and postsynaptic neuron is required to induce LTP. The incoming signal evokes a complex molecular cascade: through a transient alteration of membrane properties calcium streams into the pre-synapses and causes a release of the neurotransmitter glutamate into the synaptic gap that binds to two types of ionotropic receptors. One of them, the N-methyl-D-aspartate receptor is usually blocked by magnesium ions, which can be driven out by a sufficiently strong signal. Subsequently, calcium streams into the postsynaptic cell and temporarily changes its electrophysiological properties. Against the background of the time-based memory approach, this process reflects functional correlates of short-term memory. Conversely, a further, very similar mechanism exists: Long-term depression (LTD) induces a weakening of synaptic transmission. Initially, LTD was interpreted as a “reversed LTP”, but nowadays it is considered as yet another form of plasticity that is also necessary for memory

performance (Squire & Kandel, 2009). In summary, the synaptic consolidation is a temporary storage mechanism and does not require any changes on the anatomical level. The transition from short-term to long-term memory (consolidation) implies a qualitative switch:

1.7.2 Systems Consolidation

Already in the late 19th century, William James speculated about the existence of different qualitative memory systems, which change from a short-term and fragile into a long-term, robust state. The observation of retrograde amnesia resulting from head injuries had provided an indication for processes which were discovered decades later. Unlike synaptic consolidation, the transition to the permanent state requires the synthesis of new proteins (Squire & Kandel, 2009). The formation of proteins in turn, requires an alteration in the expression of specific genes. The expression rate in a cell is altered due to current demands: Frequent release of a neurotransmitter activates specific regulatory protein molecules, which are able to switch genes on and off ("transcriptional control"). Specific DNA-sequences at the beginning of a gene are capable of binding the regulatory protein molecules: the activators increase the gene transcription while the repressors decrease it. This connection is not permanent. Mediated by second messenger systems, a steady state equilibrium is reached.

In a second step, modifications of the neuronal architecture emerge. Therefore, a switch from functional to structural memory types takes place at the interface from short-term to long-term memory. Structural modifications concern both, the pre- and the post- synaptic neurons. Frequent discharges in the pre-synaptic neuron can lead to successive charges of previously empty synapses, formation of new synapses or even a degeneration of existing synapses. Modifications of the post- synaptic counterpart comprise growth or reduction of the according dendrites. These cytoarchitectonic modifications are supposed to be the basis of long term memory stability. Thus, during learning and consolidation processes, functional and structural changes occur on the neuronal level.

During an individual's waking hours, the hippocampus binds converging information from neocortical areas. While sleeping, a reactivation of the newly encoded memory trace occurs and thus generates a gradual strengthening and redistribution from the hippocampus into neocortical networks (Rasch & Born, 2013). Subsequently, the neocortical networks retroactively project information to the hippocampus. Buzaki et al. (1996) hence coined the term "hippocampal-neocortical dialogue". The exact underlying processes and the timeframe of hippocampal involvement in episodic memory were formulated in the standard model of memory consolidation (SMC) and the multiple trace theory (MTT).

1.7.3 The Role of Sleep in Memory Consolidation

In the late 19th century Ebbinghaus (1885) observed that senseless syllables were better remembered after a period of sleep. This effect was reinforced with increasing length of sleep. But the underlying mechanisms that contribute to sleep-dependent memory consolidation were elucidated much later by evidence from behavioural, physiological, cellular and molecular studies (Walker & Stickgold, 2004). Sleep consists of different sleep stages that alternate in multiple cyclic sequences. The sleep stages are characterized by typical EEG- features and are assumed to contribute to memory consolidation in different ways. In 1971, Yaroush et al. observed a major contribution to declarative memory consolidation in the first half of the night (Yaroush, Sullivan, & Ekstrand, 1971). This time frame is known to be naturally rich in slow wave sleep, leading to the assumption of this sleep phase playing a crucial role for memory consolidation. Further support stems from Plihal and Born (1999), who extended this paradigm. They observed that selective deprivation of slow wave sleep impairs declarative memory consolidation, while a selective deprivation of REM-sleep impairs procedural memory consolidation. This observation and further converging evidence lead to the assumption that REM sleep facilitates procedural memory consolidation whereas non-REM sleep facilitates declarative memory consolidation ("dual process hypothesis"). Nowadays, the dual process hypothesis as a simplified model is still valid, but procedural and declarative memory processing do not seem to be entirely independent.

But what exact mechanisms promote memory consolidation during sleep? Supposedly, in the sleeping brain a covert reactivation of the same neural excitation patterns takes place, which were activated during encoding. This reactivation (co-)occurs selectively in the hippocampus as well as in the neocortex, suggesting a gradual transfer of declarative memory traces from a rather conscious to an automated, semantic state. Slow waves and sleep spindles as specific sleep- associated features are linked to the extent of memory consolidation. Sleep-spindles are generated in the thalamus and spread widely over the neocortex, whereas slow oscillations derive from neocortical structures. They are characterized by a depolarizing up phase (intense neuronal firing) followed by a hyperpolarizing down phase (neuronal silence). The transitions from down to up phases impact sleep- spindles as well as hippocampal sharp wave ripples via efferent pathways.

Combined with electrophysiological specifics, the cholinergic tone plays a crucial role in sleep-associated memory consolidation. Especially during slow wave sleep the concentration of acetylcholine, which is deemed to be a key regulator of hippocampal neuronal activity, reaches its minimum. The model of cholinergic memory consolidation (Hasselmo, 2006) postulates a facilitation of encoding in the hippocampus during wakefulness by an elevated cholinergic tone. During slow wave sleep the diminished cholinergic activity enables hippocampal reactivations of previously encoded memory traces. These findings reveal some fundamental mechanisms explaining the functionality of consolidation, but why is sleep an essential condition? Some authors suppose that sleep is needful for these processes because of the absence of encoding and therefore interference. Tononi and Cirelli (2006) postulated synaptic potentiation during daytime and synaptic downscaling during sleep, leading to an enhancement of the signal-to-noise-ratio and recreation of the synaptic homeostasis.

Does sleep temporarily modulate the connectivity of the declarative and the procedural memory system?

1.8 Two Models of Episodic Memory Consolidation:
Standard Model of Memory Consolidation vs. Multiple Trace Theory

Following the specifications concerning long-term memory consolidation, I will now explicate theoretical assumptions about the nature of hippocampal contribution to autobiographical memories. It concerns the question if the medial temporal lobe is permanently or only temporarily involved in the retrieval of autobiographical memories.

In the early seventies Marr identified the hippocampus as a temporary buffer that encodes daily events that are recapitulated during sleep and transferred into neocortical areas as described above (Marr, 1971). The standard consolidation model is based on this assumption. Squire (1995) supposes that the hippocampal function is time- dependent and therefore less involved in older episodic memories. At the beginning of the consolidation process, the hippocampus plays a major role which can take months or even decades. Subsequently, neocortical structures resume the retrieval of memory traces and the hippocampus is no longer needed. Thus, the standard consolidation model predicts that hippocampal lesions lead to a time- graded retrograde amnesia in sense of Ribot.

In contrast to the standard consolidation model, the multiple trace theory postulates a persistent involvement of the hippocampus in the retrieval of remote memories as well (Nadel & Moscovitch, 1997). Just as the SCM, the MTT also suggests a gradual transfer from the hippocampus to the neocortex during sleep. Every retrieval leads to the creation of multiple

traces in the hippocampus which are thus linked to cortical networks. This assumption is an indication of the difference between the SCM and the MTT: the SCM in contrast localizes this reorganization within neocortical networks and not in the hippocampus. However, the authors propose a stronger involvement of episodic than semantic memories in the MTL, namely that the hippocampal complex participates permanently in the retrieval of episodic memories, while semantic memories will become entirely independent from the hippocampus if enough time is passed by. The extent of the hippocampal damage determines the retrieval deficits. Correspondingly, small lesions produce deficits in more recent episodic memories while older memories are more resistant because of the higher number of related traces.

1.8.1 Excursus: CA1 Neurons in the Human Hippocampus are Critical for Autobiographical Memory, Mental Time Travel and Autonoetic Consciousness

In our own research project we also made a contribution to the issues mentioned above. Is the hippocampus persistently involved in the storage and recall of autobiographical memories? In order to assess the time-dependent topography of episodic memory without hippocampal contribution, an autobiographical interview was conducted with TGA patients in the acute state as well as in a follow-up condition and with healthy, age-matched controls. This interview contains systematic questions about personally experienced episodes referring to (i) childhood and youth, (ii) the young adulthood, (iii) adulthood, (iv) the last five years except the last year and (v) the last year. Accordingly, we obtained five values per interview which reflect a quantification of vividness and the amount of details per point of time.

The data revealed a temporally graded retrograde amnesia in acute TGA patients following Ribot´s law with a virtually complete lack of episodic memories regarding the recent past. After the acute TGA state, episodic memory switched back to the base level, as measured in the controls. These results provide an insight into the time-dependent role of the hippocampus, especially the CA1 neurons in episodic memory processing. They show a dynamic interaction in the hippocampal- neocortical connectivity upon retrieval of autobiographical memory. The gradual consolidation extends over years and even decades. During this process the contribution of the hippocampus decreases gradually while the memory trace gets redistributed into neocortical networks as the location of final long-term storage. However, the significant impairment of the

memories relating to one's childhood and youth indicates a hippocampal involvement in episodic memory across the individual's lifespan. This finding contributes to the debate on the competing models of memory consolidation in favour of the multiple trace theory.

1.9 Methods - Testing Declarative Memory

1.9.1 The Rey Auditory Verbal Learning and Recognition Test (RAVLT)

The Rey Auditory Verbal learning and recognition test measures declarative, semantic verbal memory. It consists of a word list that is read out by the investigator five times. After each run the patient has to recall the whole list. Afterwards the investigator reads out a distraction list once that has to be recalled additionally. Immediately, the original list has to be recalled. After that, a mixed list, containing words of the original list, the distraction list and new words are read out. Here, the patient has to detect whether the words are part of the original list or not. Once again, after a 30 minutes delay, the original list has to be recalled freely. Following this procedure, four statistical values are obtained: the sum score, the retention span, delayed recall and recognition. This simple paradigm is highly sensitive to hippocampal impairment: While the STM remains intact, the delayed recall unravels severe deficits in consolidation (anterograde amnesia). The RAVLT is well suited for TGA patients because of its minor scope and simple instruction.

1.9.2 The Rey- Osterrieth Complex Figure Test (ROCF)

The ROCF measures declarative figural memory, more precisely the spatial visual construction and memory. The patients have to copy an abstract geometric figure. Doing this, they encode the figure, without knowing that they have to reconstruct it later (in about 30 minutes). The reconstruction serves as an estimator for the figural memory.

1.10 Procedural Memory – Characteristics

According to the content- based approach, procedural memory is a subsection of non-declarative, implicit memory. It contains the unconscious memory of various motor skills that can be applied automatically. Motor skill is a collective term that encompasses fine- tuned finger movement sequences (playing an instrument), movement synergies that enable the organism to behave appropriately in its environment (handling of fragile objects) and activities that require proper hand- eye coordination (painting a picture) to name a few examples. They

can be divided into different classes: motor sequence learning (the former) and motor adaptation (the latter two). Usually, motor skill acquisition takes place through repetition and practice. In comparison to declarative memory encoding, procedural memory encoding is slower and more rigid (Mishkin et al. 1984). During the initial learning phase, attention and conscious processing are necessary. This stage is characterized by a significant improvement of the performance. With increasing practice, the improvement continues to a lesser extent and the acquired skills shift into an unconscious, automated state. Between these stages an offline consolidation phase has been proposed that is reflected in a skill increase by a mere passing of time without further practice (Robertson, Pascual-Leone, & Miall, 2004). Commonly, the learning progress is measured by a reduction of reaction time and errors. A prevalent motor sequence learning paradigm for measuring a typical motor performance is the sequential finger tapping motor task.

1.11 Procedural Memory: Anatomical and Physiological Basis

Like declarative memory, procedural memory relies on large-scale circuits, including the cerebellum, basal ganglia and cortical regions of the frontal lobe. Based on animal and human studies, two distinct, but interconnected circuits have been identified that provide the acquisition and/ or retention of motor skills: a cortico- striato- thalamo- cortical loop and a cortico- cerebello- thalamo- cortical loop (Doyon, Penhune, & Ungerleider, 2003). Hikosaka, Rand, Miyachi, and Miyashita (1995) assume that both circuit loops acquire the same sequence simultaneously in different coordinates and speed. They require different states of attention and awareness and they differ in robustness.

Imaging studies provide insights into brain areas involved in motor skill learning. The specific time course of activity enables us to draw conclusions about their functional role and connectivity. During encoding, the activation of the premotor cortex, the supplementary motor area (SMA), striatum, cerebellum and parietal regions increases (Dayan & Cohen, 2011). Studies in nonhuman primates indicate an important role of the supplementary motor area in acquiring a new motor sequence (Shima & Tanji, 2000). Neurons of the SMA were shown to be active in conjunction with the presupplementary motor area (preSMA), a cortical region next to the SMA during the initial learning phase. During the late learning phase and after practice a decrease of neuronal activity in the cerebellum, the primary motor cortex and the preSMA was observed, when the motor skill switched into an automated, well learned state (Dayan & Cohen, 2011). The striatum is uniformly active in the fast initial learning phase as well as in the

automated state. This observation suggests a critical role of the striatum both during encoding and in the long-term storage of well learned movement sequences.

Does the Hippocampus participate in motor learning?

1.12 Motor Learning and Hippocampal Involvement

Initially, the hippocampus- and the striatum- based memory systems were deemed to be functionally independent. This assumption was supported with regard to motor skill learning in patients who had an MTL- excision or hippocampal lesions. They showed typical impairments in declarative memory tasks but they were still capable of acquiring motor skills.

However, in the last decade an increasing number of studies concerning the involvement of the MTL in motor skill learning as well has been published (Schendan, Searl, Melrose, & Stern, 2003b). The findings with regard to the nature of hippocampal contribution vary considerably. Several studies have shown that the interaction of both memory systems is competitive in nature during some learning situations, reflected in an enhancement of one memory system to the detriment of the other (Poldrack & Packard, 2003). An indication for this assumption may be that most efferences from entorhinal and hippocampal neurons to the striatum are inhibitory (Finch, Gigg, Tan, & Kosoyan, 1995). Schroeder, Wingard, and Packard (2002) suggest an antagonism of both memory systems. The difficulty in addressing this issue obviously lies in the heterogeneity of research paradigms (operationalization) of both memory concepts: as aforementioned, “motor skill” is a broad category, ranging from simple and primitive movements to complex behaviour, from sequence learning to motor adaptation. Depending on the paradigm, the activity in underlying neuroanatomical structures will be at least differently pronounced. This also applies to declarative memory, albeit to a lesser extent. Finally, one last remark on this point: several behaviour patterns include declarative and procedural parts.

Additionally, the process level has to be taken into account: there is evidence of a dynamic relationship between the hippocampal and the striatal memory system. This is a matter of functional connectivity that varies depending on the processing state: Albouy et al. (2008) suggest a switch from competitive interaction during the encoding phase to a cooperative interaction during consolidation at night. Brown and Robertson (2007) however, hypothesize a functional disconnection during sleep, leading to a consolidation process while the memory systems operate independently. Pennartz et al. (2004) found evidence for a simultaneous neuronal activity of the ventral striatum and hippocampal CA1 during slow wave sleep, comparable to the dialogue between hippocampus and neocortex during off-line consolidation.

1.13 Motor Sequence Learning and Hippocampal Involvement

Two main observations suggest a contribution of the MTL to motor sequence learning in particular: First, a correlation of MTL- engagement and the level of awareness during learning and secondly the type of representations that are needed to learn the task (Poldrack & Rodriguez, 2003). The results from Schendan, Searl, Melrose, and Stern (2003a) indicate that the representation hypothesis explains the nature of MTL contribution to sequence learning better than the awareness hypothesis: They could show activation in the MTL during both, implicit and explicit sequence learning. These findings fit with the fact that the hippocampus produces temporal and spatial context representations. The study of Gilbert, Kesner and Lee (2001) underpins this assumption. Lesions in the CA1 region in rats lead to an impairment in the distinction of the temporal order of stimuli, especially when presented in rapid succession. A study of artificial grammar learning suggests that the hippocampal role exceeds the mere conscious and declarative domain (Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 2010; Lieberman, Chang, Chiao, Bookheimer, & Knowlton, 2004).

What impact does a functional hippocampal disconnection during TGA have on motor sequence acquisition and consolidation?

1.14 Methods - Testing Procedural Memory Function

In the sequential finger tapping motor task the participants press numeric keys presented on the screen individually in succession. The numbers recur in a given sequence order. Conducting the task, motor learning takes place that can be measured by speed- and accuracy improvement. In our study, TGA patients conducted this task. Their data revealed the motor-driven learning and consolidation progress without the contribution of the hippocampus.

An alternative to the tapping task for the investigation of the interaction between the hippocampal and the striatal memory system is a reversed paradigm: patients suffering from Parkinson´s disease carry out a task that is primarily based on hippocampal functioning (spatial orientation). These data reveal the learning progress without the contribution of the striatal system (see: Congress Abstract: Neuroscience 2012).

PART 2

Content

Overview

My aim was that the three main parts can be read separately. A short overview of the studies and manuscripts in particular provides the introduction to Part 2.

1. Stress-related Factors in the Emergence of Transient Global Amnesia with Hippocampal Lesions

As described in detail in the review, several theories about the etiology and pathogenesis in transient global amnesia coexist. Some typical clusters of precipitating events give a hint of the underlying pathological mechanisms, one of which indicates an emotional trigger. There is relatively little literature on this issue and, to our knowledge, no study about the role of stress in TGA etiology. We addressed this topic retrospectively by four questionnaires concerning stress and emotional arousal. Our results indicate a contribution of an elevated anxiety level as well as a disposition to certain coping strategies in TGA etiology.

2. Motor Skill Learning and Off-line Consolidation in Patients with an Acute Hippocampal CA1 Lesion

The focus of this manuscript lies on the dynamic interaction of procedural and declarative learning and off-line consolidation in TGA patients. The procedural memory system basically relies on cortico- striatal- cerebellar based circuits, but converging evidence indicates that the hippocampal system might also be involved in procedural learning and consolidation. TGA patients in the acute and in a follow up phase, as well as healthy controls took part in a declarative (RAVLT) and a procedural test (sequential finger tapping motor task). Our data suggest that an acute hippocampal dysfunction slightly impairs learning but facilitates off-line consolidation.

3. Transient Global Amnesia

This paper is a review; hence, it does not deliver any new insights into this enigmatic syndrome, but it summarizes the current state of knowledge. In this context it should be read as a detailed example of an amnestic syndrome and a natural lesion model that forms the basis of the former two studies.

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Stress-related factors in the emergence of transient global amnesia with hippocampal lesions

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The transient global amnesia (TGA) is a rare amnesic syndrome that is characterized by an acute onset episode of an anterograde and retrograde amnesia. Its origin is still debated, but there is evidence for psychological factors involved in TGA. In neuroimaging, selective lesions in the CA1 field of the hippocampus can be detected, a region that is particularly involved in the processing of memory, stress and emotion. The aim of this study was to assess the role of psychological stress in TGA by studying the prevalence of stress related precipitating events and individual stress-related personality profiles as well as coping strategies in patients. The hypothesis of a functional differentiation of the hippocampus in mnemonic and stress-related compartments was also evaluated. From all 113 patients, 18% (n = 24) patients experienced emotional and psychological stress episodes directly before the TGA. In a cohort of 21 acute patients, TGA patients tend to cope with stress less efficiently and less constructively than controls. Patients who experienced a stress related precipitant event exhibited a higher level of anxiety in comparison to non-stress patients and controls. However, there was no difference between the general experience of stress and the number of stress inducing life events. The majority of patients (73%) did show typical magnetic resonance imaging (MRI) lesions in the CA1 region of the hippocampal cornu ammonis. There was no clear association between stressful events, distribution of hippocampal CA1 lesions and behavioral patterns during the TGA. Disadvantageous coping strategies and an elevated anxiety level may increase the susceptibility to psychological stress which may facilitate the pathophysiological cascade in TGA. The findings suggest a role of emotional stress factors in the manifestation of TGA in a subgroup of patients. Stress may be one trigger involved in the emergence of transient lesions in the hippocampal CA1 region, which are thought to be the structural and functional correlate of TGA.

Keywords: amnesia, CA1, hippocampus, stress, transient global amnesia

INTRODUCTION

The transient global amnesia (TGA) is a rare amnestic syndrome, that is characterized by a sudden onset of a selective antero- and retrograde amnesia (Bartsch et al., 2010). In patients with a TGA, transient lesions confined to the CA1 field of the hippocampal cornu ammonis can be detected in high-resolution magnetic resonance imaging (MRI) 24–72 h after the amnestic phase (Bartsch et al., 2006, 2007). These MRI lesions can be considered the structural correlate of the amnestic deficit reflecting a transient perturbation of hippocampal function (Bartsch et al., 2006, 2010, 2011).

As the etiology of TGA remains enigmatic even 50 years after its first systematic clinical description, the incidence of events directly preceding a TGA has therefore attracted great interest (Fisher and Adams, 1964; Quinette et al., 2006; Bartsch and Deuschl, 2010). In the majority of patients, precipitating events encompassing physical, psychological and emotional factors can be observed. In recent years, especially the association with psychopathological factors has been elucidated (Merriam et al., 1992; Inzitari et al., 1997; Pantoni et al., 2005; Noël et al., 2007, 2008, 2011). These complementary studies suggest that certain personality traits might be relevant in TGA. Quinette et al. (2006) found an increased frequency of patients showing a psychological or emotional instability. Pantoni et al. found a higher prevalence of a personal or family history of psychiatric conditions and diseases or phobic traits in comparison with patients who have had a transient ischemic attack (TIA) or healthy controls (Pantoni et al., 2005). These studies also suggest that the occurrence of TGA might be associated with events involving a stress response, changes of bodily homeostasis and emotional state in persons susceptible to these factors (Quinette et al., 2006; Bartsch and Deuschl, 2010; Bartsch and Butler, 2013). The role of stress related personality factors in the etiology of TGA, however, has not been studied so far.

The hippocampus, and in particular the CA1 region, is critically involved in the formation of memory, but also in the neuroendocrine regulation of stress responses to emotional challenges including fear and anxiety (Howland and Wang, 2008;

Joëls et al., 2008; Joëls, 2009). The hippocampal involvement in the regulation of stress is reciprocal: this structure influences the hypothalamic-pituitary-adrenal axis but is also affected by stress hormones, a mechanism that is thought to constitute a conceptual bridge to neuropsychiatric disorders (de Kloet et al., 2005; Wingenfeld and Wolf, 2014). The deleterious effects of stress and cortisol on the hippocampus are thought to lead to changes in synaptic plasticity, structural alterations and functional impairments in CA1 neurons (McEwen et al., 1968; de Kloet, 2012). With regard to the organization of CA1 networks, recent animal data suggest a differential organization of CA1 networks into functional compartments, such as the dorsal hippocampus performing cognitive functions and the ventral hippocampus subserving the processing of stress, emotion, and affect (Moser and Moser, 1998; Dong et al., 2009; Fanselow and Dong, 2010).

These considerations raise the possibility that the emergence of hippocampal CA1 lesions in the pathophysiological cascade of TGA is associated with stress related environmental factors, characteristic personality profiles and coping strategies, leading to an enhanced vulnerability of hippocampal function.

Therefore, our aim in this study was threefold: first, to study the prevalence of stress-related precipitating events in a cohort of 113 patients with a TGA. In a cohort of 21 acute TGA patients, secondly we analyzed individual stress related personality profiles and coping strategies by means of established questionnaires focusing on mental handling of stress, stressful life events of the two years preceding the attack and coping strategies. Further, considering a differential function-structure relationship of the human hippocampus in the processing of emotional stress and memory, we also analyzed the association of stress related factors with the behavior during TGA and the distribution of hippocampal lesions.

PATIENTS AND METHODS

PREVALENCE OF STRESS-RELATED PRECIPITATING EVENTS

Between 2003 and 2010 data of 113 TGA patients (65.4 ± 7.6 yrs, 62 females) presenting to our neurological emergency unit were collected. Only patients who fulfilled the Hodges and Warlow's diagnostic criteria were included (Hodges and Warlow, 1990). The data comprised a characterization of precipitating events occurring directly before acute TGA onset. The precipitating events were divided into the following classes: 1. emotional stress, 2. physical effort, 3. acute pain, 4. water contact/temperature change, 5. sexual intercourse, 6. other factors and 7. unspecified, according to the classification of Quinette et al. (2006). The classification of a precipitating episode as stressful was based on the patients' and the accompanying relatives' evaluation of its intensity and valence as well as on the assessment and review of the episodes by the investigator. Only non-ambiguous episodes were classified as stress episodes. There were no incidents of precipitating psychological trauma. To further distinguish psychological stress factors from non-emotional factors such as physical factors, we dichotomized the precipitating events in emotional stress (visiting a grave, visit to a critically ill relative, emotional quarrel, big birthday celebration) and physical precipitating events (physical effort, pain, water contact, temperature change and sexual intercourse). With regard to a structure-function analysis of hippocampal lesion patterns and behavioral phenotypes, the patient's behavior during TGA was also documented in grossly classified subdivisions of hyperactive (concerned, disquietness, restlessness), hypoactive (lethargy, quiet wakefulness) and normal mental states as judged by the accompanying relatives and the investigator. The study was approved by the Ethical Committee of the University of Kiel and participants gave informed consent.

NEUROIMAGING

Standard whole-brain MRIs were performed on a 3T unit (Philips Intera Achieva) in 108 patients (95.6%) 24 to 72 h after onset of TGA symptoms when the detectability of hippocampal lesions is highest (Bartsch et al., 2007). Distributions of hippocampal CA1 lesions as seen on MRI were correlated with behavioral results (Bartsch et al., 2011). In patients, a standardized clinical routine MRI (T1- and T2-weighted turbo spin echo sequences and diffusion-weighted images with subsequent maps of the apparent diffusion coefficient (ADC), slice thickness 2 mm) was performed. The voxel size for the diffusion-weighted images was 1.67 × 2.12 × 3 mm and 0.51 × 0.65 × 2 mm for the T2-weighted images.

STRESS-RELATED PERSONALITY FACTORS AND LIFE EVENTS

For a detailed study of stress-related personality profiles and coping strategies we recruited a cohort of 21 TGA patients (age: 69.7 ± 5.7 yrs, 9 males) with a recent amnestic episode, whose precipitating events could be clearly assigned to either one of the two categories (stress-related and physical). Twenty healthy, age-matched persons (age: 69.7 ± 6.6 yrs, 8 males) acted as controls.

ASSESSMENT OF STRESS-RELATED PERSONALITY FACTORS AND LIFE EVENTS

We used four established self-rating questionnaires that measure several facets of stress including subjective and objective stress load, personality traits as well as coping strategies and mental handling of stress.

1. The *Perceived Stress Scale (PSS*; Cohen et al., 1983) is one of the most common psychological instruments for measuring the perception of stress. The PSS is an ordinal rating scale concerning the subjective evaluation of perceived stress. The sum score of its 10 items was used for the statistical analysis.
2. The *Stress coping scale* [Stressverarbeitungsfragebogen (SVF)] measures 20 different coping strategies in the context of time- and situation stable personal traits as coping strategies influence the handling of stress (Janke and Erdmann, 1997). Thus, every person has an individual spectrum of coping strategies leading to a variable handling of stress. The SVF is adapted from the instructions of the Ways of Coping Questionnaire (WCQ; Folkman and Lazarus, 1988). It comprises 114 items, which sum scores constitute the 20 subscales of coping strategies.
3. The *Social Readjustment Rating Scale* (SRRS; Holmes and Rahe, 1967) measures the objective experience of 43 specific critical personal life events including negative as well as positive (though stress inducing) emotional events of the two years

preceding the episode. The subject has to mark all personally experienced events on a given list. The sum score is calculated from values that are assigned to each event representing its degree of severity. Thus, a high sum score is interpreted as a great extent of objective stressors. Critical live events pertain to stress in a broader sense. We supposed that vulnerability increases according to the experience of stressful life events.

4. The *Hospital Anxiety and Depression Scale (HADS-D)* consists of 14 Items accounting either for the anxiety or depression subscale. The sum scores of the subscales refer to the general mental state 1 week before the attack. The HADS-D extends the concept of stress as stress-related factors can be critically involved in the development and maintenance of depression and anxiety.

NEUROPSYCHOLOGICAL ASSESSMENT

In the acute amnestic TGA phase (Study 2), declarative memory was tested using the Rey Auditory Verbal Learning Test (RAVLT) as well as visuoconstructive memory using the Rey-Osterrieth Complex Figure Test (ROCF). In the follow up, both domains were retested using parallel versions of the RAVLT and the ROCF. General cognitive assessment in the follow up encompassed an estimation of the intelligence level (Mehrfachwahl-Wortschatz-Intelligenztest, an equivalent to the National Adult Reading Test (NART)), word fluency (Regensburger Wortflüssigkeits-Test, RWT) and executive functions (Trail Making Test A and B).

NEUROLOGICAL ASSESSMENT

All patients had a standard neurological examination on admission. The characteristics and time course of the TGA episode was documented including events and factors precipitating the TGA episode. We registered the presence of cardiovascular and other risk factors including the history and prevalence of migraine using the classification criteria of the International Headache Society ((IHS) ICHD-II).

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (version 17.0) was used for data analysis. Interrelations between variables were calculated by Pearson's product- moment correlation and Spearman's rank based correlations, respectively. Continuous variables were compared with independent Student t tests (TGA patients and healthy controls) or t tests for dependent samples, respectively (patients in the acute TGA state vs. follow up). The normal distribution of continuous variables was tested by Kolmogorov- Smirnov statistics. Interrelations between nominally scaled variables were calculated using contingency tables and the corresponding Chi-square independence tests. Significance of 2 × 2 contingency tables was determined by Fisher's Exact test. The level of significance was set at 0.05. Data are quoted as mean ± standard deviation.

RESULTS

PREVALENCE OF STRESS-RELATED PRECIPITATING EVENTS

The categorization of precipitating events immediately before TGA onset within a cohort of 113 TGA patients (mean age 65.4 ± 7.6 yrs; 45% males, 55% females) shows that 18% (n = 24) patients experienced emotional and psychological stress episodes (such as marital conflict, surgery of son at day of TGA and seeing grandchild for the first time; **Figure 1**). Forty-four percent of patients (n = 48) had a clear physical precipitant event, such as heavy lifting, cycling or swimming in a lake. This group of patients also includes those who experienced acute pain, sexual

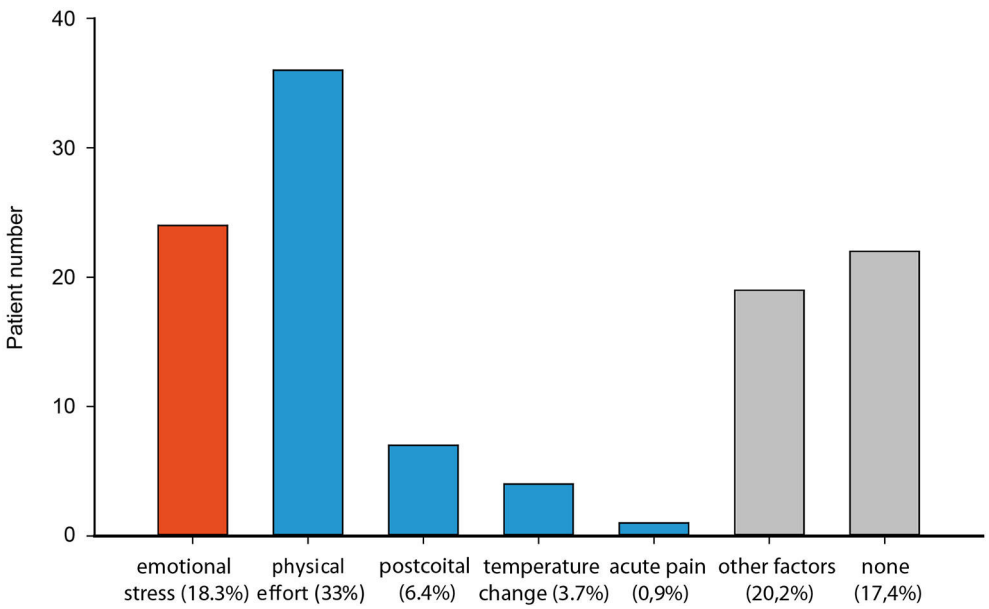

FIGURE 1 | Distribution of precipitating events of 113 patients with a TGA classified as emotional stress (red) and physical (blue) (physical effort, postcoital, temperature changes, acute pain) and others (grey).

intercourse and temperature change immediately before TGA. The latter group was dominated by males, whereas significantly more women experienced an emotional stress-related precipitant, χ^2 (Pearson) = 11.90, $df = 1$, Fisher's exact test: $p < 0.001$. About a third of TGA patients experienced no designated precipitating situation or reported other factors, which could not be specified in the sense of both main categories.

Neuroimaging

The majority of patients (73%) did show typical MRI lesions in the CA1 region of the hippocampal cornu ammonis (unilateral lesion: 61.1%, bilateral lesions: 11.5%, and respectively ventral: 30.1%, intermediate: 20.4%, dorsal: 8.0%). In 23% of patients no lesions could be detected. In five patients, an MRI could not be performed. The type of precipitating event did not have an influence on the side of the hippocampal lesion (left/right), $\chi^2 = 27.31$, $df = 20/p = 0.13$, on the position within the longitudinal extension of the hippocampus, $\chi^2 = 11.42$, $df = 16/p = 0.78$, or on the total lesion load, χ^2 (Pearson) = 0.63, $df = 1$, Fisher's exact test: $p = 0.71$. There was no statistically significant relationship between laterality or location of CA1 features and risk factors.

Behavior during the acute TGA episode

The majority of amnesic patients (34.5%) displayed hyperactive behavior such as restlessness and concern during the acute TGA episode including the typical display of helplessness due to the retention span of a few minutes. Eighteen percent of patients showed hypoactive behavior. About a third could not be clearly classified within the described scheme and 11% of patients exhibited normal behavior. There was no influence of sex, $\chi^2 = 3.79$, $df = 2/p = 0.15$, age, Spearman's $\rho = 0.03$, $p = 0.85$, and precipitant events, $\chi^2 = 1.25$, $df = 2/p = 0.54$, on the acute behavioral patterns. Neither the side of the hippocampal lesion (left/right), $\chi^2 = 8.58$, $df = 8/p = 0.38$, nor the position within the longitudinal extension of the hippocampus (ventral, intermediate, dorsal), $\chi^2 = 6.89$, $df = 8/p = 0.55$, nor lesion load, $\chi^2 = 1.54$, $df = 2/p = 0.46$, exerted an influence on the acute behavior.

Risk factor profile

The prevalence of risk factors in the large cohort corresponds to the distribution within the healthy, age-matched population (Quinette et al., 2006; Enzinger et al., 2008; Romero et al., 2013; Mangla et al., 2014). This applies to transient ischemic attacks, arterial hypertension, coronary heart disease, cardiac arrhythmia, subcortical arteriosclerotic encephalopathy, preexisting insults, lacunar stroke and diabetes. The only exception was the apparently high proportion of migraine in the medical history (thirty-two persons = 28.3%) (Quinette et al., 2006; Lin et al., 2014).

STRESS RELATED PERSONALITY FACTORS AND LIFE EVENTS IN TGA

The results of the Stress coping scale revealed two significant differences between TGA patients and healthy controls: TGA patients tended to increased feelings of guilt, $t_{(48)} = -2.30$, $p = 0.03$, whereas controls downplayed their troubles by comparing with other people, $t_{(48)} = 2.83$, $p = 0.01$. No significant differences in the general experience of stress, measured by the sum score of the PSS could be detected between TGA patients and controls, $t_{(43)} = 0.00$, $p = 1.00$. Further, the SRRS revealed no disparity with a view to the number of stress inducing life events, $t_{(43)} = 0.04$, $p = 0.97$. The HADS-D did not show differences in the anxiety, $t_{(46)} = -1.32$, $p = 0.19$, and depression scores, $t_{(46)} = -0.49$, $p = 0.63$.

Personality factors and life events in patients with emotional stress and physical effort

For further analyses, the cohort of study 2 was dichotomized into two groups of precipitating emotional stress and physical events. The HADS-D revealed a significant higher anxiety level in the stress group, $t_{(26)} = 3.42$, $p < 0.01$. This also applies to the comparison to healthy controls, $t_{(30)} = -2.22$, $p = 0.03$. Furthermore, the Stress coping scale showed a significant difference in coping strategies: Persons who had an emotionally arousing precipitating event are more likely prone to downplay of their troubles, $t_{(26)} = 2.23$, $p = 0.03$, (comparison to healthy controls: $t_{(32)} = 2.57$, $p = 0.15$) and tended to use more medication, $t_{(26)} = 1.99$, $p = 0.06$. We neither could detect any significant influence of general subjective stress-experience (measured by the PSS, $t_{(26)} = 0.87$, $p = 0.39$), nor any influence of the objective amount of stressors (measured by the SRRS, $t_{(26)} = 1.45$, $p = 0.16$), on the type of precipitant events.

Neuropsychological assessments

During the acute phase, declarative memory of TGA patients (word pairs, measured by the RAVLT) was severely impaired (acute vs. follow up: $t_{(16)} = -10.72$, $p < 0.01$; **Figure 2**) compared to follow-up and control levels (Bartsch et al., 2011). Additionally, visuoconstructive memory was significantly affected during the attack, $t_{(18)} = -9.59$, $p < 0.01$. A comparison between patients with an emotional and patients with a physical precipitant did not detect any significant difference in auditory verbal learning, $t_{(15)} = 1.03$, $p = 0.32$, and visuoconstructive memory, $t_{(17)} = -1.14$, $p = 0.27$, during the acute phase. Executive functions, intelligence and word fluency tested during follow up were within the normal range. With regard to laterality, the majority of patients were right-handed (95%).

Distribution of hippocampal lesions

The MRI analysis showed typical focal lesions in the CA1 region of the cornu ammonis (67% unilateral, 19% bilateral) (**Table 1**). In three subjects, no lesion could be detected. In 29% of patients, the lesion was located in the ventral hippocampus, in 52% in the intermediate and in 24% in the dorsal hippocampus (**Figures 3**, **4**). There was no significant association between the position of lesions and age (left/right: $r = -0.07$, $p = 0.79$, ventral/dorsal: $r = -0.53$, $p = 0.18$), sex (left/right: $\chi^2 = 0.78$, $df = 1$, Fisher's exact test = 0.60, ventral/dorsal: $\chi^2 = 0.95$, $df = 3$, $p = 0.81$), stress related factors (left/right: PSS: $r = -0.7$, $p = 0.55$, HADS-A: $r = -0.07$, $p = 0.79$, HADS-D: $r = 0.22$, $p = 0.42$, SRRS: $r = 0.38$, $p = 0.15$, vent/dor: PSS: $r = 0.67$, $p = 0.07$, HADS-A: $r = -0.31$, $p = 0.46$, HADS-D: $r = -0.13$, $p = 0.76$, SRRS: $r = 0.02$, $p = 0.96$) and precipitating events (left/right: $\chi^2 = 3.31$, $df = 1$,

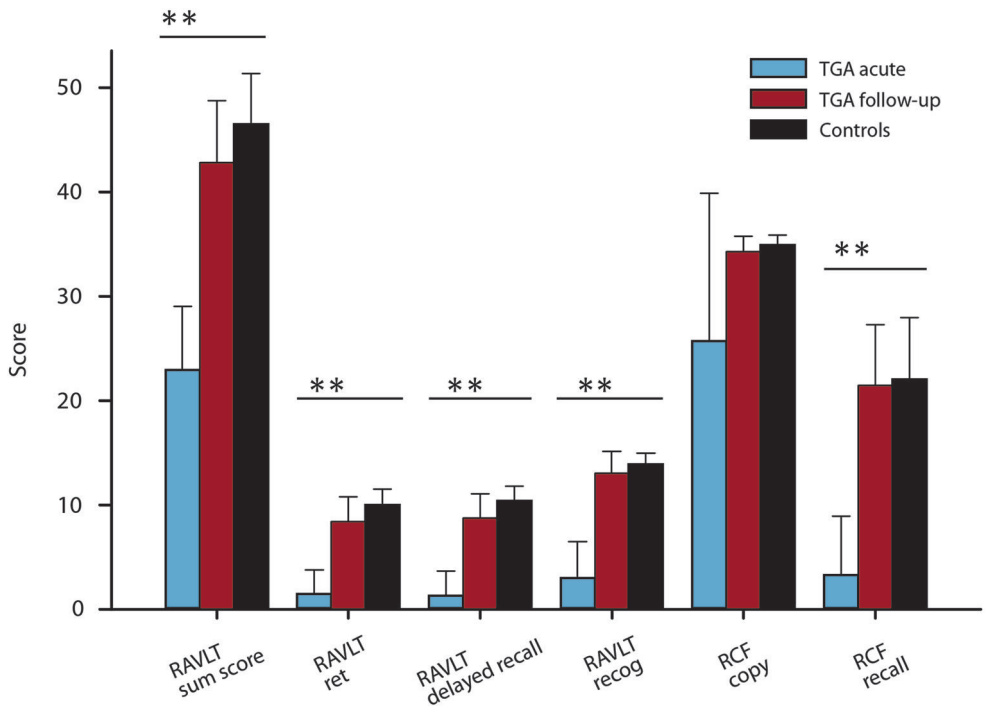

FIGURE 2 | Verbal and visuoconstructive memory results of the RAVLT and the Rey-Osterrieth complex figure of TGA patients (acute and follow-up) (mean ± SD). *P* values from t tests; $^{**}P < 0.01$. Control values are from Bartsch et al. (2011).

Table 1 | Epidemiological and imaging data of TGA patients with a stress-related and physical precipitant event.

Pat.ID	Sex	Age	Precipitating events	Position of hippocampal lesions
Stress-related				
S1	F	74	Son had brain surgery that day	Left-ant
S2	F	71	Emotional arousal after quarrel	none
S3	F	65	First encounter with new-born grandchild	Left-ant, right-mid
S4	M	71	Discharge from hospital with diagnosis of cancer	Left-ant
S5	F	67	Fear for sick child	Left-ant
S6	F	65	Emotional stress with sick husband	Left-mid
S7	M	69	Acute marital conflict	None
S8	F	65	Emotional Stress with mother	Left-mid, right-post
Physical				
P1	F	66	After cycling	Left-mid, left-post
P2	F	61	Postcoital	Left-mid
P3	F	66	Swimming in a lake	Right- mid
P4	M	67	Snow- shoveling	Right- mid
P5	M	67	During cycling	Left-mid, right-mid
P6	M	66	Postcoital	Right-post
P7	M	68	After renovation work	Left-mid
P8	F	69	After heavy lifting	Right-mid
P9	F	62	Heavy gardening	Left-post
P10	M	70	After work on a boat	Left-mid
P11	M	57	After weight lifting	Left-post, right-ant
P12	M	57	After chain sawing	Right-ant
P13	M	50	After weight lifting	none

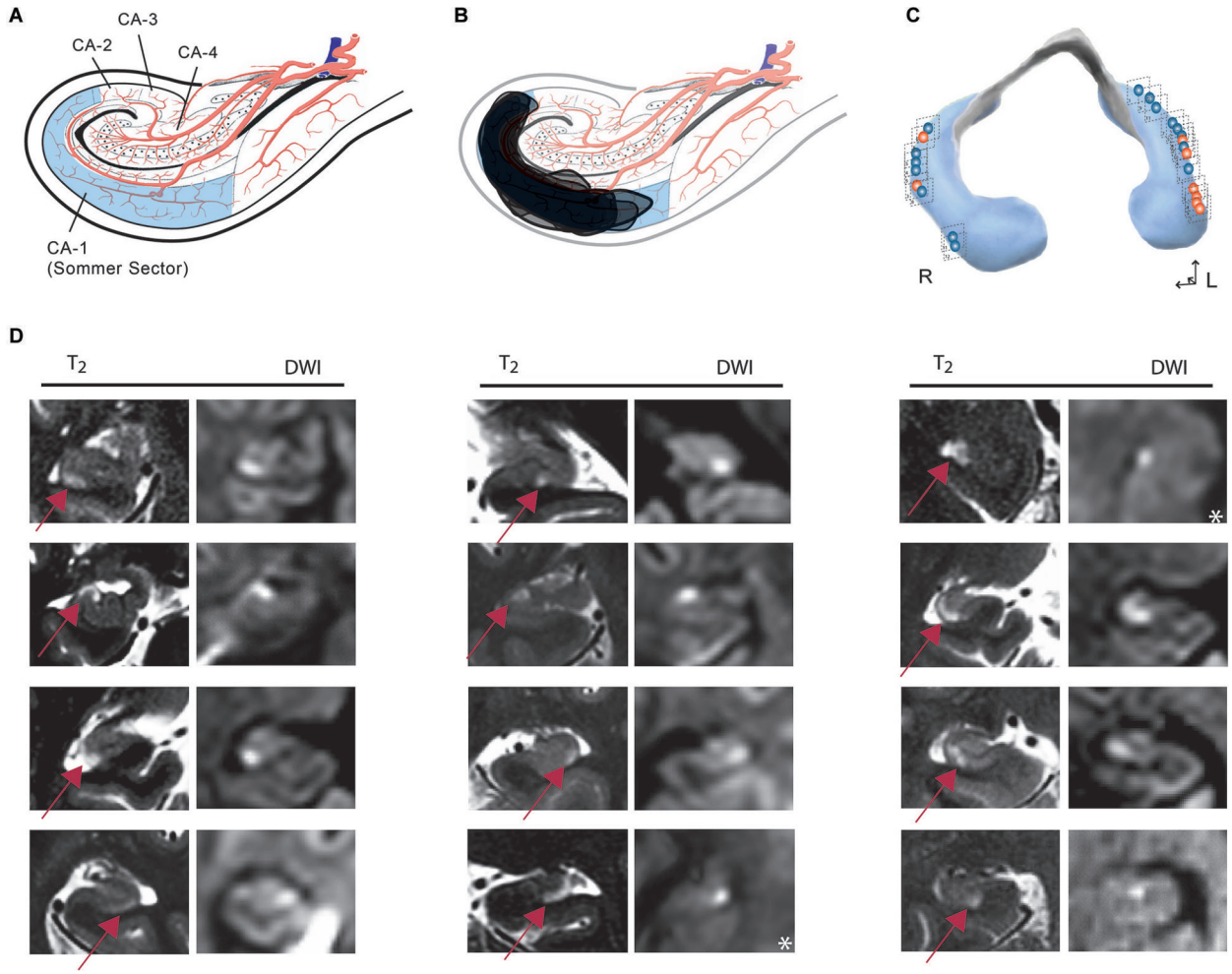

FIGURE 3 | (A) Anatomical template showing a representative coronal slice of the hippocampal cornu ammonis indicating sectors after Lorente de Nó. **(B)** Synopsis of all DWI/T2 lesions transferred to an anatomical template of the cornu ammonis. **(C)** Distribution of lesions along the longitudinal axis of the hippocampus. Red lesions: stress-related precipitant episodes; blue: physical episodes. **(D)** Columns show representative coronal MRI images of the hippocampus [T2/Diffusion-weighted images (DWI)] illustrating that lesions were confined to the CA1 area of the cornu ammonis. In each CA1 lesion, signal changes in diffusion-weighted and corresponding T2-weighted imaging can be observed. The arrow illustrates the CA1 lesions in T2 imaging. *DWI image in an axial plane.

Fisher's exact test = 0.12, ventral/dorsal: $\chi^2 = 4.39$, $df = 3$, $p = 0.22$).

DISCUSSION

Our results show that about a fifth of patients experienced a stress related precipitant event immediately before an acute TGA episode. In patients who experienced an emotional precipitating event a significant higher anxiety level was observed. Additionally, TGA patients differed from healthy controls in certain aspects of coping behavior. Taken together, our findings indicate a role of stress in TGA manifestation in a subgroup of patients but no direct association between precipitant stress episodes and the emergence of CA1 lesions. We could not detect a clear functional differentiation of hippocampal anatomy into mnemonic and stress-related compartments.

PRECIPITANT EVENTS AND STRESS

In the clinical study of TGA, the incidence of events directly preceding a TGA has been of great interest as the etiology of TGA decades after its first clinical description remains cryptic (Fisher and Adams, 1964; Quinette et al., 2006). Typically, precipitating events that include physical or emotional episodes can be detected in the majority of patients. In terms of different classes (emotional stress, physical effort, acute pain, water contact, temperature change, sexual intercourse etc.), the distribution of precipitating events in our large cohort is comparable to the observation of Quinette et al. (2006). Based on a hierarchical cluster analysis, they identified three distinct groups of TGA patients: a physical precipitating event in men, younger patients with a history of migraine and women with an emotional precipitant. Relating to the latter cluster, we could show a significant association between

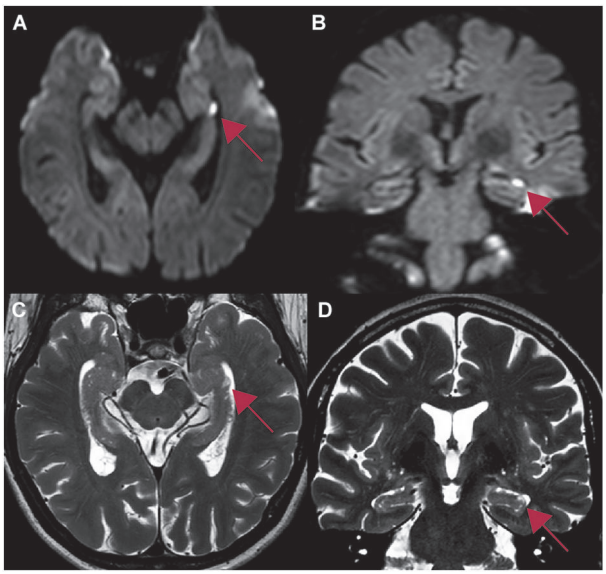

FIGURE 4 | Whole brain 3T MR-imaging of one patient showing a focal lesion in the head of the left hippocampus in CA1 (red arrow) after an emotional stressful event. The lesion in the diffusion-weighted imaging **(A,B)** correlates with the lesion in T2-weighted sequences **(C,D)**. **Table 1**: Study 2: demographic data, precipitating events and distribution of hippocampal lesions. Ant, anterior; post, posterior.

an elevated level of anxiety preceding the attack and the appearance of an emotionally induced TGA. Two significant differences in coping strategies between controls and patients show that controls tend to downplay their troubles by comparing with other people, whereas patients experience more often feelings of guilt. This poses the hypothesis that TGA patients tend to possess less advantageous strategies in handling of stress than healthy controls. In stressful situations, TGA patients apparently focus on internal processes, whereas the controls tend to regulatory strategies maintaining the self-esteem by beneficial social comparisons and distraction. Considering this, coping and stress are directly related to each other: inadequate strategies impair the emotional adjustment and other intrinsic factors that affect the individual stress response. Within a neurobiological framework, it has been suggested that the individual variability in the adaptation and coping to stress is dependent on the interaction between genetic and cognitive/emotional factors in which glucocorticoid hormones and receptors play a critical role (Oitzl et al., 2010). Depressed mood and a high number of stress inducing life events in the past two years before the TGA (measured by the SRRS), however, exerted no influence on precipitant events. However, as a limitation of our study, we cannot rule out, that the patient sample size was not large enough to reach significance with the other stress-related measures. Alternatively, the link between stress, hippocampal (CA1) dysfunction and memory disorders might be an association between more complex functional, neuroendocrine and genetical factors (Schwabe et al., 2012; Wingenfeld and Wolf, 2014). Studies with larger sample sizes are necessary to extend our findings in the future.

TRANSIENT GLOBAL AMNESIA AND EMOTIONAL FACTORS

In recent years, the association of TGA with psychopathological factors became a greater focus of attention emphasizing the role of psychological factors in TGA (Merriam et al., 1992; Inzitari et al., 1997; Pantoni et al., 2005; Noël et al., 2007, 2008, 2011). In their large case series, Quinette et al. (2006) observed an association between the occurrence of a TGA in women, a history of anxiety and a pathological personality. About a third of that sample was found to have a personality disorder, an anxious depressive profile or emotional instability. Our data corroborate their finding of a particular sensitivity to psychological stress in TGA patients. Similarly, Pantoni et al. (2005) observed a higher prevalence of a personal or family history of psychiatric conditions and diseases and phobic traits.

The most frequently studied stress related concepts in connection with TGA are anxiety and depression. Neri et al. found a negative association between retrograde amnesia and depression (Neri et al., 1995). Noël et al. (2007) suggest that high levels of anxiety and depression can aggravate the deficits in episodic memory and might have a detrimental influence on the recovery process of TGA. In terms of anxiety, a more specific investigation was published by Inzitari et al. (1997). They examined selective personality traits (agoraphobic and simple phobia attitudes) as possible predisposing factors for TGA, compared to controls with a TIA. Both, agoraphobic and simple phobia attitudes were significantly higher amongst patients with TGA. Additionally, many patients in this study had symptoms resembling a panic attack during TGA. Pantoni et al. (2005) conceptualize the involvement of the limbic regions in anxiety and emotion with the hypothesis of a local CBF decrease in patients during panic attacks. Other concepts complement the idea of an association between a predispositional vulnerability and diathesis with functional neuronal changes during a precipitating event. The coincidence of these factors may lead to a cascade of stress induced release of steroid stress mediators and glutamatergic neurotransmitters eliciting cytotoxicity in the hippocampus (Quinette et al., 2006; Joëls et al., 2008; Bartsch and Deuschl, 2010). Kessler et al. also suggested a major role of psychological stress and the release of stress hormones in both, the etiology and the recovery process of TGA (Kessler et al., 2001). Future studies should therefore focus on the characterization of the neuroendocrine response in TGA (de Kloet et al., 2012), a clear limitation of our study. Our data fit into the aforementioned concepts of TGA being a result of a cascade with a stress related trigger in a subgroup of patients. From a mechanistic viewpoint, several triggers including stress responses may therefore promote the final pathophysiological pathway in TGA with a functional and structural dysfunction of CA1. The CA1 region of hippocampus is selectively vulnerable to a variety of metabolic and excitotoxic insults which can be most prominently seen in acute neurological conditions such as hypoxia-ischemia, hypoglycemia and epilepsy. In TGA, hippocampal CA1 lesions as seen on MRI are a reflection of signal changes due to impaired intracellular diffusion and cytotoxic edema in the affected region. Thus, the lesions most likely emerge as a results of a noxious input affecting the cellular metabolism in hippocampal neurons (Bartsch et al., 2008). The basis of this regional susceptibility is, however, poorly understood (Michaelis,

2012). Under consideration of this regional vulnerability, the question arises, whether acute psychological stress can directly facilitate the emergence of hippocampal CA1 lesions. Further future research directions should also include the impact of stress on the structural integrity of CA1 neurons and an evaluation of the genetic background of hippocampal vulnerability (Schmidt et al., 2008; Papassotiropoulos and de Quervain, 2011; Molendijk et al., 2012). With regard to the neuropsychological deficit in TGA, recent experimental studies suggest that local dysfunction in hippocampal CA1 neurons may lead to a transient perturbation of hippocampal function (Cohen et al., 2013). Alternatively, lesions in TGA may lead to in a diachisis of memory function in widespread hippocampal networks (Peer et al., 2014).

STRESS AND THE HIPPOCAMPUS

The concept of stress is defined as a multidimensional construct consisting of "(i) stress input with perception and appraisal of the stressor, (ii) the processing of stressful information and (iii) the stress response itself with the objective of restoring homeostasis through behavioral and physiological adaptations" (de Kloet, 2012). The hippocampus with its CA1 neurons is particularly integrated in the stress responses to emotional stressors including fear and anxiety (Howland and Wang, 2008; Joëls et al., 2008; Joëls, 2009). The hippocampus has a reciprocal involvement in the regulation of stress by influence on the hypothalamic-pituitary-adrenal axis, which in turn affects the hippocampus by the release of stress hormones (de Kloet et al., 2005). Harmful effects of stress are thought to lead to various cellular and systemic effects in terms of changes in synaptic plasticity and excitability, hippocampal neurogenesis, structural changes and memory deficits (McEwen and Milner, 2007; Sandi and Pinelo-Nava, 2007; de Kloet, 2012). In animals, it has repetitively been shown that acute behavioral stress leads to a reduction of hippocampal long term potentiation (LTP) and an enhancement of long term depression (LTD) in CA1 (Howland and Wang, 2008). Similarly, stress enhanced glutamatergic transmission leads to an increase of calcium influx in CA1 neurons and in succession to a metabolic vulnerability and, under certain circumstances, to an impairment of structural integrity (Joëls, 2009).

Recently, a functional compartmentalization of the hippocampus based on gene expression in animals has been suggested of the existence of a confined, dorsal "cognitive hippocampus" as a critical relay unit for learning and memory processes. Complementary, the concept of a ventral "emotional" hippocampus suggests that this compartment is involved in emotional, affective and stress regulation. An intermediate zone of this structure is thought to integrate cognitive and spatial processing into behavioral relevant actions (Gray and McNaughton, 1983; Moser and Moser, 1998; Fanselow and Dong, 2010; Maggio and Segal, 2012). Our results in TGA as natural lesion model of hippocampal function, correlating hippocampal lesions with cognitive and behavioral deficits as well as stress-related factors, however, did not show evidence for a similar longitudinal unitization existing in humans. Further research should therefore evaluate the concept of a functional differentiation of the hippocampus in humans using functional imaging.

AUTHOR CONTRIBUTIONS

Juliane Döhring designed the experiment, performed the analysis, interpreted the results, drafted and revised the manuscript. Alexander Schmuck recruited the participants, performed data acquisition and revised the MS. Thorsten Bartsch designed the experiment, performed data acquisition, interpreted the data, drafted and revised the manuscript.

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NEUROSCIENCE 2012

Presentation Abstract

Program#/Poster#: 591.12/YY20

Presentation Title: Deep brain stimulation of the subthalamic nucleus (STN) and the VIM thalamic nucleus modulates spatial reversal learning in patients with Parkinson's disease and essential tremor

Location: Hall F-J

Presentation time: Tuesday, Oct 16, 2012, 11:00 AM -12:00 PM

Authors: *T. BARTSCH[1], S. SVENSSON[2], J. DÖHRING[2], S. PASCHEN[2], R. ROSENTRAEGER[2], G. DEUSCHL[2], R. SCHÖNFELD[3];
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Abstract: Learning and the formation of memory is reflected in various memory systems in the human brain such as the hippocampus based declarative system and the striatum-cortex based system involved in motor sequence, habit and reversal learning. Here, we studied the role of striato-thalamic circuits in spatial memory and reversal learning in patients with Parkinson's disease (PD) and essential tremor (ET), who underwent a deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the ventral intermediate thalamic nucleus (VIM). Non-depressed and non-demented DBS patients (PD-STN: n=22, ET-VIM: n=14) and healthy subjects (n=14), matched by age, sex, and educational level, were tested in a spatial task based on a virtual Morris water maze. All subjects were trained to navigate to a distinct spatial location hidden within the virtual environment during 16 learning trials. Patients were randomized into 4 groups respective to PD vs. ET and into an DBS On- vs. Off-condition. Two hours later, subjects were retested in a delayed recall and reversal learning condition. The reversal learning was realized with a new hidden location that should be memorized during 6 consecutive trials. The performance was measured by means of an index indicating the improvement during the reversal learning.
A free recall of the location during a probe trial showed a comparable stable memory in patients and healthy subjects immediately after the training. In the delayed recall, neither patients vs. healthy subjects nor the DBS On- vs. Off-groups showed a clear difference of the former trained location. Healthy

subjects (reversal index 2.0) and patients in the DBS On-condition (reversal index 1.6) showed a significant improvement. However, patients in the DBS Off-condition (reversal index 1.1) performed significantly worse and did not improve. There were no differences between all groups in a final visually guided navigation task with a visible target.
These results suggest that DBS of striato-thalamic circuits restores spatial reversal learning in a virtual navigation task in patients with Parkinson's disease and essential tremor.

Disclosures: **T. Bartsch:** None. **S. Svensson:** None. **J. Döhring:** None. **S. Paschen:** None. **R. Rosentraeger:** None. **G. Deuschl:** None. **R. Schönfeld:** None.

Keyword(s): DEEP BRAIN STIMULATION

PARKINSON'S DISEASE

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NEUROSCIENCE 2011

Presentation Abstract

Program#/Poster#:	287.23/TT7
Presentation Title:	Interaction between the declarative and procedural memory systems - insights from consolidation effects of sleep in patients with an acute hippocampal CA1 lesion
Location:	Hall A-C
Presentation time:	Sunday, Nov 13, 2011, 3:00 PM - 4:00 PM
Authors:	***T. BARTSCH**, J. DÖHRING, A. STOLDT, A. SCHMUCK, K. WITT, G. DEUSCHL; Dept. of Neurol., Univ. of Kiel, Univ. Hospital, Dept. of Neurol., Kiel, Germany
Abstract:	Learning and the formation of memory is reflected in various memory systems in the human brain such as the hippocampus based declarative system and the striatum-cortex based system involved in motor sequence learning. A certain role in learning and consolidation of motor sequence skills has been attributed to an activation of the hippocampus. It has also been recognized that sleep has an important effect on the consolidation of both, motor skills and declarative knowledge. It is unclear, however, how both memory systems interact in humans. Here, we studied the effect of acute selective and focal lesions to hippocampal CA1 neurones on procedural and declarative learning and off-line consolidation in patients with an acute transient global amnesia (TGA). The TGA is a rare amnestic syndrome that is characterized by a sudden onset of a selective antero- and retrograde amnesia that usually lasts 6-10 h. In patients with a TGA, highly focal lesions confined to the CA1 field of the hippocampal cornu ammonis can be detected in MR- imaging. Patients (68±4,7 yrs of age, n=16) were studied in the acute phase and during follow-up using a declarative (RAVLT) and a procedural (sequential finger tapping) test and were compared with 10 control subjects. Off-line consolidation and retrieval were tested after a 2-day interval without retesting. Patients showed 17 focal lesions in the hippocampus as detected with high-resolution magnetic resonance imaging. All lesions were selectively found in the CA1 sector of the hippocampal cornu ammonis. Patients with an acute TGA exhibited a profound deficit in declarative memory. During the acute amnestic phase, however, patients were able to show

sequential motor learning reflected in an improvement in the sequential finger tapping, albeit to a lesser degree than to follow-up and controls. Retrieval of motor skills showed that sleep had a stronger effect on post-sleep consolidation in the acute state than during follow-up and controls. The post-sleep improvement of the motor sequence learning was negatively correlated to the hippocampal dysfunction reflected in the RAVLT.
These results highlight the role of human hippocampal CA1 neurones in motor sequence learning and sleep associated off-line consolidation suggesting that an acute hippocampal dysfunction slightly impairs learning but facilitates off-line consolidation.

Disclosures: **T. Bartsch:** None. **J. Döhring:** None. **A. Stoldt:** None. **A. Schmuck:** None. **K. Witt:** None. **G. Deuschl:** None.

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Motor skill learning and off-line consolidation in patients with an acute hippocampal CA1 lesion

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Keywords: transient global amnesia – motor skill learning- hippocampus – sequence learning- amnesia - CA1 – sleep - consolidation

Abbreviations: TGA, transient global amnesia; DWI, diffusion-weighted imaging; CA, cornu ammonis

This article is designated for submission in Brain *or* Journal of Neuroscience

ABSTRACT

Learning and the formation of memory is reflected in various memory systems in the human brain such as the hippocampus based declarative memory system and the striatum-cortex based system involved in motor sequence learning. In recent years, a role in the acquisition and consolidation of motor sequence learning has been also attributed to an activation of the hippocampus. It has also been recognized that sleep has an important effect on the consolidation of both, motor sequence and declarative learning. It is, however, a matter of debate, how and in which stages both memory systems interact in humans.

Here, we studied the effect of an acute dysfunction of hippocampal CA1 neurons on the acquisition and off-line consolidation of procedural and declarative memories in patients with a transient global amnesia (TGA). The transient global amnesia (TGA) is a very rare amnestic syndrome that is characterized by a sudden onset of a selective antero- and retrograde amnesia which usually lasts <24 h and which is accompanied by selective lesions in the CA1 region of the cornu ammonis. Sixteen patients (68 ± 4,7 yrs) were studied in the acute phase and during follow-up using a declarative test (RAVLT) and a procedural (sequential finger tapping) test and were compared to healthy controls. Off-line consolidation and retrieval were tested after a 2-day interval without retesting. Patients with an acute TGA exhibited a profound deficit in declarative memory. During the acute amnestic phase, patients were able to acquire motor learning reflected in increased speed in the sequential finger tapping, albeit to a lesser degree to follow-up and controls. Off-line retrieval two days later showed that sleep had a stronger effect on the off-line consolidation in acute patients than to follow-up and controls. The off-line gain of the motor sequence consolidation was negatively correlated to the degree of hippocampal deficit.

These results suggest a differential interaction of the procedural and declarative memory systems during acquisition and consolidation of motor sequences. During acquisition of motor memories, hippocampal dysfunction leads to an attenuation of the dynamic and fast learning curve and thus unmasks the slow and rigid learning curve of striatum based procedural learning. The stronger effects of sleep on procedural memory in CA1 lesioned patients showing a facilitated consolidation of procedural memories indicates a rather competitive interaction between procedural and declarative memory systems in off-line consolidation.

Introduction

Learning and the formation of memory within a given behavioral context requires an adaptive plasticity that is reflected in the presence of multiple memory systems in the human brain (Sherry, 1987, Willingham, 1997). Learning of declarative or relational memory such as facts and events is thought to rely on the hippocampus and the medial temporal lobe system whereas non-declarative procedural learning such as acquisition of a new motor skill, habits or sequence learning is thought to be relayed by cortical-striatal-cerebellar based circuits (Mishkin, 1984, McDonald and White, 1993, Willingham et al., 2002, Squire, 2004). The declarative memory system is considered flexible and being involved in rapid learning, whereas the striatum based learning system is considered performing a gradual learning by trial and error and being slower and more rigid (Mishkin, 1984, Krakauer and Shadmehr, 2006). Learning of a motor skill such as the sequential finger tapping task is associated with activity within the cortico-striatal-cerebellar circuit in encoding, consolidation and retrieval (Karni et al., 1998, Doyon et al., 2003, Albouy et al., 2008, Debas et al., 2010, Debas et al., 2014). With regard to consolidation of newly formed memory, it has been shown that sleep has an important effect on the consolidation of both, motor sequence learning and declarative memories (Walker and Stickgold, 2004, Diekelmann and Born, 2010, Debas et al., 2014).

Initially, the different 'dual' memory systems have been considered rather functionally independent and segregated as suggested by early findings from chronic amnesiac patients after bilateral medial temporal-lobe excision or hippocampal lesions. These patients were capable of acquiring and maintaining motor skills (Milner, 1962, Corkin, 1968), habits (Knowlton et al., 1996, Hay et al., 2002), perceptual sequence learning and motor tasks (Cohen and Squire, 1980, Gabrieli et al., 1993, Reber and Squire, 1994, Tranel et al., 1994). However, recent evidence shows an involvement of the hippocampus also in motor sequence learning and overnight motor memory consolidation (Walker et al., 2005, Albouy et al., 2008). During classification learning, a negative association between the MTL system and basal ganglia activity has been observed in rats (Poldrack and Rodriguez, 2004). A similar dissociation has been suggested for motor sequence learning in humans (Jenkins et al., 1994), an interaction that could not been found in implicit and explicit sequence learning (Schendan et al., 2003). Further imaging data studying motor sequence learning suggest that

both, the striatum and the hippocampus may be activated and interact cooperatively and competitively either during learning or consolidation, respectively (Poldrack and Packard, 2003, Albouy et al., 2008, Albouy et al., 2013b). Conversely, animal data show that lesions to either the hippocampus or striatum result in a double dissociation in learning paradigms suggesting an interaction or even an antagonism between memory systems (Packard and Teather, 1997, Schroeder et al., 2002, Logothetis et al., 2012). The nature of the interaction between the striatal and the hippocampal memory system during consolidation is thus still considered a matter of debate (Albouy et al., 2013b).

To further elucidate the mechanistic interaction between the hippocampal and striatal system in learning and off-line consolidation and to dissect the hippocampal involvement in particular, we studied the effects of acute lesions to hippocampal CA1 neurons on learning and off-line consolidation of a sequence finger tapping task in patients with a TGA. The transient global amnesia (TGA) is a rare amnestic syndrome that is characterized by a sudden onset of a selective hippocampal amnesia whereas procedural memory remains intact (Eustache et al., 1997, Evers et al., 2002, Bartsch et al., 2010). The time course of the acute amnestic syndrome is limited up to 24h. In patients with a TGA, highly focal lesions confined to the CA1 field of the hippocampal cornu ammonis (CA-) can be detected in high-resolution magnetic resonance imaging (MRI) (Bartsch et al., 2006, Bartsch, 2007). These MRI lesions can be considered the structural correlate of the amnestic deficit reflecting a transient diaschisis of CA1-dependent circuits in terms of functional disconnection of the hippocampus (Bartsch et al., 2006, Bartsch et al., 2008, Bartsch et al., 2010, Bartsch et al., 2011).

Patients and methods

Study cohort

Patients presenting to our Neurological emergency unit and fulfilling the following diagnostic criteria of a TGA were studied (Caplan, 1985, Hodges, 1990, Bartsch et al., 2010): i) the presence of an anterograde amnesia, that was ii) witnessed by an observer, iii) no clouding of consciousness or loss of personal identity, iv) cognitive impairment was limited to amnesia, v) no focal neurological or epileptic signs, vi) no recent history of head trauma or seizures, and vii) resolution of symptoms within 24 hours. Patients were studied by one neurologist who remained 24/7 on-call for this study. Age-matched healthy subjects were recruited as controls. Every participant gave informed consent to the study, which was approved by the Ethical Committee of the University of Kiel and which was conducted according to the Declaration of Helsinki. The recruitment of a relatively high number of TGA patients is the result of a regional stroke awareness program with very early admittance of large numbers of patients with suspected stroke to our neurological emergency unit. Some of the results have been published in abstract form (Bartsch, 2011).

Neurological assessment

All patients had a standard neurological examination on admission and follow-up and underwent a structured interview to assess vascular and nonvascular risk factors and a history of cardiovascular and neurological diseases. The characteristics and time course of the TGA episode were documented including events and factors precipitating the TGA episode (Table 1).

Neuropsychological testing

Neuropsychological assessment was performed i) in the acute episode (< 6 h after onset of symptoms) and ii) in the follow-up after the acute phase when patients were fully recovered from all TGA symptoms, thus patients acted as their own controls. In order to study the interaction of hippocampal lesions on motor sequence learning two established tests were used.

Declarative memory testing. Declarative memory in the acute phase included the *Rey Auditory Verbal learning and recognition test (RAVLT) and the Rey-Osterrieth / Taylor*

Complex Figure copy and delayed recall (RCF-copy and RCF-recall) test (Geffen et al., 1990). The RAVLT was used to assess the magnitude of the amnestic deficit of episodic memory, the severity of TGA and thus hippocampal dysfunction. During follow-up testing alternative versions of the *RAVLT* and the *Complex Figure* test were used when the patient was completely recovered. Additionally, healthy subjects (59,3 ± 5,8 yrs, 6 males, total n = 10) were used as controls for the motor skill learning without performing a declarative memory test.

Motor skill learning. We used the established finger sequence tapping task to quantify patients´ motor learning improvement in comparison to controls and follow-up- performance likewise (Walker et al., 2002, Walker et al., 2003b, Walker and Stickgold, 2004, Sheth et al., 2008, Witt et al., 2010) based on the paradigm by Karni et al. (Karni et al., 1995, Karni et al., 1998). This task is considered a motor *skill* task, because performance is quantified in speed (and accuracy) and not in the acquisition of a sequence order (Krakauer and Shadmehr, 2006). We investigated the contribution of sleep on off-line consolidation by retesting two days later ("off-line retesting").

Procedure: The finger sequence tapping task includes pressing four numeric keys in a given order "as quickly and accurately as possible". All persons were right handed. No feedback about speed and accuracy was given, but each time any key was pressed, a ">"-symbol appeared to confirm the keystroke. The sequence to be tapped was displayed at the screen during testing in order to avoid any effort of working memory and to counterbalance mnestic inequalities caused by the severity of TGA. Performance was defined by the number of correct and complete five-digit sequences, tapped in 30 sec. First, subjects performed 15 contiguous 30-second trials (each with a 30-second interval of rest), which altogether took 15 minutes ("initial learning phase"). Second, off-line retrieval (four trials, same sequence) was performed after an episode of two days without retesting. Thus, in accordance with the literature, consolidation was read out by the first three trials after the off-line period (Walker et al., 2003a, Walker et al., 2003b, Walker and Stickgold, 2004, Walker et al., 2005, Witt et al., 2010). Again, patients performed both steps in the follow-up testing 14,9 ± 3,4 (SEM) months after recovery from the acute TGA using an alternative version of the finger sequence tapping task using different five-digit sequences. Two parameters were used to characterize tapping performance: The number of correctly tapped sequences per trial was utilized as measuring unit for speed (which is the main parameter). The accuracy was defined

as the relative number of errors per correctly tapped sequence in a 30-second trial (errors per sequence= (total number of keystrokes – (number of correct keystrokes/5))/number of correct sequences). Consequently, the measurement of speed contains the measurement to a certain extent.

In order to examine interaction effects in procedural and declarative memory processing we first calculated the learning increase of the motor task, which was defined as difference between the average of the first three trials and the last three trials before off-line period and the difference between the last three trials before, and the first three trials after the off-line period. This difference indicates the number of correct sequences that could be tapped at the end of the training beyond the baseline. In the second step we correlated these deltas to the declarative memory performances (measured by the RAVLT sum score).

General neuropsychological testing. After recovery, naming and conceptual knowledge was tested by means of verbal fluency (*letters s and p)* of spontaneous speech within the *Regensburg Word Fluency Test (RWT)* (Aschenbrenner, 2000). An estimate of premorbid general intellectual ability was obtained using a 32-item multiple choice vocabulary test which is the equivalent of the NART-Test (Nelson and O'Connell, 1978, Lehrl, 2005). The test requires the identification of correct German words in a series of words and non-sense words. The level of attentional performance, cognitive speed and flexibility was assessed by means of the *Trail-Making-Test A & B (TMT)* (Reitan and Wolfson, 1992).

Magnetic resonance imaging

Whole brain clinical MRI's of patients were performed 24-72 h after onset of TGA symptoms when the detectability of hippocampal lesions is highest (Bartsch, 2007). High-resolution MRI's were performed on a 3 T unit (Philips Intera Achieva). The following sequences were acquired: DWI-Echo Planar Imaging (SE-EPI) with subsequent maps of the apparent diffusion coefficient (ADC), slice thickness 2 mm and T2-weighted turbo spin echo sequences transverse oblique plane parallel to the hippocampus and coronal perpendicular to the hippocampus. All MR images were studied with respect to structural abnormalities in the whole brain including temporal and frontal lobe structures.

Only those lesions that were detectable in both DWI and T2 – weighted images (Fig. 4 and 5) were considered a CA-1 hippocampal lesion in a consensus agreement. For this,

hyperintense DWI and T2 lesions had to correspond to identical locations within the different sectors of the *cornu ammonis* in the coronal plane and the rostral-occipital position within the hippocampus (Fig. 3). The consensus was reached by visual inspection of the MR images by two readers experienced in the detection of hippocampal signal abnormalities in TGA patients. In all patients a clear consensus was reached. Lesions were mapped with the specification of the location within the different sectors of the cornu ammonis after Lorente de Nó according to the anatomical reference atlas of Duvernoy (Duvernoy et al., 2013).

Statistics

The Kolmogorov-Smirnov-Goodness-of-fit-Test was used for assessing normality of distribution, as well as the Levene´s test for assessing the homogeneity of variances. Paired T-tests (two tailed) were conducted to compare performance of various neuropsychological functions in the acute TGA state and the follow-up. Paired T-tests were used to compare the entire performance in the finger sequence tapping task within TGA-patients and independent T-tests for the comparison between TGA-patients and the control group, respectively. Further, we analyzed motor performances using repeated measures ANOVAs to quantify gains over time and to detect interaction effects. In the correlation analysis, Pearson´s product-moment correlation was used. Data are expressed as mean ± SEM, if not otherwise stated.

Results

Declarative memory testing

TGA patients (68 ± 4,7 yrs, 5 males n = 16, mean ± SD) in the acute phase showed profound deficits in verbal declarative learning as measured by the sum score of the REY Auditory-Verbal learning test (RAVLT) and the Rey-Osterrieth Figure ($p<0,001$, Fig.1). Memory impairments returned to normal levels in the follow-up testing indicating a complete recovery after the TGA attack. In patients with TGA, working memory and executive functions are typically spared duirng the amnestic episode (Quinette et al., 2003).

Acquisition of a finger tapping sequence in the acute state of hippocampal amnesia

Despite their pronounced deficit in declarative memory, patients showed a learning effect in sequential motor skills during the acute phase reflected in an improvement in the sequential finger tapping task, albeit to a lesser degree to follow-up and controls (Fig. 2). All three groups continuously improved their finger tapping speed in the initial learning phase (on-line condition). The total on-line gain in acute TGA-patients (4,6 ± 2,3 sequences) was comparable to the gain in controls (4,7± 2,1) and patients in the follow-up (3,9 ± 2,6). The factor time was statistically significant in all three groups (acute vs. follow-up: [$F (14,322) = 19,86$, $p = 0,044$]. Acute vs. controls: [$F (14,308) = 23,52$, $p = 0,004$]. Follow-up vs. controls: [$F (14,266) = 16,18$, $p = \leq 0,001$]. We found no significant group x time interaction. A repeated measures ANOVA yielded significant between-subjects effects, revealing deficits in performance in acute TGA patients compared both with controls [$F (1,22)= 131,75$, $p=0,004$] and themselves in the follow-up [$F (1,19)= 187,5$, $p = \leq 0,001$]. No difference between follow-up values and the controls could be found.

In the initial learning phase, acute TGA patients tapped significantly less sequences in the first three trials (5,9 ± 3,7 sequences) in comparison to controls (10,6 ± 4,6, $p = 0,011$) and the follow-up condition (11,0 ± 3,9, $p = 0,002$). Notably, acute TGA patients also showed a considerably slower gain in the first three trials (2,0 ± 0,64 sequences) compared to follow-up (3,56 ± 1,59) and controls (4,0 ± 0,93). The difference in the initial learning speed of acute patients and follow-up/controls accounts for a dynamic logarithmically-shaped learning course in the initial learning trials whereas acute patients exhibited a linear increase of tapping performance (Fig. 2).

In relation to the average of the last three trials patients in the acute TGA state enhanced their tapping performance up to 9,9 ± 4,7 sequences (corresponding to 177,5 percent of the baseline). During follow-up we measured a tapping increase up to 136 % and in control patients 146,5 %, respectively.

Although acute TGA patients tapped significantly less sequences (mean of the 15 trials: 8,9 ± 4,3 Student´s T-Tests (two tailed)) than in the follow-up condition (13,05 ± 4,56, p = 0,004) and compared to healthy controls (12,71 ± 4,54, p = 0,022) (Fig. 2) they maintained constant accuracy (main effect of time: [F (14,112) = 1,24, p = ≤ 0,001]. Mean accuracy in the acute phase was 0,62 (SD = 0,43) and in the follow-up 0,45 (SD = 0,25), which corresponds to the published level of accuracy in healthy elderly persons (Witt et al., 2010). A dependent t-Test for paired samples revealed no significant difference between accuracy in the acute stage and in the follow-up (p = 0,38). We found a significant relation between speed and accuracy to the effect that faster tapping led to a higher number of errors (correlation coefficients between -0,46 and -0,80). There was no significant correlation between the increment of motor learning and age in our cohort.

Off-line consolidation of finger sequence skills

For quantification of the memory consolidation over the off-line period we used the mean of the last three trials before sleep as baseline and the mean of the first three trials thereafter as reference, measured as difference and in percent. Off-line consolidation in the acute phase was tested 48,1 ± 15,4 h and in follow-up 54,5 ± 15,5 h (p = 0,31) after learning. Neither patients in the follow-up (mean of the off-line delta: 0,3 ± 3,1 sequences) nor healthy controls (mean 0,2 ± 1,9) improved their performance significantly over the off-line period. However, in acute TGA patients we observed an off-line improvement of tapping performance (mean 2,0 ± 3,2, p < 0.05, paired t-test). The accuracy in the acute phase as well as in the follow-up state was maintained over the off-line period.

Performance within the off-line retrieval condition was quantified by bisecting the four trials comparing the mean of the first two trials with the last two trials. Neither patients in the acute stage, nor controls improved their speed significantly. However, follow-up patients significantly increased from 14,5 ± 5,6 to 16,5 ± 5,0 sequences per trial (p = 0,005).

Interrelation between hippocampal amnesia and finger sequence tapping skills

Learning phase. A correlation analysis between acute hippocampal memory deficits in the on-line phase as measured by the RAVLT sum score and the on-line tapping skill performance did not indicate a significant correlation in the acute on-line condition. Due to pronounced floor-effects in the acute amnestic phase, we could not compute an analysis for other measures of the RAVLT. In the follow-up state, we observed a non-significant negative trend in the on-line condition ($r = -0,41$, $p = 0,21$).

Off-line consolidation. The consolidation effect of the finger tapping task in the off-line condition was correlated with measures of the acute hippocampal amnesia in acute patients (RAVLT sum and recognition score). Both measures were negatively correlated with the degree of motor skills in the off-line condition (RAVLT sum score, difference: $r= -0,51$, $p < 0,05$, RAVLT recognition score, difference: $r= -0,52$, $p < 0,05$) (Fig. 3) suggesting that the gain of the off-line motor skill consolidation was associated with the degree of the hippocampal dysfunction in the acute state. In the follow-up, however, hippocampal performance was trend-wise positively correlated with off-line consolidation gain of motor skill learning ($r = 0,41$, $p=0,15$) thus suggesting an inverse relation. The difference between the correlation coefficients of the acute state and the follow up WAS significant ($p= 0,02$).

General neuropsychometric assessment

General neuropsychometric testing of TGA patients during follow-up did not show evidence for alterations in the verbal fluency of spontaneous speech (RWT, Regensburg Word Fluency Test (letters s and p): (s) 18,13 ± 5,5, (p) 16,44 ± 4,4) (Aschenbrenner, 2000), attentional performance, cognitive speed and flexibility (Trail making test: TMT-A 40,44 ± 10,8 s; TMT-B 88,53 ± 30,7 s) (Reitan and Wolfson, 1992), premorbid general intellectual abilities (MWT-B: 32,81 ± 2,4) (mean ± SD) (Nelson and O'Connell, 1978, Lehrl, 2005). A comparison to a published age-matched healthy control group did not show alterations in cognitive performance, either (Bartsch et al., 2011).

MRI Study

Fourteen out of sixteen patients had a total of 17 hippocampal lesions in a time window of 48 – 72 h hours after onset of symptoms. In 11/16 patients one lesion was detected, while in 3/16 patients two lesions were found (Table 1). In 7 patients we detected lesions only within the left, in 5 patients within the right cornu ammonis. Two patients

showed bilateral DWI lesions. A detailed analysis of the distribution of lesions showed that all lesions were selectively found in the area corresponding to the CA1 sector (Sommer sector) of the hippocampal cornu ammonis. Lesions were randomly distributed along the anterior-posterior axis within the hippocampus. A detailed whole brain study did not show evidence for diffusion restricted lesions outside the hippocampal cornu ammonis.

Discussion

Patients with acute hippocampal CA1 lesions exhibited a substantial declarative memory deficit but were able to learn a sequential finger tapping task, although their performance differed from their follow-up condition and healthy controls in some respects: acute TGA patients performed a significantly lower number of sequences and the learning curve was more rigid and linearly shaped in contrast to the rather logarithmically shaped learning curve of follow-up and controls. More importantly, during motor skill acquisition, patients with a CA1 dysfunction showed an enhanced off-line gain of motor skill consolidation.

The central network activated during the acquisition of a sequential motor learning task has only recently been elucidated. Neuroimaging studies show that during the early acquisition phase of various implicit, explicit, manual as well as oculomotor learning tasks (Albouy et al., 2013b, Debas et al., 2014) the striatum is a critical relay unit. It receives projections from the premotor cortex, the supplementary motor area, cerebellum and parietal regions. During later, more automatically executed stages of learning, it receives projections from dorsolateral prefrontal cortex (DLPFC), the pre-supplementary motor area (SMA) and the primary motor cortex (and the HC) (Dayan and Cohen, 2011). It has also been shown that sleep has a critical role in the consolidation of motor skill memory leading to an enhanced representation and connectivity within the cortico-striatal system (Korman et al., 2007, Witt et al., 2010, Barakat et al., 2012, Debas et al., 2014, Schonauer et al., 2014).

Only recent experimental evidence indicated a relevant involvement of the hippocampus in motor sequence learning. Using the serial reaction time task as a motor sequence task, Schendan et al. (2003) showed activation of the hippocampus, entorhinal and parahippocampal cortex structures in implicit and explicit learning (Schendan et al., 2003). Subsequent studies could confirm that indeed the hippocampus is engaged in sequence learning as well as learning of explicit and implicit motor tasks (Poldrack and Rodriguez, 2003, Schendan et al., 2003, Poldrack et al., 2005, Walker et al., 2005, Albouy et al., 2008, Gheysen et al., 2010, Rose et al., 2011, Albouy et al., 2013b). The role of the hippocampus in motor skill learning has initially been attributed to the incorporation of higher-order formations (Schendan et al., 2003). In this context, the hippocampus is particularly involved in processing higher-order temporal sequence learning leading to involvement of declarative

memory mechanisms (Devito and Eichenbaum, 2011). In rats, lesions to CA1 perturbate the performance to arrange the temporal order of stimuli (Gilbert et al., 2001). In contrast to hippocampal CA3 neurons, CA1 neurons in rats seem to be particularly important in processing the temporal order of events as lesions to CA1 neurons significantly disrupt learning the longer sequence order of an odor task (Farovik et al., 2010). In the same vein, Albouy et al. suggest that the hippocampus participates in the formation of an allocentric 'spatial' map of the finger sequence particular in the early learning phase, similar to the established role of the hippocampus in spatial memory (Rose et al., 2011, Albouy et al., 2013a). This is in line with our results showing that CA1 hippocampal neurons in humans are involved in the processing of allocentric spatial maps (Bartsch et al., 2010). Furthermore, it has been shown that the hippocampus is critically involved in the process of pattern separation and remapping in which overlapping and similar representations are discriminated and stored in an non-overlapping (orthogonalized) fashion, making them more distinct, thus allowing the formation of associative memory representations (Colgin et al., 2008, Yassa and Stark, 2011). Hence, hippocampal dysfunction in particular during the early stages of motor sequence acquisition might impair pattern separation and remapping function of the hippocampus. This could result in an impairment of the formation of higher motor associations and account for the slower learning curve of TGA patients (Schendan et al., 2003, Gheysen et al., 2010). This hippocampal contribution is reflected in the dynamic time course of hippocampal activation during motor skill acquisition (Schendan et al., 2003, Albouy et al., 2008). In the first phase of learning of a sequential oculomotor task the hippocampus is activated but it is less dynamically involved and connected to the striatum in the subsequent phase despite an improvement of performance speed which is reflected in an increase of striatal activity (Albouy et al., 2008, Gheysen et al., 2010). These observations led to the hypothesis of a competitive or phase-dependent interplay between striatum and hippocampus during learning of a motor sequence task (Packard and McGaugh, 1996, Albouy et al., 2013a). Albouy et al. also report a stronger recruitment of the hippocampus in an oculomotor learning task in fast learners in contrast to 'slow learners' (Albouy et al., 2008). Our results can be reconciled with a phase-dependent impairment of the formation of higher-order temporal associations during CA1 hippocampal amnesia. In this respect, acute TGA patients phenomenologically behave like 'slow learners' or pure 'striatal strategy learners', who are not able to benefit from the dynamic hippocampal contribution during

acquisition of a motor skill. However, the exact temporal dynamics between a possible phase-dependent interplay between hippocampal and striatal activation during learning is not fully understood (Poldrack and Packard, 2003).

In recent years, the interaction between the striatal and the hippocampal system in memory formation has been the focus of intense research suggesting that the association of both systems can be interactive, cooperative or competitive in nature (Poldrack and Packard, 2003, Poldrack and Rodriguez, 2004, Izquierdo et al., 2006, Brown and Robertson, 2007b). Striatal circuits are also activated in other learning tasks such as mirror-reading (Poldrack and Gabrieli, 2001) and classification learning (Poldrack et al., 2001) in which, during learning, the MTL system showed a deactivation. A negative correlation between the hippocampus and the striatal system with regard to an activation of the basal ganglia and a decreased activity of the hippocampus was also observed in neuroimaging studies (Jenkins et al., 1994, Poldrack and Gabrieli, 2001). The differential interaction between the striatum and the hippocampus during learning of an arbitrary associative learning task was dissociated in a recent high-resolution fMRI study (Mattfeld, 2011, Mattfeld and Stark, 2011). It was shown that striatal activity indicated the rate of learning and that sensorimotor and ventral striatum were associated with correct probability. Medial temporal lobe activity indicated how well the associations were learned. During this task, the activity in the ventral striatum was correlated to MTL activity, whereas the associative striatum and the MTL were negatively coupled indicating a differential-anatomical interaction between the MTL and striatal circuits in terms of parallel cooperative and competitive functional networks.

With regard to the functional interaction or separation of both systems, animal data also suggest that striatal and hippocampal learning may occur in parallel but independently, resulting in different behavioral consequences (Packard and McGaugh, 1992). On the other hand, it was shown that lesions to the fornix thus impairing hippocampal function in rats lead to improved performance in procedural tasks (Eichenbaum et al., 1986) or to a double dissociation in hippocampal and caudate memory tasks due to hippocampal and caudate lesions (Packard et al., 1989, Packard and McGaugh, 1996) which was assumed to be a result of a reduction of cognitive interference. A similar double dissociation has been described in patients with hippocampal amnesia and patients with Parkinson’s disease (Knowlton et al., 1996, Bayley et al., 2005). The mixed results with regard to the nature of the interaction between both memory systems may also be ascribed to various research protocols and

differences in motor tasks used, e.g. it has been argued that the serial reaction time task is more complex and makes other demands on performance than a simple motor sequence task ("skill learning"), a rotary pursuit or a mirror-tracing task, which are all subsumed under the concept of a procedural motor skill task (Krakauer and Shadmehr, 2006).

Off-line consolidation of motor sequence skills

Consolidation of newly formed memory refers to the process of stabilization of a memory trace either by strengthening or reduction of the vulnerability of interference. In recent years, it has been shown that sleep has an important effect on the consolidation of both, motor sequence and declarative learning. In this context, consolidation of motor skills has been linked to NREM sleep and sleep spindles whereas declarative memory benefitted from slow-wave sleep (Karni et al., 1994, Peigneux et al., 2003, Walker and Stickgold, 2004, Clemens et al., 2007, Marshall and Born, 2007, Sheth et al., 2008, Witt et al., 2010, Barakat et al., 2012, Debas et al., 2014, Schonauer et al., 2014), although this attribution may be flexible and task-dependent (Walker and Stickgold, 2006, Debas et al., 2010). Theories of systems consolidation suggest that newly acquired memory traces are being reactivated during post-learning 'off-line' periods in order to transfer them to neocortical structures (Wilson and McNaughton, 1994). This reactivation can also be observed in the striatum (Pennartz et al., 2004).

Using the same skill task as in our study, Debas et al. (2010) showed that sleep-dependent off-line consolidation occurs with activity in the striatum, including in particular the putamen, the cerebellum, bilateral primary motor cortex, the right sensory cortex, and the SMA. Interestingly, only the activity increase in the striatum was associated with overnight sleep reflecting the consolidation of a newly learned skill. These findings also suggest that sleep has a facilitating effect on this consolidation process in the striatum (Debas et al., 2010). With regard to sequential finger tapping skills, recent neuroimaging studies analyzed functional components of motor skill consolidation after a period of sleep and wake, respectively. Activation of the left cerebellum, the right primary motor cortex (M1), the medial prefrontal lobe and the hippocampus with concomitant decrease of activity in parietal cortical areas was measured after sleep compared to activations after a period of wake (Walker et al., 2005). On the other side, sleep-dependent consolidation of a sequence

task was associated with decreased activity in prefrontal, premotor and primary motor cortical areas but with activations in parietal cortical regions (Fischer et al., 2005).

In this context, Brown and Robertson using a declarative and a procedural memory task, showed that both systems, the MTL and the striatal system, interact reciprocally during wakefulness, whereas after a night of sleep no interaction could be found. They ascribe this outcome to specifics of the consolidation and not the encoding phase. Further, they allow for changes in functional connectivity in dependence from sleep/wake stages, more precisely a functional disconnection of declarative and procedural systems, enabling an independent operation. Alternatively, novel mechanisms supporting the consolidation of the two memory systems could be opened by sleep, leading to distinct neuronal resources that subserve declarative and procedural memory processing independently (Brown and Robertson, 2007b, a). For procedural memory consolidation it could be shown that, using fMRI, implicit oculomotor sequence learning results in a linearly shaped activation pattern in the hippocampus and striatum task only in an overnight condition. This was interpreted as a competitive interaction between the hippocampus and the striatum during training, which changes into a cooperative interaction during overnight memory processing (Albouy et al., 2008).

In contrast, the nature of the interaction between memory systems in sleep was recently elucidated by Logothetis et al. (2012). Using a combination of electrophysiological recordings in the primate hippocampus with ripple-triggered functional magnetic resonance imaging during sleep, fast hippocampal oscillations such as sharp-wave ripple events in CA1 were tightly coupled with extensive suppression of activity in the basal ganglia. Such a silencing of basal ganglia during hippocampal sharp-wave ripple events in the hippocampus in sleep indicates a competitive interaction between striatal and hippocampal memory systems in the off-line state (Poldrack and Packard, 2003, Poldrack and Rodriguez, 2003, Logothetis et al., 2012). Thus, this directionality between hippocampus and striatum during sleep is in line with our observation of a facilitated off-line consolidation of procedural memory in CA1 lesioned hippocampal patients. Similarly, other animal experiments show that inactivation of the hippocampus during the post-training off-line memory consolidation period results in an attenuation of hippocampal-dependent place learning whereas striatal response learning is enhanced (Schroeder et al., 2002). A competitive antagonism between memory systems during off-line consolidation can be best put into the context of an

optimized adaptive processing of memory traces during consolidation by reducing interference (Martel et al., 2007, Henson and Gagnepain, 2010, Logothetis et al., 2012). Thus, our results of an enhanced off-line consolidation in acute CA1 patients would best be attributed to a disinhibition of striatal circuits during consolidation. This dynamic relationship between hippocampus and striatum is corroborated by our observation that the degree of hippocampal CA1 deficit in the acute state was correlated to the degree of the off-line gain of motor sequence consolidation. A similar antagonistic relationship between memory systems has already been indicated in earlier lesion and inactivation experiments in rodents showing enhanced striatal-mediated response learning, attenuated hippocampus-associated acquisition of place learning and novel object recognition memory after lesioning of the hippocampus (Eichenbaum et al., 1986, Schroeder et al., 2002, Oliveira et al., 2010). Further, Hagewoud et al. (2010) induced a functional impairment of hippocampal function in mice by sleep deprivation and studied the (hippocampus-based) spatial and striatal-based response strategies in a maze on the behavioral level. Sleep deprivation did not affect performance during training, but had a delayed effect on subsequent training. The authors concluded that the impaired hippocampal memory system facilitates a compensatory, but functionally limited performance of the striatal system (Hagewoud et al., 2010). In this respect, Gabrieli et al. reported on an overnight consolidation of mirror tracing performance in patients with hippocampal amnesia including patient H.M. (Gabrieli et al., 1993). In this study, H.M. maintained his skill for several months.

Anatomical connections between the hippocampus and the striatum

The association between hippocampus and striatum is mediated via functionally relevant anatomical connections describing several differently organized streams directly from the CA1 hippocampus/entorhinal cortex to substructures of the striatum (Sorensen and Witter, 1983, Finch, 1996, Lansink et al., 2009, Pennartz et al., 2011). Several functional modules have been proposed in the striatum (Pennartz et al., 2011): the dorsolateral ‘sensorimotor’ striatum relays stimulus-response learning and habit formation, the dorsomedial striatum is thought to be involved in cognitive tasks and action-outcome learning whereas the ventral ‘limbic’ striatum is associated with motivational and affective modulation. The latter one receives a prominent projection from the hippocampus being traditionally considered a ‘limbic-motor interface’ (Groenewegen et al., 1987, Pennartz et al., 2011). Interestingly, both,

the shell and core region of the VS, receive strong projections from dorsal and ventral CA1 (Floresco et al., 1997, Pennartz et al., 2002, Ito et al., 2008, Pennartz et al., 2009).

Age effects

Motor learning and sleep-dependent memory-consolidation in aging has only recently been addressed indicating plastic changes in different components of memory formation (Seeck-Hirschner et al., 2012, Mander et al., 2013, Fogel et al., 2014). In general, elderly person´s performance in motor learning tasks suffers from slower responses to novel / unpredictable and more complex stimuli as well as decreases in speed (Tucker et al., 2011, Harand et al., 2012, King et al., 2013). Rieckmann et al. suggest that sequence learning is relatively little affected during aging (Rieckmann et al., 2010). Further, in younger subjects a reciprocal relationship between striatal activity and activation in the medial temporal lobe (MTL) across time was observed whereas in older subjects a combined activation in both striatum and MTL was detected. In addition, elderly seem to benefit from off-line consolidation ("immediate improvement") effects in a lesser degree than younger persons, presumably as a function of demands of the particular motor task. The patient cohort of our study consisted of older patients that may account for the lack of off-line consolidation as suggested by other studies using procedural tasks in older patients (Brown et al., 2009). In contrast, Tucker et al. suggest that sleep optimizes motor skill performance across the entire life span. Retesting 24 hours after training (including sleep) revealed no immediate improvement as in our study (last three trials before off-line consolidation in contrast to the first three trials thereafter) in elderly participants (2 percent gain) in comparison to younger (16 percent) (Tucker et al., 2011). After several retest trials, however, a plateau (in both groups about 17 percent gain from the baseline in training) was reached suggesting that the learning rate in older subject may be slower.

Conclusion

Our results show that acute CA1 hippocampal lesions cause an attenuated acquisition of a procedural finger tapping task, whereas after an off-line consolidation period, we observed a stronger procedural memory gain that was negatively correlated to the degree of hippocampal deficit. These findings suggest a differential interaction of the procedural and

declarative memory systems during acquisition and consolidation of motor sequences indicating a rather competitive interaction between both memory systems.

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Tables

Pat.	Sex	Age (yrs)	Circumstances of onset / precipitating event	Location of CA1 lesion
1	F	62	Gardening	L post
2	F	65	Common cold, emotional upset	L mid/ R ant
3	F	77	Doing the laundry	L ant
4	F	69	Pulling heavy weights	R mid
5	F	74	After vomiting, straining	L ant
6	F	65	Emotional upset	L post/ R post
7	F	66	Swimming in a lake	R mid
8	F	66	Cycling	L mid/ L post
9	F	75	During consultation of GP	-
10	F	67	Emotional upset	L ant
11	F	74	Seeing grandchildren	R mid
12	M	67	After shoveling snow	R mid
13	M	70	Working on a boat	L mid
14	M	71	After discharge from hospital due to malignancy	L ant
15	M	66	Postcoital	R post
16	M	61	After a nap	-

Table 1. Demographic and clinical characteristics of the patients with TGA, including the distribution of MR-lesions.

Figure legends

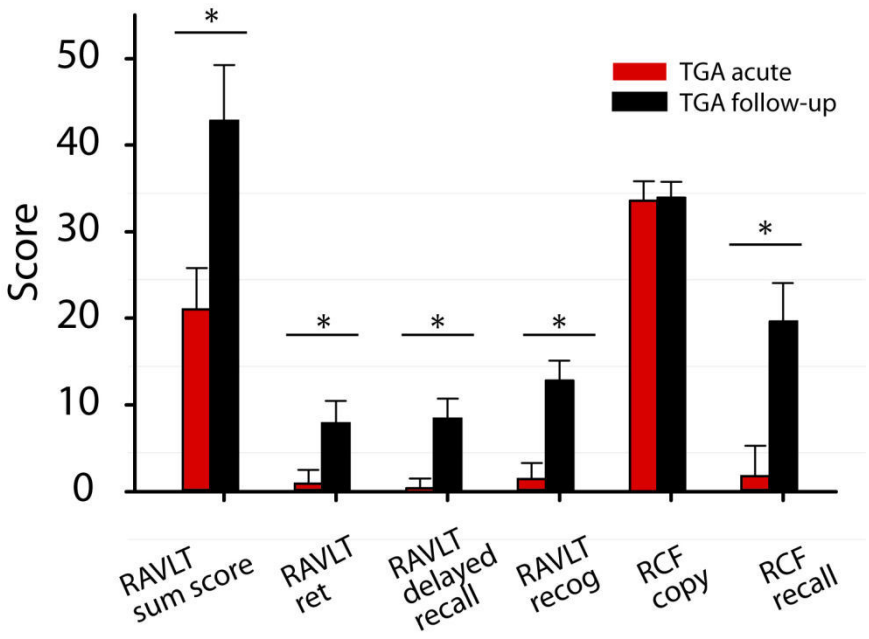

Fig. 1 Verbal and visuo-spatial memory results of the RAVLT and the Rey-Osterrieth complex figure of TGA patients (acute: red bars; follow-up: black bars; mean ± SD). P values from paired-samples t tests.

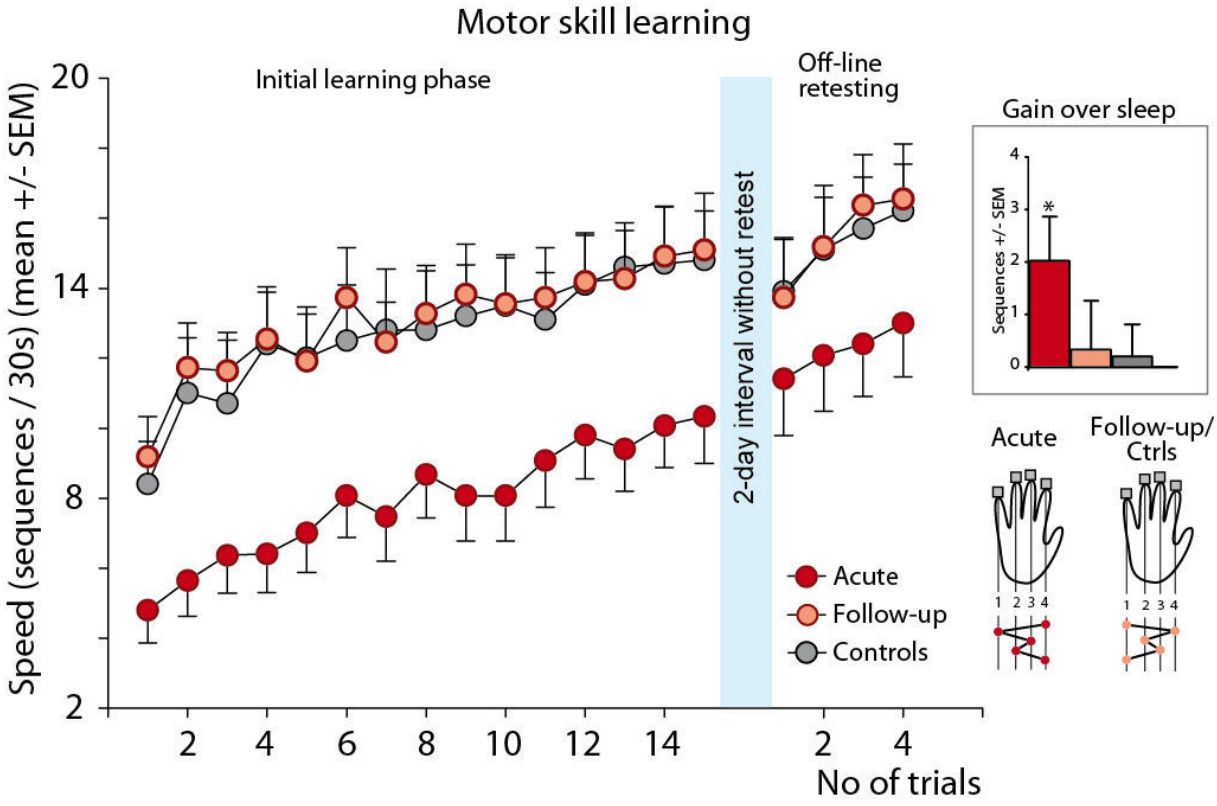

Fig. 2 Average number of correctly tapped sequences per 30 second trial (± SEM), subdivided into acute patients (dark red dots), during the follow-up (light red dots) and controls (grey dots). The initial learning phase was trials 1-15 and off-line retest trials 1-4. Gain over sleep was calculated by subtracting the average of the last three trials of the initial learning phase from the first three trials of the off-line retesting (mean difference ± SEM). Inset shows the quantitative off-line gain in sequences.

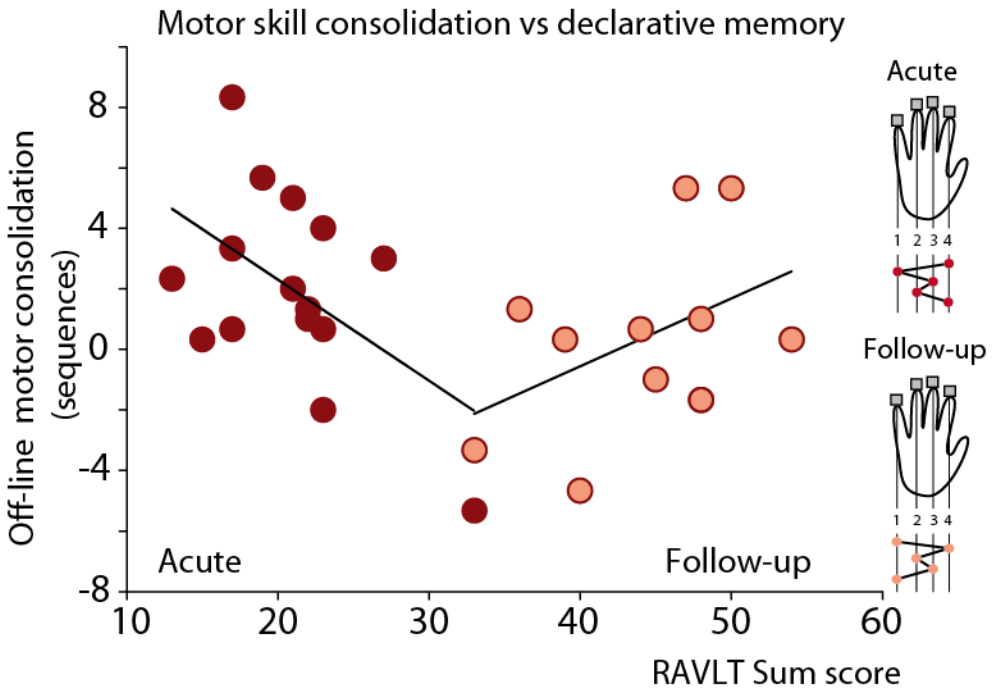

Fig. 3 Correlations between motor skill consolidation and declarative memory. Motor skill consolidation ("off-line gain") was computed from the average of the last three trials of the initial learning phase subtracted from the average of the first three trials of the off-line retesting. Declarative memory is indicated by the sum score of the RAVLT. Subdivided into acute TGA patients (dark red), r = -0,51, p = 0,05 and TGA follow-up values (light red), r = 0,46 p = 0,15. Inset right indicates the sequences to be typed in the acute phase and in the follow-up.

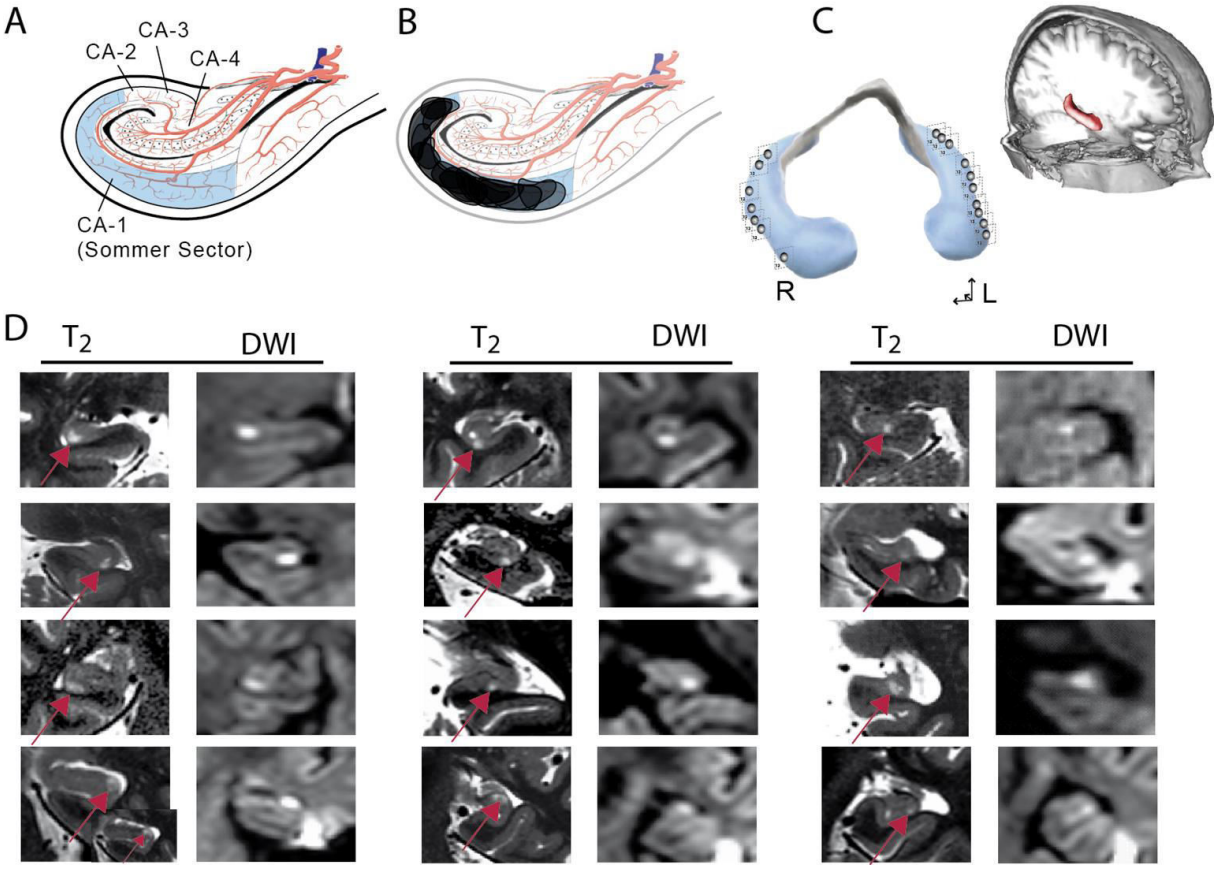

Fig 4. A) Anatomical template showing a representative coronary slice of the hippocampal cornu ammonis indicating sectors after Lorente de Nó. B) Synopsis of all DWI/T2 lesions transferred to an anatomical template of the cornu ammonis. C) Three-dimensional model of the hippocampus showing the anterior-posterior distribution of hippocampal CA1 lesions. Lesions were located in the lateral hippocampus and were distributed along the anterior-posterior axis of the hippocampus. D) MRI of representative lesions shows that lesions were confined to the CA1 area of the cornu ammonis.

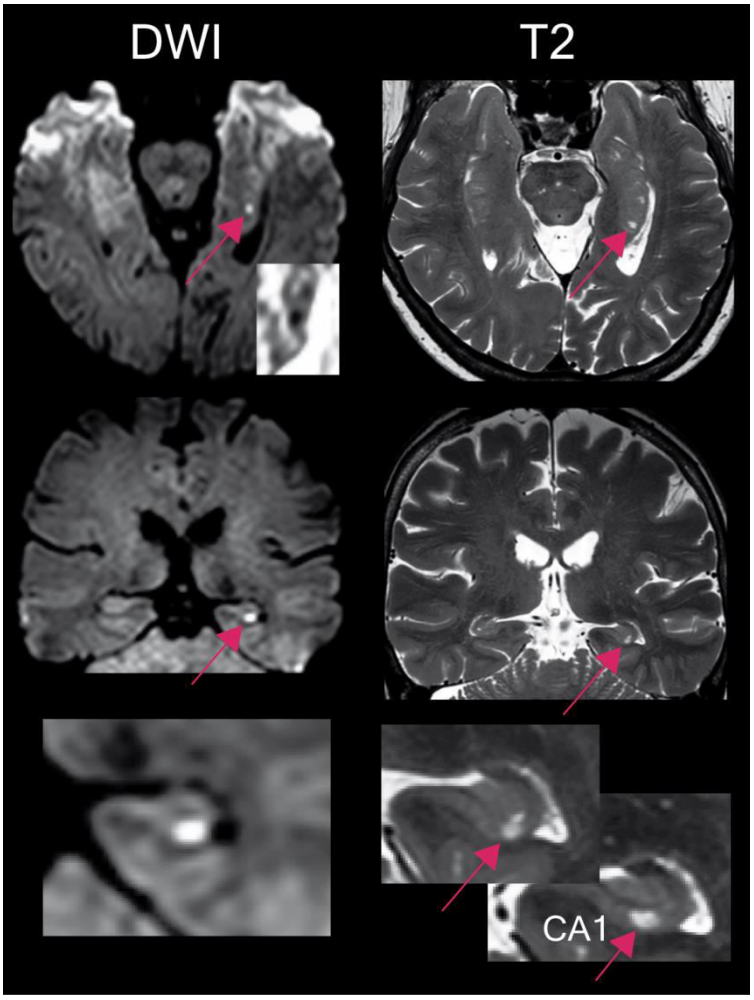

Fig. 5 (A) MRI showing the hippocampal CA1 lesion in diffusion- and T2-weighted images in different planes. Red arrows indicate the lesion. Right lower inset indicates that the CA1 lesion extended over two slices (slice thickness 2 mm). Inset upper right shows the corresponding ADC map of the DWI lesion documenting the decrease of the ADC value.

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Transient Global Amnesia

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Abstract

Transient global amnesia is an acute onset amnesia characterized by an anterograde and retrograde amnesia of declarative memory lasting less than 24 h without concomitant neurological deficits. The prognosis of this enigmatic syndrome is benign. Although the exact etiology and pathogenesis remain cryptic, focal lesions confined to the CA1 field of the hippocampus can be detected in magnetic resonance imaging. These findings indicate a perturbation of hippocampal dependent memory circuits as the correlate of the amnesia. Here, we will describe the clinical presentation of transient global amnesia and illustrate associated pathogenetic mechanisms.

Introduction

Short-lasting amnesic syndromes were recognized already in the nineteenth century (Ribot, 1882; Sollier, 1892). In the classic French neurological literature of the nineteenth century, cases of transient amnesia have been reported that occurred as a consequence of an emotional event (Gil et al., 2010). Guyotat and Courjon (1956) provided the first systematic phenotypical description of the syndrome by characterizing its clinical and epidemiological properties in 17 patients. Fisher and Adams (1964) referred to this phenomenon as 'transient global amnesia' (TGA) and suggested hypotheses about its possible etiology.

Nowadays, TGA is a defined clinical syndrome that is characterized by a sudden onset of a severe amnesic syndrome that extends to all sensory modalities (therefore 'global'). An amnesic syndrome is defined by the inability to learn new, consciously accessible – or explicit – information (anterograde amnesia). This deficit is accompanied by difficulty recalling events that occurred prior to the damage (retrograde amnesia). Retrograde amnesia is often temporally graded in that remote memories, acquired well before the lesion, are better preserved than recent memories. By definition, nonmemory cognitive domains such as perception, cognition, general intelligence, and praxis are intact.

In the following, an overview of the present state of TGA research will be provided, beginning with its epidemiological properties, its anatomical underpinning, the diagnosis, and possible differential diagnosis. The majority of TGA patients report certain precipitating events before TGA onset that will be characterized in the next section. Further, the main hypotheses of TGA pathology will be presented. Finally, some findings from imaging studies will be summarized.

Clinical Presentation

The clinical presentation of TGA is temporally limited, ranging from a few hours up to (per definitionem) 24 h (Bartsch and Butler, 2013). The onset is sudden and manifests in an inability to recollect recent experiences or form new memories. The amnesia affects all modalities of senses (visual, verbal, tactile). The retention span of the anterograde deficit at its peak may last only 2–3 min. When the attention shifts, the retention span may be even shorter. Stereotype repetition of statements or repeated questioning concerning situational circumstances or objects that changed in the recent past is typical. Because of the inability to reconstruct recent events, patients are frequently confused and disorientated in time and place (Owen et al., 2007). The retrograde amnesia varies between individuals and can extend to weeks or decades into the past. Most patients cannot recollect what they had been doing at the beginning of the attack.

Apart from the amnesia, TGA patients do not show impairments of cognition, vigilance, or procedural knowledge. Their intellectual functions are preserved and they are in fact able to accomplish complex operations like driving a car, cooking, or gardening. Working memory is largely maintained as well as procedural memory, priming, conceptual, and public knowledge. During the acute state social skills, awareness of the own identity or the identity of close family members should be retained. A loss of self-awareness and consciousness excludes the diagnosis of a TGA. However, mostly patients are not explicitly aware of their memory failure. Instead they 'feel' something is not quite right without being able to name it explicitly.

Beyond amnestic symptoms, an altered emotional state can sometimes be observed: some patients exhibit a certain helplessness, perplexity, irritation, and/or anxiety or fear to die. Some patients cry and exhibit symptoms close to a panic attack (Inzitari et al., 1997). An altered emotional state and signs of depressed mood can aggravate the amnesic deficit. Deteriorations of the emotional state improve following the dynamic of the episode (Noel et al., 2008).

TGA can be accompanied by mild vegetative symptoms such as headache, vertigo, nausea, cold extremities, chills, or flushes and may be accompanied by a moderately elevated blood pressure (Quinette et al., 2006).

After a few hours, the retrograde amnesic deficit gradually resolves from remote to recent memories. Likewise, the short-term memory recovers gradually, reflected by an extending retention span. Typically after recovery an amnesic gap for the acute TGA episode remains (Sander and Sander, 2005).

Case Example

Mrs. E. is a 71-year-old biologist who had an open-heart surgery several years ago and since then, thoughts about this episode stirs up

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her emotions. In general, she describes herself as a rather anxious person with a past history of migraine. In April she watched a medical documentary in TV, dealing with the subject 'heart surgery.' She asked her husband to switch off the TV program because she did 'not want to be confronted with it again.' Minutes after this event she repeatedly asked the same questions ("Who put the suitcase there?" "Where does the flower vase come from?"). Both objects were quite recently arranged on that place. On the way to the hospital she was alert, but her repeated questioning indicated a profound anterograde amnesia with a retention span of 2–3 min. After several hours, she fully recovered but a lack of memory covering the acute phase remained. Neurological examination, EEG, and cerebrovascular ultrasound were normal. Subsequent magnetic resonance imaging (MRI) 2 days later showed a diffusion lesion in her left hippocampus.

Diagnosis and Differential Diagnosis

Diagnosis

Diagnosis of TGA is based entirely on the clinical history and examination. Caplan (1985) proposed diagnostic criteria that were supplemented by Hodges and Warlow (1990a,b). The diagnosis of TGA relies primarily on clinical findings and comprises the criteria in Table 1. Caplan and Hodges added the exclusion of other causes of amnesia. Although not explicitly mentioned, there is a temporally graded retrograde amnesia present during the attack. Certain mild vegetative symptoms may occur additionally.

Differential Diagnosis

If the clinical symptoms do not match the diagnostic criteria (due to an ambiguous symptomatology, no reliable witness, presence of vascular risk factors), certain differential diagnoses have to be excluded (Bartsch and Deuschl, 2010) (Table 2). The first category of differential diagnosis that may rarely mimic a TGA includes (1) vascular diseases: stroke in hippocampus and thalamus (Berli et al., 2009), transient ischemic attack (TIA) in the vascular distribution of the posterior cerebral artery, infarction in the territory of the anterior choroidal artery (Bartsch and Deuschl, 2010) as well as strategic diencephalic lacunar syndromes. If stroke risk factors have been detected, an MRI and/or CT, an echocardiography, as well as a cardiac check-up are required. (2) The second category, which can mimic a TGA refers to epileptic activity including prolonged complex partial seizures or nonconvulsive status epilepticus as well as a transient epileptic amnesia (TEA) (Table 3). TEA may be difficult to differentiate from a TGA, but usually attacks are shorter (~1 h) but more frequent (~3–4 per year) and respond well to anticonvulsive medication (Berli et al., 2009). In contrast to TGA, TEA carries a risk of developing persistent memory impairment, which can be mistaken for dementia (Zeman and Butler, 2010). Epilepsy can be ascertained by means of an electroencephalogram. In young patients suffering from diabetes, hypoglycemic seizures or hypoglycemia itself can lead to TGA-like symptoms. (3) Subacute prodromal encephalitis such as herpes simplex encephalitis or limbic encephalitis can lead to an amnesic syndrome. (4) Head injuries like cerebral contusion sometimes produce posttraumatic retrograde amnesia. (5) Amnesic syndromes caused by drug intake (hypnotics, benzodiazepines, opioids, antidepressants, marijuana, alcohol) have to be excluded. Side effects of psychotropic medication such as psychiatric pharmacotherapy should be considered (Bartsch and Deuschl, 2010). Hence, a drug history should be obtained. (6) Also psychogenic syndromes might elicit TGA-like presentations: functional dysfunctions after emotionally affecting events in general as well as psychiatric disorders (e.g., dissociative episodes, psychogenic fugue, acute episode of depression). Psychogenic amnesia typically involves profound retrograde amnesia, often with loss of personal identity, in the context of preserved new learning.

Table 1 Diagnostic criteria for transient global amnesia

Diagnostic criteria for transient global amnesia after Caplan and Hodges (Caplan, 1985; Hodges and Warlow, 1990a,b):
● The presence of an anterograde amnesia, that is witnessed by an observer
● No clouding of consciousness or loss of personal identity
● Cognitive impairment limited to amnesia
● No focal neurological or epileptic signs
● No recent history of head trauma or seizures
● Resolution of symptoms within 24 h

Mild vegetative symptoms (headache, nausea, dizziness) might be present during the acute phase. Temporally graded retrograde amnesia is usually present during the acute attack, although this feature is not included in the current diagnostic criteria.

Table 2 Differential diagnostic considerations of transient global amnesia

Differential diagnostic considerations of transient global amnesia
● Vascular diseases: ischemia in the posterior cerebral circulation
● Intoxication, adverse drug side effects
● Complex focal seizures, 'transient epileptic amnesia,' postictual conditions
● Psychogenic syndromes: functional amnesia, psychogenic fugue, dissociative conditions, acute episode of depression
● Posttraumatic amnesia after head injury
● Hypoglycemia

Table 3 Diagnostic criteria of transient epileptic amnesia

Diagnostic criteria of *transient epileptic amnesia* after Zeman et al. (1998) and Butler et al. (2007)
● A history of recurrent witnessed episodes of transient amnesia
● Cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
● Evidence for a diagnosis of epilepsy based on one or more of the following:
▪ Epileptiform abnormalities on electroencephalography
▪ The concurrent onset of other clinical features of epilepsy (e.g., lip-smacking, olfactory hallucinations)
▪ A clear-cut response to anticonvulsant therapy

Epidemiology

The incidence of TGA per year ranges between 3 and 8 per hundred thousand (Miller et al., 1987; Hodges and Warlow, 1990a,b; Berli et al., 2009). A Finnish study found a higher incidence (10 per hundred thousand per year in the general population, 32 per hundred thousand for patients older than 50 years (Koski and Marttila, 1990)). The peak of incidence is located in the 7th decade of age (mean = 60.3 years of age, based on 246 patients described in the literature (Quinette et al., 2006)). The majority of attacks (75%) occur between the age of 50 and 70 years. An occurrence in persons younger than 40 years and above 80 years is rare.

Gender Distribution

Gender seems almost uniformly distributed in TGA. In their metaanalysis, Quinette et al. (2006) did not find a significant gender difference (46.4% men, 53.6% women) among 1333 patients collected from 86 published studies. However, men and women probably differ in terms of the risk factor profile. Women more frequently report a history of migraine and tend to develop a TGA after an emotionally arousing event more often than men. Men were more frequently engaged in physical exerting activities before TGA.

Time of Onset

In the literature, an unequal seasonal distribution of TGA is reported, peaking in spring and summer (61%). In autumn and winter only 33% of the cases have been described (Quinette et al., 2006). With respect to the time of day, a TGA attack most frequently occurs in the morning (59% from 6.00 to 11.30 a.m.), the remaining part is distributed equally between afternoon and evening. There is no reported case of TGA starting in the night (between 0.00 and 6.00 a.m.) or waking up with a TGA.

Precipitating Events

The majority of patients (about a half up to 90%, depending on subjective criteria) report precipitating events that happened immediately before TGA onset. About half of these patients experienced emotional stress or physical effort preceding the attack. About a third was exposed to water contact, temperature change or acute pain, or had sexual intercourse (Figure 1).

Typical precipitating situations of the 'emotionally induced TGA' (Merriam et al., 1992) are stressful events like quarrels, the receipt of bad news, a heated argument, attending a funeral, family reunions, overwork, money worries, or reliving of traumatic situations. Quinette et al. (2006) emphasize the importance of remote factors regarding the personality profile of TGA patients. Persons with an anxious profile and phobic personality traits seem more vulnerable to develop a TGA (Figure 2).

Men are more likely to experience a TGA after physical effort like sports, housework, gardening, and arousing manual activities like coating a boat or sawing wood. Some precipitants contain both psychic and physical arousal like sexual intercourse, health problems in general, medical diagnostic procedures and acute pain. Examples for 'merely somatic' precipitants are Valsalva-associated maneuvers (e.g., coughing, emesis, straining). TGA may be elicited by sudden changes in body temperature. TGA provoked by sudden immersion in cold or hot water tends to cluster in the summer months. Some patients were particularly exposed to temperature changes (washing their hair). Rarely, changes in the atmospheric environment (at high altitudes) are reported. Caplan (1990) suggested that the main categories of precipitants (stress, effort, water) can be considered as abrupt changes in physical activity, temperature, or atmospheric environment, which may evoke an emotional, hormonal, or autonomic body response. The circumstances of TGA occurrence can be also summarized under psychic and physical stress reactions, changes of bodily homeostasis, an allostatic overload, and changes in emotional state (Merriam et al., 1992; Kessler et al., 2001).

Cognitive Outcome

Although the recovery seems complete within 24 h, it is controversially debated whether TGA results in longer-lasting, but more subtle neuropsychological deficits (Quinette et al., 2003; Bartsch et al., 2006; Jager et al., 2009a) as subtle effects persisting for several months following an acute episode has been described (Guillery-Girard et al., 2006). Kessler et al. (2001) report slight disturbances in verbal and nonverbal long-term memory as well as in verbal fluency a few days after the TGA attack. Some patients exhibit a persistent, but subclinical impairment of memory functions (Caffarra et al., 1981). However, in a metaanalysis comprising 25 studies, Jager et al. (2009a) did not identify significant differences in long-term performance between TGA patients and healthy controls. Uttner et al. (2012) did not determine significant cognitive differences between TGA patients and healthy controls in a 2-year follow up. This was aimed at patients with and without detected diffusion-weighted imaging (DWI) lesions. Also complaints concerning the emotional state (anxiety, irritability, fatigue) resolve, though in some cases they persist for some days after the episode. Neri et al. (1995) report a higher rate of mood disorders several months after the acute state.

Recurrence

In principle, TGA is considered a benign condition. The rate of recurrence varies widely across studies, depending on the length of the follow-up duration. Melo et al. (1992) reported a recurrence rate of 2.9%, whereas Fredericks (1990) registered a recurrence rate of 26.3%. In the series of Quinette et al. (2006), 3.5% of 142 TGA patients had a second episode between 1994 and 2004. Gandolfo et al. (1992) compared the survival curve of TGA patients with the analogous curve of sex- and age-matched healthy controls. The curves did not differ significantly.

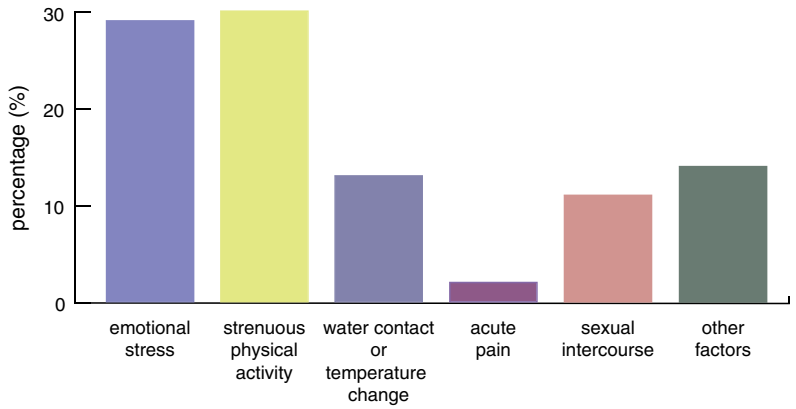

Figure 1 Frequency graphs of various precipitating events preceding the onset of an acute TGA (Quinette et al., 2006). Used with permission from Oxford University Press. Modified after Bartsch and Deuschl (2010), used with permission from Elsevier.

Neuropsychology

The central neuropsychological feature of TGA is the retrograde as well as the anterograde impairment of declarative memory with the anterograde component being more profound (Eustache et al., 1999; Guillery-Girard et al., 2004). The formation of declarative memory contents is primarily based on the hippocampus and the temporal lobe system. Declarative memory comprises semantic and episodic memory. Episodic memory represents memory of personal experiences and specific events in time and space that can be explicitly stated. Semantic memory includes facts, meanings, concepts, and knowledge about the external world and refers to general factual knowledge. The hippocampus is a central node in a large bidirectional network that is essential for declarative memory processing of encoding, consolidation, and retrieval. It includes neocortical association regions, subcortical nuclei, the medial temporal lobe (MTL), parahippocampal areas, and the hippocampus itself (Bartsch and Butler, 2013). It receives input from almost all neocortical association areas and the entorhinal cortex. The severe impairment of episodic memory is thought to be caused by hippocampal dysfunction during TGA. It is thought that the hippocampus is involved in the representation of recent episodic memory contents to remote ones by a gradual information transfer from the hippocampus to neocortical structures. Accordingly, the hippocampal dysfunction in the acute TGA state produces a retrograde amnesia as defined by Ribot (1881) who states that remote memories are more robust than more recent memories. Such a temporal gradient in TGA could be shown by Bartsch et al. (2011). Autobiographical memories are considered a part of episodic memory and refer to the recollection of episodes of a person's history, whose temporal sequence, space, and setting can be vividly relived. These aspects are subsumed under the term 'recollection.' Familiarity-based recognition memory (the feeling that the event was previously experienced, typically with spared

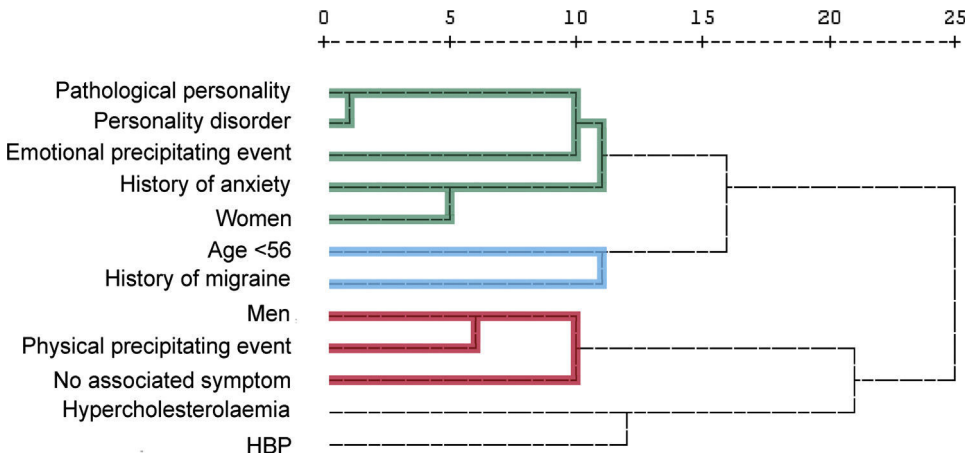

Figure 2 Cluster analysis of 63 TGA patients characterizing the three different classes of patients according to their clinical and epidemiological phenotype (Quinette et al., 2006). Used with permission from Oxford University Press. Modified after Bartsch and Deuschl (2010), used with permission from Elsevier.

contextual information) is thought to be supported by extrahippocampal brain regions. It appears to be preserved during the acute state (Jager et al., 2009b). This differentiation between recollection and familiarity is explained by dual-process models that postulate two distinct memory phenomena, which contribute to the recognition of personal experiences; however, alternative models have been suggested as well (Mandler, 1980).

Spatial memory is a further subtype of declarative memory and can also be impaired during TGA. Patients navigating through a virtual water maze performed more poorly than follow-up or healthy controls. Place and reversal learning and retrieval were impaired (Bartsch et al., 2010). Hainselin et al. (2011) further revealed an impairment of prospective memory during TGA, which describes the ability to remember a previously determined intention to act at the right time.

Several memory functions in TGA are preserved during the acute phase, such as priming, sensitization, habituation, and Pavlovian (classical) conditioning. These implicit, non-declarative memory functions are not essentially dependent on hippocampal functioning. Findings concerning affection of working memory during TGA are mixed due to the diversity of paradigms. Working memory is responsible for temporary information storage. It is necessary for complex cognitive tasks such as semantic speech, comprehension, forming a mental representation of the actual environment, learning, and reasoning and is thought to rely on prefrontal processing (Ngo et al., 2012). Working memory is considered preserved in the acute TGA state but there is evidence for impairment in specific executive functions regarding the limits of short-term memory (Quinette et al., 2003).

Taken together, the neuropsychological profile in TGA is a reflection of a hippocampal impairment.

Pathophysiological Mechanisms

The exact pathophysiological mechanisms of TGA are still unclear. The precipitant events, albeit heterogenous, can be subsumed under three higher order clusters that might shed light on the underlying pathophysiological mechanisms: emotional stress, physical effort as well as abrupt temperature change. Three pathogenic main hypotheses have been formulated: a link to migraine-related mechanisms, TGA as an epileptic phenomenon and a relation to hypoxic-ischemic events. Additionally, TGA has been linked to venous flow abnormalities and psychically induced mechanisms (Bartsch, 2012).

TGA and Migraine

Due to its ictal nature, migraine-associated mechanisms have been suggested to be involved in the pathophysiology of TGA (Olivarius and Jensen, 1979; Crowell et al., 1984; Schmidtke and Ehmsen, 1998). Several studies found a higher incidence of migraine in TGA patients (Olesen and Jorgensen, 1986; Schmidtke and Ehmsen, 1998). A prior history of migraine is assumed to be a risk factor for TGA patients younger than 56 years of age (Quinette et al., 2006). Nevertheless, TGA does not seem to reflect an episode of acute migraine because very few patients experience an acute migraine attack before or during a TGA. A key mechanism in the pathophysiology of migraine with aura is a transient wavelike spreading decrease of neuronal activity called 'cortical spreading depression' (CSD). This is a glutamate-mediated depolarization propagating across the cortex at a rate of 3–5 mm min^{-1} in which hyperperfusion is followed by a cortical hypoperfusion. This reversible process can be observed in several pathological conditions such as epilepsy and stroke. In animals, a CSD can also originate in the hippocampus, leading to an altered excitability of CA1 neurons amongst others (Wernsmann et al., 2006). These phenomena could theoretically act as a neurophysiological trigger evoking cellular metabolic changes that eventually result in a TGA, although this has not been shown in humans (Olesen and Jorgensen, 1986). Bartsch and Deuschl (2010) argue that the findings from Wernsmann et al. (2006) based on rodent studies cannot easily be translated to humans given the substantially higher threshold for eliciting a CSD in the hippocampus compared to the neocortex. Moreover, a hippocampal-elicited CSD has not been shown so far in humans. Additionally, patients during an acute TGA state do not exhibit symptoms typical for an acute migraine attack. In summary, the link between TGA and migraine-related mechanisms is controversial. In a comparison between TGA patients and healthy controls, Schmidtke and Ehmsen (1998) did not find an association between TGA and migraine.

TGA and Epilepsy

Certain similarities between TGA and epilepsy suggest a TGA being an epileptic phenomenon. In patients suffering from transient epileptic amnesia anterograde ictal amnesia and persistent retrograde amnesia can be detected. However, most EEG studies in TGA do not confirm this assumption. Epileptic activity was detected neither during the acute TGA state (Bartsch and Butler, 2013) nor after TGA (Jacome, 1989). In addition, relevant symptoms of epilepsy during the acute TGA phase are lacking, such as impaired consciousness and other cortical dysfunctions, automatisms, staring, and motor signs. Also temporal factors (the comparatively short duration of epileptic seizures) and its high rate of recurrence deviate from TGA. Considering the evidence, an epileptic origin of TGA seems rather unlikely.

TGA and Hypoxic-Ischemic Events

Some studies suggested an association between TGA and stroke in terms of a hemodynamic or thromboembolic event (Logan and Sherman, 1983; Felix et al., 2005; and Di Filippo and Calabresi, 2007). Accordingly, TGA came into consideration as a manifestation of a transient cerebral ischemia in memory-relevant structures (Jensen and De Fine Olivarius, 1980). It has also been suggested that in a subgroup of TGA patients, Valsalva-like activities may elicit a cerebral venous congestion (Winbeck et al., 2005). TGA patients show a low incidence of cerebrovascular events after the acute TGA state (Miller et al., 1987; Zorzon et al., 1995; Pantoni et al., 2005). A comparison between TGA patients and patients with reversible ischemic

attacks or lacunar syndrome revealed a statistically significant better prognosis for TGA patients (Haberman, 1984). Enzinger et al. (2008) compared vascular risk factors, magnetic resonance imaging markers of cerebral small-vessel disease, and other evidence of a cerebrovascular disorder between TGA patients and sex- and age-matched healthy controls. Because of a comparable risk factor profile and concomitant changes on brain MRI a cerebrovascular etiology of TGA could not be supported. In terms of the development of dementia, the findings from Gandolfo suggest no enhanced risk for TGA patients. Winbeck et al. (2005) detected an increased intima-media thickness in the common carotid arteries and a higher prevalence of carotid plaques in patients with hippocampal diffusion lesions combining duplex sonography and MRI. This outcome may indicate a higher incidence of atherosclerosis. In contrast, Pantoni et al. (2000) point out that laboratory investigations in TGA patients usually reveal slight abnormalities that presumably correspond to normal aging effects. Several studies compared the cerebrovascular risk factor profile of TGA patients with patients who had a TIA (Hodges and Warlow, 1990a,b; Zorzon et al., 1995) and failed to provide evidence of a connection of high stroke risk factors and TGA. In their metaanalysis, Quinette et al. (2006) confirmed this good outcome.

Stress and TGA

Already in the 1950s (Bender, 1956) a psychogenic origin of TGA was considered. Emotional arousal and stress was identified as a precipitant event in a relevant proportion of patients ranging from 14 (Hodges and Warlow, 1990a,b) to 29% (Quinette et al., 2006). Some patients exhibit emotional changes such as anxiety, helplessness, and depressed mood during the acute phase. Moreover, symptoms of a panic attack (dizziness, palpitations, chest pains, and nausea) have been observed (Inzitari et al., 1997). About 40% of the patients in Pantoni et al.'s (2000) study had symptoms that are typical for panic attacks. They state these patients could be particularly predisposed to hyperventilation during emotionally arousing events, leading to transient changes in cerebral blood flow. Situational circumstances seem to play a role as in about a half of the patients experience a TGA relapse under similar local/situational conditions as during the first TGA attack (Pantoni et al., 2000).

Some authors suggest that states of vulnerability in terms of personality traits like anxiety, phobic attitudes, pathological avoidance behavior, or depressive symptoms as predisposing factors for a TGA (Yesavage, 1983; Neri et al., 1995; Inzitari et al., 1997). Pantoni et al. (2000) point out that psychiatric disorders are more common in the family history of TGA patients compared to controls. It is worth mentioning that more women are affected by an emotionally induced TGA than men, possibly due to their increased vulnerability to affective disorders (Quinette et al., 2006).

Various studies about the impact of emotional changes (depression, anxiety, and stress) on the hippocampus revealed anatomical and functional modifications, leading to certain memory deficits. The hippocampus plays a central role in the glucocorticoid feedback-loop. Acute emotional and behavioral stress enhances the glutamatergic transmission and increases the intracellular calcium influx in hippocampal CA1 neurons. Joels et al. (2009) considers the increased calcium exposure as a potential risk factor for CA1 neurons that elicits a metabolic vulnerability and leads to an impairment of its structural cellular integrity. In the rodent hippocampus, acute stress causes a reduction of long-term potentiation as well as an enhancement of long-term depression, thus affecting hippocampus-dependent memory circuits (Howland and Wang, 2008).

Neuroimaging in TGA

DWI and other imaging techniques (positron emission tomography (PET), single photon emission computed tomography (SPECT)) provide the tool for studying hemodynamic and metabolic changes in mesiotemporal regions that are affected in TGA. The number of reported changes in these studies, however, varies considerably probably due to the sensitivity of the imaging technique and the study time relative to the TGA attack. Several SPECT studies conducted during TGA revealed cerebral blood flow reductions in MTL structures (Stillhard et al., 1990; Takeuchi et al., 1998; Venneri and Caffarra, 1998), however but also in (pre)frontal, occipital, pre- and postcentral areas, and other anatomical structures including the thalamus, cerebellum, amygdala, nucleus lentiformis, and striatum (Lin et al., 1993; Sakashita et al., 1997; Schmidtke et al., 1998; Eustache et al., 2000). Generally, in follow-up analyses the cerebral hemodynamics have returned to a normal state (Lampl et al., 2004).

However, the advent of high-resolution imaging techniques such as magnetic resonance imaging provides a step forward in the anatomical analysis of TGA. Two to three days after the episode, punctuate lesions (1–5 mm) can be detected in the CA1 region of the hippocampal cornu ammonis (Bartsch and Deuschl, 2010) (Figure 3). The detectability peaks between day 2 and 3 after the acute phase. On magnetic resonance spectroscopy, the emergence of lactate in these lesions could be shown that are interpreted as metabolic cellular stress (Bartsch et al., 2008). Lesions resolve spontaneously in the postacute phase within 14 days. Usually lesions outside the hippocampus are not detected.

Due to the fact that neurons of the CA1 region of the cornu ammonis play a key role in the formation and consolidation of memory, these lesions constitute the neuronal correlate of the memory deficit in terms of a transient perturbation of CA1 networks, presumably leading to a functional disconnection of the hippocampus. This assumption is supported by two single case MRI studies during the acute TGA state that uncovered reduced or no activation in temporal lobe structures during encoding and recognition of visual scenes (LaBar et al., 2002; Westmacott et al., 2008).

Summary

TGA is a rare amnesic syndrome known since half a century. The clinical onset is subacute, and mainly characterized by a severe anterograde and retrograde amnesia. After a few hours, symptoms typically resolve. It is diagnosed on clinical grounds and its

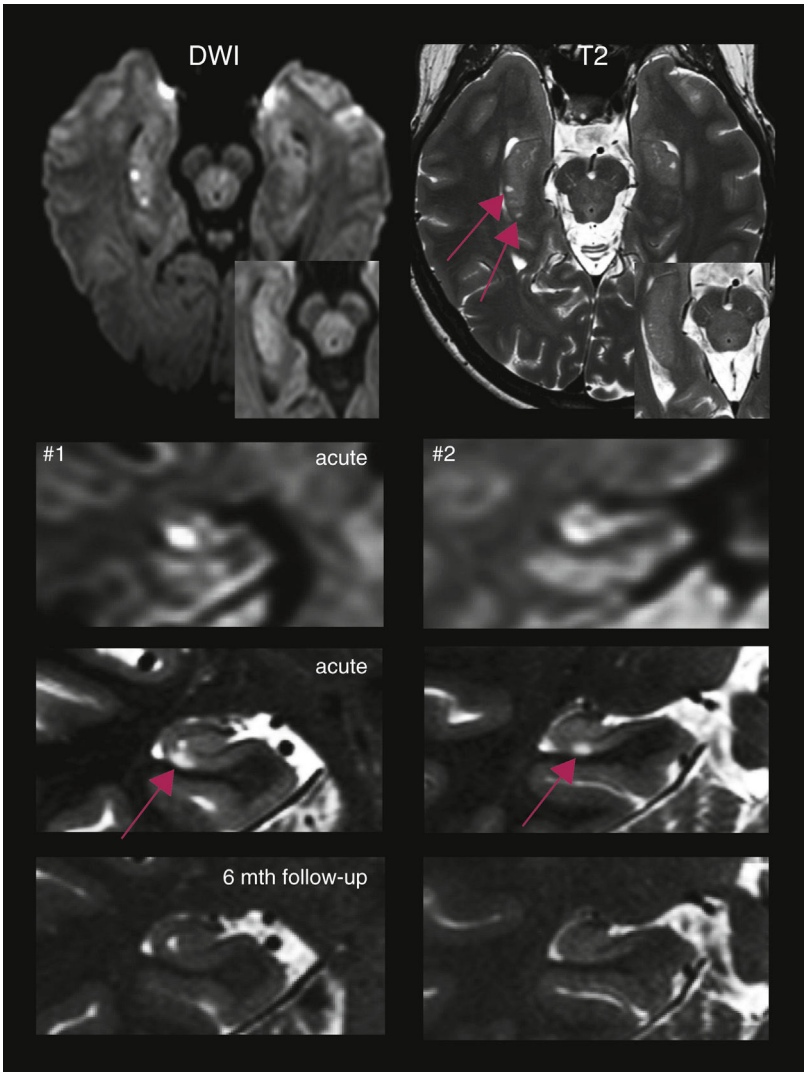

Figure 3 High-resolution MRI (3T) in TGA showing typical hippocampal lesions in the CA1 region of the cornu ammonis. Follow-up 6 months after the TGA shows a complete resolution of lesions. Modified after Bartsch and Deuschl (2010), used with permission from Elsevier.

outcome is considered benign. Intellect, personality, and other neuropsychological and cognitive functions remain unaffected. In many cases, certain precipitant events are reported that form clusters referring to physical effort, emotional arousal, or changes in body homeostasis. The etiology of TGA is still cryptic, but hypoxic-ischemic events, migrainelike mechanisms, epileptic activity, and stresslike mechanisms were taken into consideration. Using high-resolution imaging techniques functional correlates of the transient amnesia have been identified: in many patients, focal lesions confined to the CA1 sector of the hippocampus could be detected, a region that plays a major role in the functioning of episodic and autobiographical memory, place memory, prospective memory, and others. However, this region is also vulnerable to oxidative and metabolic stress.

See also: Amnesia: General; Amnesia: Psychogenic; Declarative Memory, Neural Basis of; Episodic Memory; Hippocampal Amnesia; Hippocampus and Related Structures; Learning and Memory, Neural Basis of.

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PART 3

Summary of Studies and Manuscripts

Finally, I will summarize the studies and manuscripts with particular regard to the study design and importance of the results.

3.1 Stress-related Factors in the Emergence of Transient Global Amnesia with Hippocampal Lesions

Already in 1956, Bender speculated about an emotionally induced origin of TGA. About a third (Quinette et al., 2006) of TGA patients tell of an emotionally charged situation immediately before the attack, ranging from marital quarrels to death of the child or even positive ones like the birth of a grandchild. Considering the nature of the emotional precipitants, it seems reasonable to assume that the experience of stress may play a certain role in the pathophysiology of TGA. Except for the study of Inzitari et al. (1997), there is sparse literature concerning the connection between stress, emotional arousal and TGA. Stress manifests in various negative feelings such as depressed mood, anxiety, anger, helplessness and others.

In our own contribution to the research on the emotionally induced TGA (Merriam, Wyszynski, & Betzler, 1992), we measured several chronological as well as less specific aspects of stress and emotional tension by means of four questionnaires described above.

We hypothesized that in some patients a stressor may elicit a stress reaction or emotional tension that causes the clinical presentation of TGA. Furthermore, our goal was a descriptive characterization of epidemiological properties and clinical parameters (cerebrovascular risk profile) within a large sample of patients (n= 113).

The psychopathological test battery (PSS, SVF, SRRS and HADS-D) was performed by patients, whose precipitant events could be clearly identified and categorized. Due to the sample size, we dichotomized the precipitants by emotional and physical precipitates, the latter including physical effort, pain, water contact, temperature change and sexual intercourse. 20 healthy, age- matched persons served as controls.

The psychopathological assessments showed that TGA patients are more prone to self-accusations than controls, whereas the latter oftentimes downplay their troubles by comparing themselves with other people. Possibly, the controls have more advantageous attribution patterns at their disposal, are able to deal more efficiently with stress and become, as result,

more robust against stress. This manifests in a diminished susceptibility of CA1. However, it should not be omitted that there were no differences between patients and controls concerning depressed mood, general perception of stress and the number of stress- inducing life events.
The comparison between patients with emotional precipitants and patients with physical precipitants revealed a significantly higher anxiety level in the former group, which is the main result of this study. This finding may indicate a higher susceptibility of the CA1 region due to an increased level of anxiety.

While this study explains a small proportion of variance in TGA etiopathology, we are of the opinion that it will be worthwhile for future research to identify and specify further potential psychopathological factors. They exemplify the significant role of emotional experience in physiological and pathological aspects of memory processing.

3.2 Motor Skill Learning and Off-line Consolidation in Patients with an Acute Hippocampal CA1 Lesion

The second manuscript deals with the hippocampal involvement in and the nature of interaction with the implicit striatal memory system. Although the hippocampus is deemed to be the core structure in declarative memory processing, several studies revealed a hippocampal contribution to procedural memory processing, whereby the debate about the nature of this interaction is still going on.
In order to elucidate the role of the hippocampus in procedural memory processing, acute TGA patients carried out declarative memory tasks (RAVLT and ROCF) and an established sequential finger tapping motor task before sleep and thereafter. The number of retained words served as characteristic values of declarative memory, whereas the speed and accuracy of the tapping task quantified procedural memory performance. Secondly, a follow up was conducted using the same procedure and thirdly, a sample of healthy controls was also tested in the same way.
For each of the three samples we calculated the motor learning improvement before sleep (the difference between the average of the first three trials and the average of the last three trials before sleep), the “pre-sleep-delta” as well as the “post-sleep-delta” (the difference between the average of the last three trials before, and the average of the first three trials after sleep). The post-sleep-delta therefore reflects the motor skill consolidation. I foreclose that we found no difference between the follow up and healthy controls in all tests, as expected. Thus, in the

following I will use the term “controls” for both, TGA patients in the follow up and the control group.

Our main results were (i) a comparatively improved performance in motor learning before sleep in both groups, with the difference that the overall level of speed in TGA patients was significantly decreased. This finding indicates that they could not benefit from the subsidiary hippocampal contribution to motor learning.

(ii) Visual inspection of the learning progress displayed a linear slope at the beginning in TGA patients, whereas the control group displayed a rather logarithmically-shaped slope in the first trials. This applied to both, the pre-sleep and the post-sleep condition, but exclusively in the control conditions. We suggest this trend being the result of the stronger hippocampal (CA1-) involvement in the initial learning phase. We interpret both mentioned observations in the pre-sleep-condition as the “unmasked” temporal course of procedural learning without hippocampal engagement.

(iii) In acute TGA patients we found a negative correlation between the off-line motor skill consolidation and the deficit in declarative memory performance. This finding might be an indication of a competitive interaction of both systems during learning and a subsequent decoupling during consolidation as postulated by Brown and Robertson (2007). A further explanatory approach might be the “passive” mirroring of hippocampal deficiency that caused an “active” compensatory increase in the striatal memory system. In view of future research, the following limitation must be noted: we cannot exclude age-effects. Elderly persons’ performance in motor tasks suffers from quick, unpredictable and more complex stimuli. Further, age-related decreases in speed as well as a minor benefit from off-line consolidation must be taken into account. Hence, the external validity of our findings is slightly reduced. Nonetheless, this study provides an insight into the dynamic interaction between the declarative and the procedural memory system.

3.3 Transient Global Amnesia

The third manuscript is a review on transient global amnesia, a rare syndrome that is characterized by a severe anterograde, and a temporally graded retrograde amnesia. Hence, TGA is classified as a typical amnesic syndrome. The clinical presentation ranges from a few hours up to 24 hours. During the acute TGA state, other cognitive functions - except for declarative memory - remain intact. Therefore, during the acute state it is possible to accomplish complex, automated operations like driving a car or cooking. Most patients are disorientated in time and place, some exhibit an altered emotional state or experience mild vegetative symptoms

such as headache or nausea (Quinette et al., 2006). Typically, after a few hours the amnesic deficit resolves following the law of Ribot: remote memories re-emerge first, followed gradually by more recent memories. Usually, an amnesic gap for the acute TGA episode remains after recovery (Sander & Sander, 2005).

The diagnosis of TGA is entirely based on clinical history and examination. Hodges and Warlow (1990) proposed the following diagnostic criteria: (i) attack was witnessed by an observer (ii) sudden loss of recent memory (iii) duration from one to 24 hours (iv) no clouding of consciousness or other cognitive impairment (v) no focal neurological signs or deficits (vi) no epilepsy or recent head injury. The differential diagnosis includes stroke, transient ischemic attack, strategic diencephalic lacunar syndromes, epileptic activity, hypoglycemia, subacute encephalitis, head injuries and amnesic syndromes caused by drug intake or psychotropic medication and psychogenic syndromes.

The peak of incidence is located in the 7th decade of age and ranges from 3 up to 8 of 100.000 per year (Berli, Hutter, Waespe, & Bachli, 2009; Hodges & Warlow, 1990; Miller, Petersen, Metter, Millikan, & Yanagihara, 1987). The occurrence of TGA seems to be independent from gender. An unequal distribution of occurrence was reported, depending on the season (peaking in spring and summer) as well as on the time of the day (peaking in the morning). The majority of patients tell of certain precipitant events immediately before TGA onset. About half of those who experienced precipitants experienced emotional stress or physical effort, whereas a third was exposed to water, temperature change, acute pain or sexual intercourse. In short, the precipitants are heterogeneous in nature and in many cases no specific precipitant can be identified. Therefore the conditions of etiology are difficult to interpret.

The recovery is considered complete, but some authors report on subtle memory impairments that can persist for several months after the attack (Albouy et al., 2008; Guillery-Girard et al., 2006; Kessler, Markowitsch, Rudolf, & Heiss, 2001). Generally, TGA is deemed to be a benign condition: the rate of recurrence ranges from about 3 percent (Melo, Ferro, & Ferro, 1992) up to about 25% (Fredericks 1990). The survival curve of TGA patients does not differ significantly from the analogous curve of sex- and age matched healthy controls (Gandolfo et al., 1992). Some pathophysiological mechanisms were taken into consideration but the exact conditions remain enigmatic: hypoxic ischemic events, migraine associated mechanisms or TGA as an epileptic phenomenon were taken into consideration.

Concluding Remarks

The presented manuscripts and our recent research reveal various aspects of the hippocampal memory system organization. We found evidence for the life-long involvement of the hippocampus in the recollection of autobiographical memories, even the most remote ones, according to the multiple trace theory. TGA patients performing a procedural task were able to acquire and improve new procedural abilities, but their overall level of performance was significantly poorer than in healthy controls. This finding suggests hippocampal involvement in large-scale circuits subserving procedural memory. Ostensibly, particular hippocampal subfunctions such as the incorporation of temporal and spatial order contribute to procedural memory formation. Transient global amnesia as a natural lesion model is well suited to investigate neurophysiological processes without hippocampal contribution because of the focal confinement to CA1, simultaneous integrity of other brain structures and functions and the virtually complete recovery. This rare syndrome exemplifies the vulnerability of the hippocampus because of its high plasticity and specifics of blood supply and neurotransmission. Additionally, the mentioned specifics increase its susceptibility to a deterioration of functions due to psychological stress.

Summary

Memory is the ability of the nervous system to encode, store and retrieve information. Over the course of evolution, human beings developed several memory systems of varying complexity and function that work largely independently. Some of them share individual components that may dynamically interact, depending on the type of memorized content and the stage of memory processing.

Memory is a heterogenous concept that can be classified along the time- (short-term, long-term), process- (encoding, consolidation, retrieval) and content- (declarative, non-declarative) axes. Declarative episodic memory relies basically on medial temporal lobe structures, especially the hippocampus. The hippocampus stands at the top of the processing hierarchy within the MTL-system. Here, information on quality, spatial and temporal localization, associated emotions and other specifications of experienced processes and entities converges. By binding this information, integrated and holistic representations are created. They form our perception of the world, our subjective location therein, our autobiographical past and therefore: our self.

At an early stage of the processing hierarchy, a memory trace is fleeting and fragile. In order to transform it into a stable, long- term representation, a qualitative, structural switch from the hippocampus to the neocortex is implemented (consolidation). This process is assumed to take place mainly during sleep and can extend over long periods of time (months, years, decades). In this respect, a gradient of structural representation in the topography of episodic memory is generated: the longer a memory trace dates back, the lesser is the degree of hippocampal involvement. This phenomenon can exemplarily be observed in persons suffering from transient global amnesia, which is characterized by a short-term functional disconnection of the hippocampus. Like other amnestic syndromes, TGA is representative for the vulnerability of the hippocampus, especially the subregion CA1. As CA1 constitutes the hippocampal main output area, its damage resembles an extensive functional disconnection of the hippocampus.

This high vulnerability derives from different properties, which are connected to its specific internal structure and blood supply. Therefore, hippocampal damage can be triggered by a bandwidth of factors such as physical and emotional arousal, stroke, epilepsia and inflammatory processes. This is the reason why neuropathological conditions that affect the hippocampus are so manifold and widespread. They offer us important insights into the physiological base of memory processing, whereby I close the circle to the beginning of this work.

Der Zusammenhang zwischen Struktur und Funktion des hippocampalen Gedächtnissystems bei amnestischen Patienten

Einleitung

Bei der vorliegenden Arbeit handelt es sich um eine kumulative Dissertation zum Thema „die Rolle des Hippocampus bei der Gedächtnisbildung“. Im Rahmentext wird ein breites Spektrum an Themenfeldern abgehandelt, die einerseits Hintergründe und Zusammenhänge der drei zu Grunde liegenden Fachartikel darstellen, und andererseits einen Einblick in die bisherige Forschungsarbeit vermitteln sollen.

Innerhalb dreier etablierter Klassifikationsansätze werden die verschiedenen zeitlichen, inhaltlichen und prozessbezogenen Ebenen des Gedächtnisses im Allgemeinen abgesteckt. Im Folgenden wird der Schwerpunkt auf das deklarative Gedächtnissystem gelegt, welches hauptsächlich auf Strukturen des medialen Temporallappens beruht, insbesondere auf dem Hippocampus. Im Hippocampus konvergieren verschiedenste Informationen aus weit verstreuten Hirnregionen und werden dort als integrierte Repräsentation in einen breiteren Kontext eingebunden. Diese Struktur steht demnach an der Spitze der Informationsverarbeitungshierarchie deklarativer Inhalte. Eine dauerhafte Speicherung bedarf diverser Modifikationen auf molekularer, zellulärer und Systemebene, die unter dem Begriff „Konsolidierung“ zusammengefasst sind. In den letzten Jahrzehnten rückte die Bedeutung des Schlafs für Konsolidierungsprozesse in den Fokus des Interesses. Dabei wurde auf den differenzierten Einfluss der Schlafstadien und anderer schlafassoziierter Parameter auf die Konsolidierung unterschiedlicher Gedächtnissysteme hingewiesen. Der Hippocampus, insbesondere die CA1 Region, ist vulnerabel für diverse Einflüsse, was auf Besonderheiten hinsichtlich seiner Rezeptorzusammensetzung, seiner vaskulären Anatomie und seiner Bedeutung für emotionale Verarbeitungsprozesse zurückzuführen ist. Letzterer Aspekt wird bei dem Syndrom der transienten globalen Amnesie besonders deutlich, bei dem punktuelle Läsionen nur beschränkt auf die CA1 Region für ein paar Tage nachweisbar sind. Bei den meisten Patienten kann ein physischer oder emotionaler Auslöser unmittelbar vor der akuten Episode identifiziert werden. TGA zeichnet sich durch eine eng umschriebene, schwere antero- sowie retrograde Amnesie aus, die sich nach wenigen Stunden vollständig zurückbildet. Das macht sie zu einem ideal geeigneten natürlichen Läsionsmodell, um die hippocampale Mitwirkung an unterschiedlichen Prozess- und Systemebenen des Gedächtnisses zu untersuchen, wie zum Beispiel dem prozeduralen Gedächtnis, welches lange als gänzlich unabhängig vom Hippocampus galt.

Was ist das Gedächtnis? Spekulationen über das Wesen des Gedächtnisses reichen Jahrtausende zurück. Die ersten schriftlichen Zeugnisse zu diesem Thema stammen von namhaften Persönlichkeiten aus der Antike wie Platon, in dessen Vorstellung Erinnerungen gleichsam als Gravuren in Wachstafeln existieren, bis sie unwiederbringlich gelöscht werden. Im Gegensatz zu seinem Mentor stellte sich Aristoteles das Erinnern als einen graduellen Prozess vor, an dessen Anfang die sensorische Wahrnehmung eines Objekts steht, wodurch eine interne Repräsentation des selbigen erzeugt wird. Diese mentale Repräsentation wird mit einem „sensorischen Rest" gleichgesetzt, welcher folgende Eigenschaften aufweist: er existiert ausschließlich auf der Basis von Materie, unterliegt dem Zerfall und ist willentlich abrufbar. Diese Annahmen stimmen weitestgehend mit dem heutigen Kenntnisstand überein. Im Mittelalter erkannte Thomas von Aquin, dass die meisten Erinnerungen auf rationaler Ebene rekonstruiert und somit im Sinne einer intellektuellen Einfärbung deformiert werden. Darüber hinaus beschrieb er als erster die Kategorisierung von Objekten und Prozessen anhand universeller Charakteristika. Auf diese Weise werden mentale Repräsentationen von Prototypen erzeugt, welche eine schnelle Identifikation von Neuem ermöglichen. Das Gedächtnis ist demnach also kein passiver Speicher wie lange angenommen, sondern es wirkt sich (re-)konstruierend auf unsere Wahrnehmung der Welt aus. Doch worin genau bestehen die Inhalte des Gedächtnisses? Die allgemein geläufigsten Bereiche umfassen unser Faktenwissen (semantisches Gedächtnis) und die Erinnerung an persönlich erlebte Ereignisse (episodisches Gedächtnis). Die Gesamtheit unseres episodischen Gedächtnisses ist die innere Repräsentation unserer Autobiographie, die unsere Identität konstituiert. Sie ermöglicht uns, erlebte Sequenzen erneut vor dem inneren Auge abzuspulen und uns selbst darin räumlich, zeitlich und situativ zu verorten und zu reflektieren (autonoetisches Bewusstsein). Darüber hinaus gelingt es uns ohne Schwierigkeiten, zukünftige oder rein fiktive Episoden zu ersinnen; eine Fähigkeit, die höchstwahrscheinlich dem Menschen allein zu eigen ist.

Gedächtnissysteme

Innerhalb der Klassifikation von Gedächtnissystemen anhand inhaltlicher Kriterien werden diese beiden Teilbereiche unter der Bezeichnung „explizites" oder „deklaratives" Gedächtnis zusammengefasst. Sie soll zum Ausdruck bringen, dass dessen Inhalte grundsätzlich dem Bewusstsein zugänglich und verbalisierbar sind. Im Gegensatz dazu weist das „implizite" oder „non-deklarative" Gedächtnis diese Eigenschaft nicht auf. Hierbei handelt es sich um eine Restkategorie, die deutlich heterogener als das deklarative Gedächtnis ist. Sie reicht von den primitivsten Funktionen wie Sensitivierung und Habituation (Zu- bzw. Abnahme der

Reaktionsintensität bei wiederholter Darbietung eines Reizes) über klassische Konditionierung (Assoziationslernen) bis hin zu komplexeren Funktionen wie dem prozeduralen Gedächtnis. Letzteres beinhaltet sowohl fein abgestimmte Bewegungssequenzen (ein Musikinstrument spielen) als auch -synergien (Handhabung fragiler Objekte) sowie die Hand-Auge-Koordination und viele weitere motorische Fertigkeiten. Diese Einteilung nach inhaltlichen Kriterien spiegelt sich auch auf anatomischer Ebene wider, da die verschiedenen Gedächtnissysteme durch unterschiedliche, sich teilweise überlappende neuronale Netzwerke vermittelt werden. In diesem Zusammenhang richtet sich das Hauptaugenmerk dieser Arbeit auf das hippocampusbasierte, deklarative Gedächtnis sowie das striatale, prozedurale Gedächtnis und auf die Frage, ob die Informationsverarbeitung beider Subsysteme wirklich vollständig unabhängig voneinander von statten geht.

Ein weiterer Klassifikationsansatz basiert auf der zeitlichen Ebene. Dabei werden drei Dimensionen unterschieden, nämlich erstens das sensorische Gedächtnis, welches eine Art „Nachhall der reinen sensorischen Eindrücke“ darstellt, der schon nach Millisekunden wieder zerfällt. Es verfügt über eine sehr hohe Speicherkapazität und ist frei von Interpretationen. Wegen der Kurzlebigkeit des sensorischen Nachhalls bezeichnet man es als „vorbewusst“. Noch in diesem vorbewussten Stadium finden Interpretations- und Selektionsprozesse statt, die mit dem unmittelbaren Zerfall der als irrelevant eingestuften Information und dem Transfer der relevanten Information in die zweite Dimension, das Kurzzeitgedächtnis, enden. Dieser Speicher verfügt über eine deutlich geringere Kapazität als das sensorische Gedächtnis (7 ± 2 Bedeutungseinheiten) und umfasst eine Zeitspanne von Sekunden bis wenigen Minuten. Innerhalb des Kurzzeitgedächtnisses findet eine Bearbeitung der Information hinsichtlich zeitlicher und räumlicher Sequenzen sowie der Herstellung semantischer Relationen statt. Als dritte Dimension repräsentiert das Langzeitgedächtnis den theoretisch unbegrenzten und beständigen (30 Minuten bis lebenslangen) Speicher der Informationen, die als relevant erachtet wurden. Der dritte Klassifikationsansatz steht in unmittelbarem Zusammenhang mit der zeitbezogenen Klassifikation, da er auf die Prozessebene fokussiert, die äquivalent zu den Übergängen der eben beschriebenen Stadien ist. Nachdem die Filterprozesse am Übergang vom sensorischen zum Kurzzeitgedächtnis stattgefunden haben, wird ein Teil der selektierten Information im Kurzzeitgedächtnis aufrecht erhalten und in die bereits bestehende kognitive Struktur integriert (Enkodierung). Doch anfangs ist diese Gedächtnisspur noch fragil. Indem Assoziationen gebildet werden, wird eine tiefe Elaboration ermöglicht und die Gedächtnisspur findet Eingang in das Langzeitgedächtnis (Konsolidierung). Für den erneuten Abruf ist ein

Transfer vom Langzeit- ins Arbeitsgedächtnis erforderlich, innerhalb dessen es bearbeitet und anschließend wieder enkodiert wird.

Das hippocampus-basierte deklarative Gedächtnis

in den 1950er Jahren erregte der Fall des Epilepsiepatienten Henry Molaison Aufsehen, welcher infolge einer bilateralen Temporallappenresektion die Fähigkeit verlor, sich neue, deklarative Gedächtnisinhalte anzueignen, wohingegen diejenigen Inhalte, die vor der Operation erzeugt wurden, weiterhin Bestand hatten. Interessanterweise erinnerte H.M. neu gelernte, implizite, prozedurale Fertigkeiten ebenso gut wie gesunde Personen. Dieser Fall legte die Vermutung nahe, dass erstens Strukturen des Temporallappens an der Konsolidierung des Langzeitgedächtnisses beteiligt sind, es zweitens mehrere Gedächtnissysteme geben und drittens der Speicherort des deklarativen Gedächtnisses außerhalb des Temporallappens lokalisiert sein muss. Im Verlauf der nächsten Jahrzehnte konnten die zu Grunde liegenden Mechanismen durch weitere klinische Fälle, Läsionsstudien an Tiermodellen und bildgebende Verfahren entschlüsselt werden.

Zunächst gelangen die rein sensorischen Wahrnehmungen über den Thalamus in die primären sensorischen Areale, von wo aus sie in die Assoziationsareale des Kortex verteilt werden. Von dort aus verlaufen Projektionen in neokortikale Regionen des Temporallappens. Der perirhinale Cortex erhält topographisch organisierte Projektionen der Assoziationsareale, die nach ihrer Prozessierung hauptsächlich in laterale Areale des entorhinalen Kortex gelangen. Erstere generieren integrierte Informationen über die Qualität eines Objekts. Der parahippocampale Cortex hingegen erhält Projektionen aus Arealen, welche polymodale räumliche Aspekte verarbeiten und leitet sie weiter an mediale Areale des entorhinalen Kortex. Zwischen den genannten Subarealen des Temporallappens bestehen nur wenige Verbindungen. Der größte Teil der Informationen konvergiert im Hippocampus, welcher an der Spitze der Informationsverarbeitungshierarchie im Temporallappen steht. In dieser Struktur des limbischen Systems werden Informationen verschiedenster Art integriert („binding“) und in einen Kontext gestellt.

Der Hippocampus ist eine symmetrisch angelegte, phylogenetisch alte Struktur innerhalb des Telencephalons, die ihren Namen im 16. Jahrhundert nach ihrer oberflächlichen Ähnlichkeit mit einem Seepferdchen erhielt. Er stellt den größten Teil des Archicortex dar, welcher seinerseits Teil des Allocortex ist. Eingebettet in den gyrus parahippocampalis grenzt er am anterioren Ende an die Amygdala und erstreckt sich bogenförmig am Seitenventrikel bis zum corpus callosum. Er besteht aus drei Schichten, wobei sich die mittlere Hauptschicht zwischen

zwei zellarmen Schichten befindet. Die beiden Hauptbestandteile des Hippocampus werden als gyrus dentatus und cornu ammonis bezeichnet. Das Cornu ammonis wurde nach morphologischen Aspekten in vier Kompartimente (CA1 - CA4) unterteilt. Dabei stellt die dem gyrus dentatus am nächsten liegende CA4 Region den „Eingang“ des Hippocampus dar. Der Informationsfluss des Hippocampus wird als „trisynaptischer Schaltkreis“ beschrieben, weil die Eingangssignale größtenteils über drei nachgeschaltete exzitatorische glutamaterge Synapsen weitergeleitet werden. Die Signaltransmission beginnt mit Neuronen des entorhinalen Kortex, die als tractus perforans zu den Korbzellen des gyrus dentatus projizieren. Von dort aus wird das Signal über die Moosfasern in die CA3 Region geleitet. Die Schaffer-Kollateralen der CA3- Pyramidenzellen ziehen in die CA1 Region und von dort aus in das Subiculum, dessen Projektionen teilweise wieder zurück in den entorhinalen Kortex reichen und somit den Kreis komplettieren. Der trisynaptische Schaltkreis ist ein stark vereinfachtes Modell. Es gibt darüber hinaus diverse intrinsische Schaltkreise und auch rückwärtsgewandte Projektionen der einzelnen Kompartimente, was charakteristisch für ein autoassoziatives System ist. Auf Grund seines hohen Ausmaßes an Plastizität eignet sich der Hippocampus hervorragend zum schnellen Lernen.

Gedächtniskonsolidierung

Doch wie werden Informationen gespeichert? Es finden zwei Arten der Konsolidierung nacheinander statt, welche sich als funktionelle Korrelate des Kurz- und des Langzeitgedächtnisses erwiesen. Die synaptische Konsolidierung basiert auf dem vorübergehenden Anstieg der synaptischen Transmission durch ein hinreichend starkes eingehendes Signal, welches eine komplexe molekulare Kaskade in Gang setzt: Durch eine temporäre Veränderung der Membraneigenschaften strömt Calcium in die Präsynapsen und bewirkt dort die Ausschüttung des Neurotransmitters Glutamat in den synaptischen Spalt. Das Glutamat bindet an zwei Unterarten von ionotropischen Rezeptoren. Die N-Methyl-D-Aspartat-Rezeptoren sind für gewöhnlich durch Magnesiumionen blockiert, die nur durch ein hinreichend starkes Signal entfernt werden können. Anschließend strömt Calcium in die postsynaptische Zelle und verändert deren elektrophysiologische Eigenschaften. Dieses Phänomen wurde als Langzeitpotenzierung bekannt und findet an allen Synapsen des trisynaptischen Schaltkreises statt. Eine vorübergehende Abschwächung der Signaltransmission wird als Langzeitdepression bezeichnet.

Zur erfolgreichen langandauernden Speicherung sind strukturelle Veränderungen in Form der Synthese neuer Proteine erforderlich, die ihrerseits eine Änderung der entsprechenden Gen-

Expression erfordern. Dies vollzieht sich, indem spezifische DNA-Sequenzen am Anfang eines Gens, die sich an regulatorische Proteine binden und somit die Gentranskription steigern, verringern oder abschalten können (transkriptionale Kontrolle). Sie werden über second messenger Systeme reguliert. Dies führt zu Modifikationen der prä- und postsynaptischen neuronalen Architektur (Systemkonsolidierung). Sie stellen die Basis des Langzeitgedächtnisses dar.

Das Striatum-basierte prozedurale Gedächtnis

Auch das prozedurale Gedächtnis wird über weitverzweigte Netzwerke vermittelt, die teilweise untereinander verbunden sind. Dabei handelt es sich um die „kortiko- striatal- thalamo- kortikale Schleife“ und die „kortico- zerebellar- thalamo- kortikale Schleife“, denen eine simultane Akquisition prozeduraler Fertigkeiten zugeschrieben wird, die jedoch unterschiedliche Grade des Bewusstseins erfordern und sich auch hinsichtlich ihrer Robustheit unterscheiden. Von Bildgebungsstudien wissen wir, dass in der Enkodierungsphase der prämotorische Kortex, das supplementär- motorische Areal, das Kleinhirn, bestimmte parietale Regionen sowie das Striatum aktiviert werden. Im späteren Verlauf der Lernphase und sobald der Lerninhalt sich automatisiert hat, wurde ein Rückgang der neuronalen Aktivität des Cerebellums, des primären motorischen Kortex und des präsupplementären motorischen Areals verzeichnet. Das Striatum hingegen ist durchgängig sehr aktiv, von der initialen Lernphase bis zum automatisierten Status. Doch auch Strukturen des Temporallappens scheinen bei der Verarbeitung prozeduraler Fertigkeiten eine Rolle zu spielen; auf welche Weise und in welchem Ausmaß hängt von der Art der Aufgabe und entsprechend von der Kombination der beteiligten neuronalen Teilprozesse ab. Grundsätzlich ist der Hippocampus wie beschrieben an der Repräsentation räumlicher und zeitlicher Kontextaspekte beteiligt, die auch einen Bestandteil motorischer Fertigkeiten darstellen. Diese scheinen sich teilweise dem Zugang zum Bewusstsein zu entziehen, wie Studien über den hippocampalen Beitrag zu implizitem motorischen Lernen belegen. Darüber hinaus enthält komplexes Verhalten sowohl prozedurale als auch deklarative Anteile.

Schlaf und Gedächtnis

Wie der Fall H.M. nahelegte, werden die erinnerten Informationen außerhalb des Hippocampus gespeichert. In diesem Zusammenhang spielt der Schlaf eine Schlüsselrolle. Der Schlaf besteht aus zyklisch alternierenden Schlafstadien, die jeweils als charakteristische Signale im EEG sichtbar werden. Je tiefer der Schlaf ist, desto langsamer wird die Frequenz und desto höher

werden die Amplituden der Hirnströme, was ein Korrelat der synchronen Feuerungsrate ganzer Neuronenpopulationen darstellt. In den 70ern des 20. Jahrhunderts stellte man fest, dass die Menge dieses tiefen, langsamwelligen Schlafs mit der Konsolidierung von deklarativen Gedächtnisinhalten positiv korreliert ist. Später brachte man die Konsolidierung des prozeduralen Gedächtnisses mit der Menge des REM-Schlafs in Verbindung, was als „Zwei-Prozess-Hypothese“ tituliert wurde. Es wird angenommen, dass sich während des Schlafs eine Reaktivierung von neuronalen Erregungsmustern vollzieht, die in der Enkodierungsphase generiert wurden. Diese Reaktivierung tritt selektiv im Hippocampus und im Neocortex auf, was sowohl eine Festigung der Gedächtnisspur als auch einen graduellen Transfer vom Hippocampus in neokortikale Strukturen bewirkt. Dieser „hippocampal-neokortikale Dialog“ kann sich über Jahrzehnte erstrecken. Heutzutage sind die zu Grunde liegenden Mechanismen gut verstanden: Die langsamen Oszillationen des Tiefschlafs spiegeln das Wechselspiel zwischen intensiver synchroner neuronaler Entladung und neuronaler Stille. Über efferente Bahnen wird an den Übergängen vom elektrisch negativen in den positiven Bereich die Erzeugung sowohl von hippocampalen sharp wave ripples als auch von Schlafspindeln beeinflusst. Es kommt also zu einer Kopplung neuronaler Entladungsmuster auf Netzwerkebene: Die langsamen Oszillationen entstammen neokortikalen Strukturen, während die Spindeln thalamisch und die sharp wave ripples hippocampal generiert werden. Um die Kommunikation der verschiedenen Areale zu ermöglichen, ist ein niedriger Acetylcholinspiegel, der seinen Tiefstand während des langsamwelligen Schlafs erreicht, unabdingbar. Die cholinerge Neurotransmission moduliert die hippocampale neuronale Aktivität, indem sie tagsüber durch gesteigerte Aktivität die Enkodierung erleichtert, während sie im Schlaf durch einen niedrigen Spiegel ein Milieu schafft, welches die Reaktivierung zuvor enkodierter Gedächtnisspuren begünstigt. Dieser zyklische Prozess bewirkt eine Festigung relevanter und einen Zerfall irrelevanter Erinnerungen. Tononi und Cirrelli postulierten in diesem Zusammenhang den Erhalt der „synaptischen Homöostase“ und einer qualitativen Steigerung des Signal- Rausch- Verhältnisses, indem im Wachzustand eine synaptische Potenzierung erfolgt, die während des Schlafs wieder herunterreguliert wird.

Zusammenfassung der Manuskripte: 1. „Transiente globale Amnesie“

Der Hippocampus, insbesondere die CA1 Region, ist vulnerabel für externe sowie für intra-psychische Einflüsse, die zur Einschränkung bis zum vollständigen Ausfall seiner Funktion führen können. In diesem Zusammenhang ist die transiente globale Amnesie (TGA) für uns von besonderem Interesse, da dieses Syndrom Aufschluss über die Funktionsweise verschiedener

kognitiver Prozesse ohne hippocampale Mitwirkung gibt und auf Grund der praktisch vollständigen Genesung Studien in einem longitudinalen Design ermöglicht.

Die transiente globale Amnesie ist ein seit dem neunzehnten Jahrhundert bekanntes klinisches Syndrom, welches durch eine plötzlich einsetzende, bis maximal 24 Stunden andauernde und alle Sinnesmodalitäten betreffende anterograde sowie retrograde Amnesie gekennzeichnet ist. Darüber hinaus gelten als weitere diagnostische Kriterien, dass die amnestische Episode von einer dritten Person bezeugt werden kann und dass abgesehen von der Amnesie keine weiteren neurologischen Auffälligkeiten wie Bewusstseinstrübung, Verlust der persönlichen Identität, des Urteilsvermögens oder weiterer kognitiver Funktionen bestehen. Es müssen als Ursachen ein Schädel-Hirntrauma, epileptische Anfälle, paroxysmale Phänomene und fokal-neurologische Symptome ausgeschlossen werden. Die Diagnose der TGA beruht gänzlich auf der klinischen Untersuchung.

Die Inzidenz ist mit einer Rate von ungefähr fünf Personen auf 100.000 pro Jahr als gering einzustufen. Bei den meisten Patienten ereignet sich die TGA in der siebten Lebensdekade. Drei Viertel aller Attacken beschränken sich auf ein Lebensalter zwischen 50 und 70 Jahren, wobei beide Geschlechter gleich häufig betroffen zu sein scheinen.

Das klinische Erscheinungsbild ist vornehmlich von einer abrupt einsetzenden Unfähigkeit geprägt, jüngere Erinnerungen abzurufen. Dabei zeigt sich im Regelfall ein temporaler Gradient des episodischen Gedächtnisses, der durch nahezu vollständigen Erhalt sehr alter Erinnerungen (aus der Schulzeit und dem jüngeren Erwachsenenleben) und Verlust der jüngsten Erinnerungen (Stunden, wenige Tage) geprägt ist. Wie weit die retrograde Amnesie in die Vergangenheit hineinreicht, variiert interindividuell von Wochen bis hin zu einigen Jahrzehnten. Bezüglich der anterograden Amnesie umfasst die Behaltensspanne von augenblicklich Erlebtem lediglich zwei bis drei Minuten oder auch kürzer, wenn die Aufmerksamkeit auf etwas anderes gerichtet wird. Demnach ist die Fähigkeit zur Gedächtniskonsolidierung vorübergehend außer Kraft gesetzt. Diese Umstände führen bei den meisten Patienten zu Gefühlen der Verwirrung, Hilflosigkeit und Desorientierung, was sich häufig in sich fortwährend wiederholenden Fragen äußert. Einige Patienten entwickeln auch depressive oder ängstliche Gefühle, die bis hin zu Symptomen einer Panikattacke oder sogar der Angst zu sterben führen können. Solch eine belastende emotionale Befindlichkeit kann unter Umständen das amnestische Defizit noch zusätzlich verstärken. Manchmal treten leichte vegetative Begleiterscheinungen wie Kopfschmerzen, Schwindel, Übelkeit, kalte Extremitäten, Schüttelfrost oder auch Hitzewallungen auf. TGA Patienten zeigen typischerweise keine Beeinträchtigung anderer kognitiver Funktionen wie intellektueller Fähigkeiten, semantischen Wissens, des

Arbeitsgedächtnisses, der Aufmerksamkeit oder prozeduraler Fertigkeiten. Es ist ihnen sogar möglich, komplexere Tätigkeiten wie zum Beispiel Autofahren oder Kochen durchzuführen. Innerhalb von Stunden regeneriert sich die Amnesie, indem Erinnerungen dem Verlauf des beschriebenen Gradienten (von alt nach neu) entsprechend wiederkehren, wobei typischerweise eine Erinnerungslücke an die akute Phase bestehen bleibt. Es herrscht Uneinigkeit darüber, ob unmittelbar nach der TGA eine Restitution eintritt oder ob noch länger andauernde, neuropsychologische Defizite zurückbleiben. Einige Autoren berichten von subtilen, sich über Tage bis Monate erstreckenden Einschränkungen des verbalen und non-verbalen Langzeitgedächtnisses sowie der Wortflüssigkeit. Eine Metaanalyse aus dem Jahr 2009 hingegen konnte keine Beeinträchtigungen nachweisen. In Anbetracht der Pathogenese und der geringen Wahrscheinlichkeit einer erneuten Attacke (3% bis ca. ein Viertel) ist die TGA als ein benignes Syndrom einzustufen.

Es bleibt weiterhin rätselhaft, welche pathophysiologischen Mechanismen zu ihrer Entstehung beitragen. Fest steht, dass bei den meisten Patienten mittels Magnetresonanztomographie zwei bis drei Tage nach der amnestischen Episode punktuelle Läsionen detektierbar sind, die sich ausschließlich auf die CA1 Region des Hippocampus beschränken. Das Auftreten von Laktat in den Läsionen zeugt von einer kurzweiligen Beeinträchtigung des dortigen Zellmetabolismus. Dennoch stehen auch weiterhin verschiedene Theorien über die Ätiologie der TGA zur Diskussion. Ein kontroverser Ansatz schreibt die überdurchschnittliche Inzidenz von Migräne insbesondere bei jüngeren TGA Patienten gemeinsamen Entstehungsmechanismen zu. Demnach gilt Migräne als Risikofaktor für TGA. Manche Autoren hingegen interpretieren die TGA als epileptisches Phänomen, für welches gewisse Ähnlichkeiten im klinischen Erscheinungsbild sprechen, das aber in den meisten EEG-Studien nicht untermauert werden konnte. In einigen Studien wurde eine Assoziation zu einem hämodynamischen, beziehungsweise thromboembolischen Geschehen hergestellt. Entsprechend gilt die TGA diesem Ansatz zufolge als eine Manifestation einer transienten zerebralen Ischämie in Strukturen, die für das Gedächtnis relevant sind. Darüber hinaus könnte bei einigen TGA-Patienten ein Valsalva- Manöver eine venöse Kongestion ausgelöst haben. Obwohl die Rolle eines hypoxisch- ischämischen Geschehens noch nicht abschließend geklärt ist, konnte in den meisten diesbezüglichen Studien kein abweichendes zerebrovaskuläres Risikoprofil bei TGA Patienten festgestellt werden. Auch wir fanden in unserer Studie über den Zusammenhang zwischen psychologischen Stress und TGA bei 113 Patienten kein gehäuftes Vorkommen dieser Risikofaktoren, abgesehen von Migräne, unter der ein Drittel der Stichprobe litt.

Einen wichtigen Einblick in die Ätiopathogenese der TGA liefert die Analyse der vorausgehenden Ereignisse. Abhängig von subjektiven Kriterien berichten bis zu 90 Prozent der Patienten von unmittelbar vorher stattgefundenen Vorgängen, die mit einer physischen oder psychischen Anstrengung verbunden waren, von einer sprunghaften Temperaturveränderung (zum Beispiel durch Wasserkontakt), starken Schmerzen oder Geschlechtsverkehr. Dabei findet sich bei Männern häufiger ein physischer Auslöser wie anstrengende sportliche Betätigungen oder körperlich fordernde Arbeit. Bei Frauen hingegen treten häufiger emotional aufgeladene Situationen wie Streit, aufwühlende Neuigkeiten oder das (Wieder-)erleben traumatischer Ereignisse auf. Welche psychischen Faktoren zur TGA- Entstehung beitragen, wird im nächsten Abschnitt detaillierter abgehandelt, der unseren eigenen Forschungsbeitrag zu diesem Themenfeld zusammenfasst.

In den letzten Jahren wurden viele Forschungsarbeiten den psychopathologischen Faktoren der TGA- Ätiopathogenese gewidmet. Rund ein Drittel der TGA Patienten berichtet von einer emotional belastenden Situation unmittelbar vor der Attacke. Als emotional belastende Faktoren wurden bestimmte Persönlichkeitsmerkmale, emotionale Instabilität und das Auftreten psychiatrischer Auffälligkeiten in der Familiengeschichte in Betracht gezogen.

Zusammenfassung der Manuskripte: 2. „Stressbezogene Faktoren beim Auftreten der transienten globalen Amnesie mit hippocampalen Läsionen“

In unserer Studie untersuchten wir mittels etablierter Fragebögen den Zusammenhang zwischen dem Auftreten einer TGA und folgenden stressbezogenen Faktoren: subjektives Erleben von Stress (Perceived Stress Scale, PSS), Anwendung verschiedener Coping-Strategien (Stressverarbeitungsfragebogen, SVF), Erfahrung kritischer Lebensereignisse innerhalb eines Zeitraumes von zwei Jahren vor der TGA (Social Readjustment Rating Scale, SRRS) sowie erlebtes Ausmaß von Angst und Depression in der Woche vor der TGA (Hospital Anxiety and Depression Scale (HADS-D). Die Stichprobe bestand aus 21 Patienten (69,7 ± 5,7 Jahre, 9 Männer), deren Auslöser eindeutig als emotional oder physisch eingeordnet werden konnte. Als Kontrollgruppe diente eine Stichprobe von 20 gleichaltrigen gesunden Probanden (8 Männer). Während der akut amnestischen Phase wurden zwei deklarative Lerntests mit verbalem (RAVLT) und figuralem (ROCF) Lernmaterial durchgeführt, die in der Follow-up Untersuchung als Parallelversionen wiederholt wurden. Das Verhalten während der TGA wurde protokolliert (tendenziell hyperaktiv, hypoaktiv und normal). Alle Patienten unterzogen sich einer MRT- Untersuchung in einem Zeitraum zwischen 24 und 72 Stunden nach der TGA, als die hippocampalen Läsionen am besten detektierbar waren. In der Follow-up Untersuchung

erfolgte zusätzlich zum deklarativen Gedächtnis eine allgemeine Beurteilung kognitiver Fähigkeiten: Intelligenz, exekutive Funktionen und Wortflüssigkeit. Alle Fragebögen zur Erfassung der stressbezogenen Faktoren wurden ebenfalls im Follow-up durchgeführt.
Der Stressverarbeitungsfragebogen offenbarte zwei signifikante Unterschiede zwischen TGA Patienten und Kontrollen, nämlich dass die Patienten eher zu Schuldgefühlen neigen, während die Kontrollpersonen eher ihre Sorgen durch positive soziale Vergleiche herunterzuspielen versuchen. Dieses Ergebnis legt die Vermutung nahe, dass die Patienten weniger vorteilhafte Coping- Strategien nutzen (in negativen Gefühlen verharren) als gesunde Gleichaltrige, welche ihrerseits auf selbstwerterhaltende Strategien zurückgriffen. Im Gegensatz zum Coping konnten wir keine signifikanten Unterschiede zwischen beiden Gruppen hinsichtlich des generellen subjektiven Empfindens von Stress, Depression oder Angst feststellen. Die Patienten erlebten auch nicht mehr kritische Lebensereignisse in den beiden vorausgegangenen Jahren als die Kontrollen.
Im nächsten Analyseschritt wurden die Patientengruppen einerseits in Personen mit einem emotional belastenden Vorereignis und andererseits in Probanden, deren Vorereignis ausschließlich physiologischer Art war, aufgeteilt. Es zeigte sich, dass erstere Gruppe tendenziell geneigt ist, ihre Sorgen herunterzuspielen und in Belastungssituationen häufiger zu Medikamenten greift. Außerdem berichteten sie von einem signifikant höheren Ausmaß an Angst in der Woche vor der TGA. Wir vermuten, dass die gesteigerte Angst einen prädisponierenden Faktor im Sinne der Vulnerabilität darstellt. So wird in manchen Fällen eine TGA ausgelöst, wenn funktionelle Veränderungen der neuronalen Aktivität und ein belastendes Vorereignis zusammenfallen. Quinette et al. (2006) mutmaßen, dass diese Koinzidenz in eine Kaskade münden kann, an deren Anfang das Erleben von Stress steht, welches die Ausschüttung von stress-assoziierten Hormonen und Neurotransmittern bewirkt, die Zytotoxizität im Hippocampus auslösen.

Zusammenfassung der Manuskripte: 3. „motorisches Lernen und schlafabhängige Konsolidierung bei Patienten mit einer akuten hippocampalen CA1 Läsion“

Wie in der Einleitung beschrieben, beruht das deklarative Gedächtnissystem vorwiegend auf Strukturen des medialen Temporallappens, insbesondere dem Hippocampus, während das prozedurale Gedächtnissystem durch cortico- striatal- cerebellare Schaltkreise vermittelt wird. Beide Gedächtnissysteme unterscheiden sich nicht nur hinsichtlich ihres Inhalts und der beteiligten Hirnregionen, sondern auch durch funktionelle Aspekte. Während das hippocampale System als flexibel und für schnelles Lernen geeignet erscheint, vollzieht sich das Lernen im

striatalen System deutlich rigider und langsamer. Es beruht auf Versuch und Irrtum. In unserer Studie widmeten wir uns der Frage, ob beide Systeme gänzlich unabhängig voneinander sind. In verschiedenen Studien fanden sich Hinweise darauf, dass der Hippocampus eine Rolle nicht nur beim Erlernen einer motorischen Aufgabe, sondern auch bei der schlafabhängigen Konsolidierung spielen könnte. Doch wie ist dieses Zusammenspiel beschaffen? Studien zu diesem Thema kommen zu unterschiedlichsten Ergebnissen, die von funktioneller Unabhängigkeit über generelle Kooperation oder Rivalität bis hin zu einer differenzierteren durch Schlaf modulierten Interaktion reichen. Diese Heterogenität ist wahrscheinlich hauptsächlich der Wahl der Untersuchungsmethode und des Forschungsparadigmas geschuldet, denn gerade motorische Lernaufgaben sind derart vielgestaltig, dass ihre Bewältigung sehr unterschiedliche Kombinationen aus zu Grunde liegenden Prozessen erfordert.

Wir entschieden uns für eine sequenzielle Tippaufgabe, die simpel ist und basaler motorischer Prozesse bedarf. Sie besteht darin, eine vorgegebene Reihenfolge von vier Nummerntasten in jeweils 30 Sekunden so schnell und so akkurat wie möglich zu tippen. Es wurden 15 Durchgänge vor und vier nach dem Schlaf durchgeführt. Als deklarative Lernaufgabe diente ein verbaler (RAVLT) sowie ein figuraler Lerntest (RCF). 16 TGA Patienten führten in der akuten Phase und nach ihrer Genesung in einer Follow-up Untersuchung die Tests durch. Eine Gruppe von gleichaltrigen gesunden Probanden diente als Kontrolle.

Die Hauptparameter der motorischen Lernaufgabe waren die Geschwindigkeit (Anzahl korrekt getippter Sequenzen pro Durchgang) und die Genauigkeit (relative Anzahl der Fehler pro korrekt getippter Sequenz). Der Lernzuwachs war definiert als Differenz des Durchschnitts der ersten drei und der letzten drei Sequenzen vor dem Schlaf und die Konsolidierung entsprechend als Differenz des Durchschnitts der ersten drei Sequenzen nach dem Schlaf und den letzten drei vor dem Schlaf. Diese beiden Deltas, der Lernzuwachs und die Konsolidierung, wurden im zweiten Schritt mit den Gedächtnisleistungen der deklarativen Aufgaben korreliert.

Es zeigten sich bei den akuten TGA Patienten schwere Einbußen des deklarativen Gedächtnisses, die in der Follow-up Untersuchung nicht mehr nachzuweisen waren. Trotz der vorübergehenden Entkopplung des Hippocampus waren sie in der Lage, ihre motorischen Leistungen in einem ähnlichen Ausmaß wie die Kontrollen von Durchgang zu Durchgang zu steigern, allerdings lagen sie hinsichtlich der Geschwindigkeit signifikant unter deren Niveau. In den ersten drei Sequenzen zeigte sich ein deutlich geringerer, eher linearer Lernzuwachs als bei den Kontrollen, deren Geschwindigkeit sich zu Beginn eher logarithmisch steigerte. In Bezug auf die Genauigkeit gab es keine Unterschiede zwischen den Gruppen. Diese Datenlage

lässt darauf schließen, dass der Hippocampus auch bei dieser simplen motorischen Lernaufgabe involviert ist, was insbesondere für die initiale Lernphase gilt.
Während die Patienten im Follow up und die Kontrollen über Nacht die motorischen Lernleistungen nicht steigerten, beobachteten wir eine signifikante Verbesserung der Akutpatienten über Nacht. Diesen Konsolidierungseffekt korrelierten wir mit den Ergebnissen des RAVLT als Schätzer des amnestischen Defizits. Je gravierender das hippocampale Defizit war, desto größer war die Konsolidierungsleistung der motorischen Lernaufgabe. Ein Sachverhalt, der sich weder im Follow-up noch bei den Kontrollen zeigte. Er deutet auf eine kompetitive Interaktion zwischen dem striatalen und dem hippocampalen Gedächtnissystem während der Konsolidierung im Schlaf hin, wie es bei Poldrack und Packard (2003) beschrieben wurde. Die Daten untermauern die These einer dynamischen Wechselbeziehung beider Gedächtnissysteme im Hinblick auf schlafabhängige Modulation ihrer Konnektivität.

Abschließende Bemerkungen

Die zu Grunde liegenden Manuskripte dieser Arbeit und eigene vorausgegangene Arbeiten erbrachten neue Erkenntnisse bezüglich der Organisation des hippocampalen Gedächnissystems. Wir fanden Hinweise auf eine lebenslange Einbindung des Hippocampus bei der Erinnerung an persönliche Ereignisse aus der Vergangenheit, auch wenn diese sehr weit zurücklagen. Diese Beobachtung werteten wir als einen Beleg für die „Theorie der multiplen Spuren“. Doch nicht nur das deklarative, sondern auch das prozedurale Gedächtnis beruht auf weit verzweigten neuronalen Netzwerken, in die der Hippocampus eingebunden ist, wie die letztgenannte Studie zeigt. Beiden Studien liegt das natürliche Läsionsmodell der transienten globalen Amnesie zu Grunde, welches den Verlauf kognitiver Prozesse ohne hippocampale Mitwirkung zu untersuchen ermöglicht. Neben diesem Syndrom existieren eine Reihe anderer, die ebenfalls einen teilweisen oder vollständigen Ausfall hippocampaler Funktionen nach sich ziehen. Die hohe Vulnerabilität des Hippocampus ist auf molekulare, zelluläre und vaskuläre Spezifika zurückzuführen, die ihn auch für Funktionseinbußen durch psychologischen Stress disponieren.

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